Exploring the relationship between Hemi-inattention and Functional recovery in the first six months after stroke: a longitudinal study with a multilevel modelling approach to data analysis

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Authored by

Stella (Maria) Stein

(Student number: 0323022)

Brunel University - London

College of Health and Life Sciences

Department of Clinical Sciences

Abstract

In recent years, the functional outcomes of patients with right hemisphere stroke (RHS) received considerable attention due to their impact on disability, independent living, quality of life and economic burden. Hemi-inattention (HI) is a complex condition which often accompanies RHS. It is characterised by reduced alertness, attention and low spatial awareness levels. Past studies reported poor outcomes in patients with HI and inconsistent findings in regard to the relationship of HI with functional outcome. Literature review of 13 relevant studies highlighted poor research methodology which complicated interpretation of previous results.

Aims

The aim of this study was to address the clinically important question *"What is the relationship between early HI status (HI±) and functional change in the 1st six months after right hemisphere stroke?"* by improving on research methodology from past studies.

Methods

An all-inclusive stroke severity RHS sample (58 with and 35 without HI) were recruited from two stroke units and assessed on motor and cognitive factors with validated measurement tools on four occasions; baseline, hospital discharge, 6 weeks after discharge, and 6 months after stroke. A multi-level modelling approach was used to analyse change in functional progress over time with potential explanatory motor and cognitive factors.

Results

HI status was only statistically significant when modelled alone. Its predictive importance greatly diminished when modelled with other factors e.g. stroke severity, time since stroke and age.

Conclusion

On average, HI group membership at baseline is unrelated to functional recovery when other influential factors are also considered.

The findings extend current knowledge in stroke recovery research and provide suggestions for optimal therapeutic and rehabilitation outcomes. In contrast with traditional methods of regression analysis, multi-level modelling techniques enabled important relationships to be studied in depth. This resulted in new insights into the data which can be used to inform patient management and future research in the field.

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Abbreviations and signs

1^{st}	first
ADL	Activities of Daily Living
ANOVA	Analysis of Variance
BAPEN	British Association for Parenteral and Enteral Nutrition
BBS	Berg Balance Scale
BI	Barthel Index
BIT	Behaviour Inattention Test
BMI	Body Mass Index
C	column
CASP	Critical Appraisal Skills Programme
Ch	Chapter
CI	Confidence interval
CMSA	Chedoke-McMaster Impairment Inventory
CNS	Central Nervous System
cont.	Continued
CT	Computerized Axial Tomography Scan
CVA	Cerebro-vascular accident
df	Degrees of freedom
DOH	Department of health
DV	Dependent Variable
E.g.	Example
EMS	Elderly Mobility Scale
FAI	Frenchay Activities Index
f/up	Follow-up
FIM	Functional Instrumental Measure
FMA	Fugl-Meyer Assessment Scale
GDS	General Depression Scale
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSE	General Self-efficacy Scale
HADS	Hospital Anxiety and Depression Scale

HI	Hemi-inattention condition
HI-	Without Hemi-inattention
HI+	With Hemi-inattention
HI±	With and without Hemi-inattention
HSN	Hemi-spatial neglect
i.e.	That is
ICC	Intra Class Correlation Coefficient
IGLS	Iterative Generalised Least Squares
IV	Independent variable
L1	level one (model structure)
L2	level two (model structure)
LCT	Letter Cancellation Test
LHS	Left hemisphere stroke
LOS	Length of stay
LOTCA	Lowenstein Occupational Therapy Cognitive Assessment
LR	Likelihood Ratio Test
M1	Basic model
M2	Model series (a-q)
M3	Simplified model of (M1)
Max.	Maximum
MDT	Multi-disciplinary team
MEAMS	Middlesex Elderly Assessment of Mental State
Mf	Final model
MI	Mobility Index
Min.	Minimum
MLM	Multilevel Modelling
MLwin	Software package for multilevel modelling
MMSE	Folstein Mini-Mental Test
MRI	Magnetic Resonance Imaging
MUST	Malnutrition Universal Screening Tool
N (n)	Sample size
N.B.	Nota Bene
NH	Nursing home

NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHSS	National Institute of Health Stroke Scale
No.	Number
OR	Odds Ratio
OT	Occupational Therapist
PACI	Partial Anterior Circulation Infarcts
PASS	Postural Assessment Scale for Stroke
PEDro	Physiotherapy Evidence Database
p.	Page
PT	Physiotherapist
R^2	Coefficient of determination
RC	Regression coefficient
RCA	Random Coefficient Analysis
RCT	Randomised controlled trial
REC	Research Ethics Committee
Resp.	respectively
RHS	Right Hemisphere Stroke
RI	Regression intercept
RIC-FAS	Rehabilitation institute of Chicago Functional Assessment Scale For Comprehension and Written Expression
RKE	Rabideau Kitchen Evaluation
RMI	Rivermead Mobility Index
SART	Sustained and Divided Auditory Attention Test
SCI	Spinal cord injury
SD	Standard deviation
SE	Standard error
SLT	Speech and Language Therapy
SPSS	Statistical package
T0	Baseline (the first 7 days after stroke)
T1	Discharge point (from stroke unit)
T2	45 days post discharge date
T3	Six months since stroke

TACI	Total Anterior Circulation Infarcts
TFT	Thumb Finding Test
TI1	Interim observation point 1
TI2	Interim observation point 2
UK	United Kingdom
USA	United States of America
USN	Unilateral Spatial Neglect
VN	Visual Neglect
vs	versus
VSN	Visual Spatial Neglect
WHO	World Health Organisation
e^{-x}	Denotes a base of 10^{-x}
x^2	Chi-square
α	Alpha level
β	(beta) regression coefficient
ρ	Rho
p	The probability value, p-value or statistically significance of a test
~	Approximately
$<$	Smaller than
$>$	Greater than
≤	Smaller than or equal to
≥	Greater than or equal to
-ve	negative
+ve	positive

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Chapter 1 - Introduction

Chapter one

Introduction

1.0 Introduction

This chapter provides the background and context for this PhD project, the reasons why it was undertaken and its relevance to the field of stroke and functional outcomes. The population of interest is patients with right hemisphere stroke dysfunction, specifically those with hemi-inattention syndrome (also known as neglect).

An outline of the hemi-inattention condition is presented first, followed by identification of the problem leading to the PhD study, the rationale for the research, its potential contribution to the stroke literature and clinical practice in the field. An overview of the thesis and its organisation concludes the first chapter.

1.1 Background to the project

1.1.1 The hemi-inattention condition – definition and terminology

Despite considerable research and advances in the field, hemi-inattention (neglect) remains poorly defined as a condition *per se*. This is demonstrated by ongoing debate on the cause of HI (as will be presented in section 1.1.2) and the use of multiple descriptors found in the stroke literature. Examples of such descriptor terms can be seen in the titles of reviewed publications in chapter two; they include unilateral neglect, unilateral inattention, spatial neglect, hemi-neglect, hemi-spatial neglect, hemi-inattention and various further taxonomies

(Mark 2003, Plummer et al 2003, Karnath and Rorden 2012, Kerkhoff and Schenk 2012).

In the author's view, the word 'neglect' is misleading because as will be described in section 1.1.2, patients with the 'syndrome' often lack full or part awareness of what they are supposedly 'neglecting' (Samuelsson et al 1997, Manly et al 2005). From a philosophical perspective, one cannot neglect what one is not consciously aware of in the first place. Following on from this argument, the 'umbrella' term 'hemi-inattention' will be used in this thesis to denote the general "neglect" condition. In the following text, hemi-inattention is abbreviated to HI; patients with HI as HI+ and without HI as HI-.

1.1.2 Current knowledge about Hemi-Inattention

What is HI?

Hemi-inattention (HI) is a complex, heterogeneous and disabling syndrome which is historically associated with poor functional outcomes (Heilman et al 2000, Robertson and Halligan 1999). HI acutely affects 50% to 80% of patients with right hemisphere stroke dysfunction (RHS) and 13% to 76% with left hemisphere dysfunction (LHS) (Mapstone et al 2003, Buxbaum et al 2004, Beis et al 2004, Kleinman et al 2007). The large variability in reported frequency of occurrence is due to lack of homogeneity in the RHS and LHS population across study designs; including assessment time since stroke, type of measurement tool used to assess HI and operational definition of HI (Bowen et al 1999, Plummer et al 2003). HI is thought to be more enduring after RHS and challenging to rehabilitate than LHS (Kortte and Hillis 2009, Singh-Curry and Husain 2010). This is one of the reasons why this study is focused on RHS rather than LHS, another being that current assessment tools are language-based. This would make interpretation of the results from LHS population difficult, as they would likely be confounded with language difficulties, which commonly accompany left hemisphere stroke (Teasell et al 2014).

Clinical presentation of HI

Clinically, HI is characterised by reduced attention and spatial awareness to detail in the environment (commonly towards the left side of the body).

HI can affect one or more functional domains (Robertson and Halligan 1999, Heilman et al 2000, Parton et al 2004), illustrated in Diagram 1a. These domains include, but are not limited to, sensory-motor, cognitive and mental representation areas. A further distinction is made between HI in near or far "space" with respect to the body, also known as peri-personal and extra-personal space respectively (Demerged et al 1999, Forte and Humphreys 2004, Aimola et al 2012). From the illustration in diagram 1b, it can be deduced that near HI (peri-personal) is likely to adversely impact activities performed within an arm's reach of the body (e.g. reading, bathing) and far space (extra-personal) affects activities such as walking and crossing the road. Consequently, patients with severe HI may fail to eat and dress properly, can be easily disoriented even in familiar locations, and can bump into objects and door frames, which predisposes them to falls and accidental injury.

Pathophysiology and cause of HI

The cause of HI is a matter of intense controversy and debate in the literature. Some experts argue that HI is a consequence of large stroke lesions which tend to be accompanied by diffused disturbances in brain networks that sub-serve consciousness, perception, attention, basic sensory-motor function (Appelros et al 2007, Kortte and Hillis 2009, Jacobs et al 2012, Karnath and Rorden 2012).

Diagram 1(a) – Illustration of potential Hemi-inattention sub-types

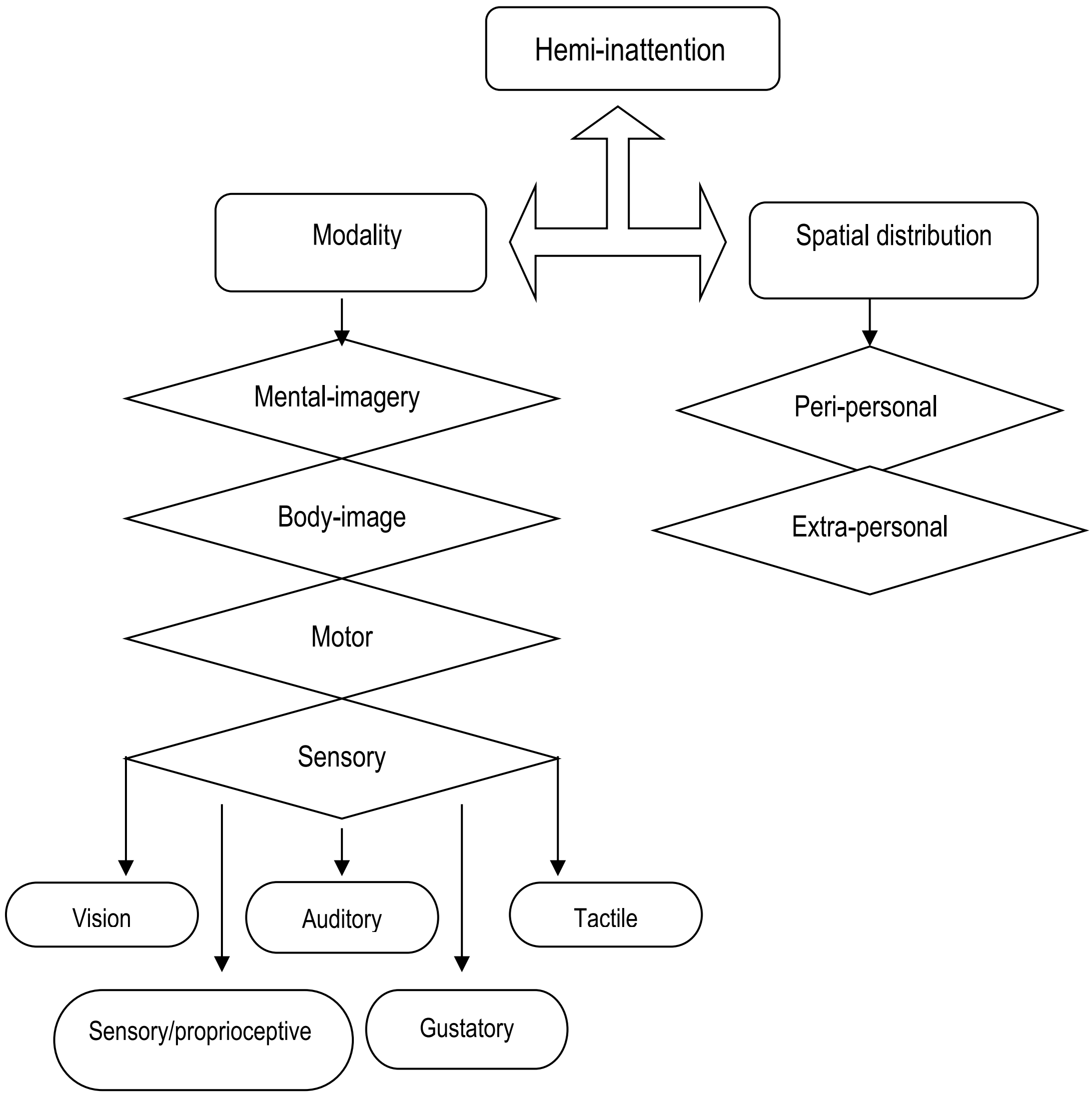
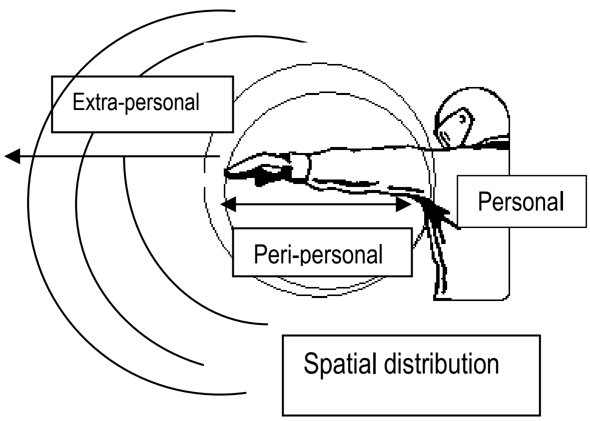


Diagram 1(b)



Others argue that HI is associated with damage to specific brain areas; commonly the inferior temporal-parietal junction (Corbetta and Shulman 2002, hut et al 2005, De Hana et al 2012) but also frontal-parietal network (Husain and Rorden 2003, Holstein et al 2012), occipital-temporal and para-hippocampal cortex (Rossi et al 2011, Harvey and Rossi 2012), sub-cortical lesions of the thalamus and basal ganglia (Karnath et al 2002, Paella et al 2004, Go lay et al 2008). Presumably, this variety of potential sites would give rise to the multi-faceted presentation of HI, its sub-types and recovery patterns.

However, current theories have moved away from the early, purely sensory-motor and motivational explanations (e.g. inability to see, hear, move) but emphasize disorders of attention, spatial cognition, perception and mental representation, and non-spatially lateralised conditions as important contributors to the syndrome (Kortte and Hillis 2009, Vandenberghe et al 2012).

In terms of cortical reorganisation, neural and functional recovery after stroke, prevalent neuro-physiological theories assert that direct disturbances in neuronal activity in the affected hemisphere after stroke also give rise to abnormally high, compensatory and uncontrolled activity in the unaffected hemisphere (Grefkes and Fink 2011, Rehme and Grefkes 2013). This theory is supported by several albeit somewhat controversial findings from relevant stroke rehabilitation reviews (Johansson 2010, Hara 2015), neuroimaging and brain stimulation studies focused on cortical reorganisation and neural plasticity in the early days after stroke (Grefkes and Ward 2013). Although inconclusive, normalisation of brain activity in the opposing hemisphere by means of e.g. Repetitive Transcranial Magnetic Stimulation (TMS) correlated with improved hand function (Takeuchi et al 2005, Tallelli et al 2006) and amelioration of mild

HI conditions (Grefkes and Fink 2011). Additional support for early initation of spontaneous neural repair mechanisms comes from studies which evaluated the impact of pharmaceutical agents on neural and angiogenesis within 4 to 6 weeks post stroke (Hermann and Chopp 2012, Chollett 2013). Collectively, the evidence available at the time of writing would suggest that the quicker the brain activity in both hemispheres is normalised and the faster the pace of restoration to near normal cerebral connectivity patterns, the lesser the overall damage and the faster the recovery rate in associated HI/functional impairments. Such a course of events is plausible; one would expect that the less damage and interruption in affected compex sensory and motor pathways is restored, the greater the motor recovery obtained. However, the quality of recovered movement with time post stroke is currently debateable and has only recently begun to receive specific research attention (Corbett et al 2014). It would appear that neuronal and up to an extent functional recovery are modulated by time since stroke, the speed at which spontaneous recovery mechanisms can be initiated in the brain after stroke and most likely specific rehabilitation inerventions (Hermann and Chopp 2011, Chollett 2013). In turn the efficiency and effectiveness of the brain recovery processes involved is believed to be dependent on pre-morbid health condition, age, overall stroke severity and extent of disturbances in the brain (Johannsen 2010, Langhorne et al 2011, Kwakkel and Kollen 2013). In summary, recovery (neuronal, functional and HI) is dependent on a complex array of multidimensional factors whose interactions give the characteristic individuality of stroke impairment profiles and type of recovery seen in patients including with and without HI condition over time.

Course and progression of HI

HI is found on a continuum of severity ranging from very mild to severe (Robertson and Halligan 1999, Parton et al 2004). Initial severity, type of HI and presentation appear to be all related to both the rate and amount of recovery from HI over time (Stone et al 1992, Mark 2003, Lindell et al 2007, Nijboer et al 2013); such that the individual course of recovery is difficult to predict due to considerable variability across the population (Karnath and Rorden 2003, Singh-Curry and Husain 2010).

Farne et al (2004) studied the course of recovery in the acute phase (first 3 months after stroke) in 33 patients who were specifically selected for rehabilitation from a larger group of patients with right hemisphere stroke (n=166). The patients were assessed three times; baseline (<6 weeks since stroke) followed by one and two weeks after. They reported that only 43% of neglect patients improved spontaneously on motor tests (hand movement and grip force) during the 2 week period. Complete recovery was observed only in 9% of the patients. In regards to extrapersonal and personal neglect, 63% of patients clearly recovered from visible symptoms, although only one of them (13%) reached a subclinical level of severity. Anosognosia did not improve in a smaller sub-group (n=8) of patients who were followed up for longer than 3 months (not clear how long). Based on the data from Farne et al 2004, spontaneous recovery in the acute phase is not self-evident and when present, does not allow for complete remission of neglect symptoms in most patients (supported by personal clinical experience and other clinical studies e.g. Parton et al 2004, Singh-Curry and Husain 2010). Findings from Farne et al (2004) were also supported by those from other studies evaluating changes in overall functional ability in patients with and without neglect, when assessed at baseline and discharge (Gillen et al 2005, Odell et al 2005, Stein et al 2009, Di Monaco et al 2011). However, there are significant methodological weaknesses in past studies which detract from the value and clinical application of their findings (they are critically evaluated in chapter two).

Data from longer term population studies is scarce because follow-up of HI beyond one year has rarely been undertaken (Jehkonen et al 2006). Nijboer et al (2013) undertook a one year follow-up cohort study (n=101) aimed at investigating recovery of visuospatial neglect (VSN) ove time. VSN was measured by the letter cancellation test (LCT) and the line bisection test (LBT). Off the 101 patients recruited, 51 patients showed VSN. All the measures were taken weekly, starting from within 14 days after stroke onset. From week 10 to 20 biweekly measurements were obtained. Follow-up measurements were performed at weeks 26, 38, and finally 52. Trend changes were obtained in between 12 and 14 weeks post-stroke with respect to the neglected side. These showed that recovery pattern of VSN tended to be linear up to week 14 for both right and left VSN but tapered sharply thereafterwards. At week 52, 30 - 40% of the patients were reported to still have VSN. However, identification and assessment of VSN were limited by the single measures used in this study. Current expert recommendation is for a battery of tests such as that comprised in the Behaviour Inattention Test (BIT) which is more likely to detect HI rather than one or two single tests (Lopes et al 2007, RCP Stroke Guidelines 2012, Schenk and Karnath 2012).

With respect to time after stroke, two types of recoveries are identified in the literature; - transient which recovers fairly quickly (in < two weeks post-stroke) and chronic which takes months or years to improve - although it is not possible to reliably distinguish between both types early on after stroke (< 2 weeks post-onset) (Robertson and Halligan 1999, Husain and Rorden 2003, Barrett et al 2006, Lindell et al 2007).

Assessment of HI

Clinical assessment of HI presents various challenges due to its unpredictable recovery, instability over time and frequent existence with other disorders such as sensory dysfunction and denial states with respect to stroke dysfunction and impairment (also known as anosognosia) (Stone et al 1993, Buxbaum et al 2004) and depression (Appelros et al 2007, Kortte and Hillis 2009). Furthermore, clinical assessment tests for HI cannot reliably distinguish between sub-types of HI (illustrated in Diagram 1.1) because the assessment tasks require a mixture of visual, sensory, motor, spatial and mental representation input (Plummer et al 2003, Menon and Korner-Bitensky 2004). Nevertheless current assessment tests are useful in diagnosing the overall HI condition (syndrome) and its severity (Singh-Curry and Husain 2010, Maxton et al 2013) – which is how they were employed in this PhD project.

Interventions for HI

In general, the clinical evidence base for HI intervention is considerably limited. Interventions fall broadly into two categories - conventional (e.g. behavioural, compensatory techniques) and more novel techniques, which are still undergoing development and testing (e.g. prisms, virtual reality, repetitive transcranial magnetic stimulation, pharmacology) (Lunate et al 2006, Kortte and Hillis 2009, Fasotti and Van Kassel 2013). Limited evidence exists for the effectiveness of conventional and novel treatment methods but neither approach is superior than the other in alleviating HI impairments - albeit some treatments work better than others in certain patients (e.g. opt-kinetic treatments with prismatic lenses for visual disturbances, virtual reality for spatial orientation and cueing, neck muscle vibration for reduced sensory attention) supported by findings from reviews by (e.g. Barrett et al 2006, Lincoln and Bowen 2006, Singh-Curry and Husain 2010, Bowen et al 2013). However, the clinical uptake of novel therapies has been very slow partly because they are still underdeveloped for routine clinical use (Maxton et al 2013, Fasotti and Van Kassel 2013) and in part due to lack of knowledge and willingness by clinicians to implement any novel strategy without firm evidence (Barrett et al 2006, Petzold et al 2014).

Potential impact and consequences of HI

Besides poor functional outcomes, HI has been regarded as responsible for prolonged and challenging rehabilitation, increase in dependency levels and risk of longer-term institutional care (Katz et al 1999, Buxbaum et al 2004, Parton et al 2004). Therefore its relationship with functional change is important because poor outcomes are associated with increased disability and dependency levels, reduced quality of life and increased care costs, which contribute to an already burdened health and social care system. The next section provides the context for this study which is focused on whether functional outcomes of HI+ patients are worse than HI- and the relationship of HI status with functional change with time since stroke.

1.1.3 Contextual information

The author of the thesis became interested in the subject whilst practising as an occupational therapist (OT) in a multi-disciplinary stroke rehabilitation team

(MDT) on a stroke unit with research links to the local university. As part of her work, the author assisted with data collection in connection with a research project on the use of an electronic version of the Behavioural Inattention Test (Wilson et al 1987) intended for the assessment of HI severity in RHS patients which was being piloted at the time. Therefore the author was able to follow the progress of RHS patients closely over weeks and sometimes months into their recovery, during which the following observations were made:

Firstly, following right hemisphere stroke, the discharge rate of patients with HI to nursing and residential institutions exceeded that of their counterparts without hemi-inattention by approximately 4:1 (Stein et al 2009). Although numerous factors such as initial stroke severity, social support networks, and patient wishes determine the discharge destination, poor functional ability in HI+ patients appeared to be a major contributor. This was supported by findings from other RHS and generic stroke studies (Paolucci et al 1996 and 2001 and Portelli et al 2005). Furthermore, community stroke rehabilitation provision tends to be patchy and substantially limited - especially in caring institutions (Rudd et al 2001, Wade 2003, Cowman et al 2010, Hickey et al 2012). Taken together, preliminary observations suggested that patients with severe stroke and HI were at increased risk of being deprived of opportunities to improve functionally - even if they were in a position to do so later on. For example, they tended to become more alert and cognisant after stroke unit discharge, as indicated by these poignant remarks from one of the author's patients after more than three months since stroke;

"*I have just realised that I have a stroke*" and "*I woke up to find myself here surrounded by strange faces wondering what has happened to my home*".

Such experiences of delayed stroke awareness are not uncommon in severely impaired patients (Tham et al 2001, Ekstam et al 2006) Therefore it could be argued that patients with HI who are frequently discharged to institutions are not being fairly or equitably treated because their chances of engaging with later rehabilitation are virtually non-existent at this stage.

Secondly, the author of the thesis noticed the apparent reluctance of rehabilitation professionals to assess and sometimes treat RHS patients especially those with significant HI. This reluctance seemed to be partly driven by a pre-determined acceptance that HI+ patients had “poor rehabilitation potential” meaning that the likelihood of achieving a good enough functional outcome necessary for home discharge was considered low compared to patients without HI. A further barrier is that HI+ patients tended to require more hands-on physical assistance for basic activity training involving movement and balance. For example, at least one experienced therapist and two helpers may be required to assist with sitting and balance training of a severely impaired patient on the side of the bed or stand supported during aspects of personal care. This factor added to the difficulties of prioritising certain patients for treatment due to a generalised lack of human resources (including nursing) and skill mix of available staff.

Both of the above situations were potentially damaging because they had the ability to disadvantage HI+ patients who tended to be also severely impaired by stroke. An untoward/unchallenged negative mind-frame was especially detrimental because it potentially underprivileged RHS patients right from the outset of rehabilitation (which in itself, could contribute to poor outcomes as a self-fulfilling prophecy). This thinking and observations were corroborated by reports from other studies indicating under-assessment and treatment for HI (Menon-Nair et al 2006 and 2007, Plummer et al 2006, Lopes et al 2007, Wilkinson et al 2011, Chen et al 2012, Yoo-Im et al 2013). Together these findings and clinical observations suggested that patients with HI were less likely to be assessed or receive adequate intervention - which is guided by thorough HI assessment in the first place (Golisz 1998, Menon and Korner-Bitensky 2004, Singh-Curry and Husain 2010).

Historically, findings from published studies have tended to report disparity in functional ability scores in RHS patients (Katz et al 1999, Cherney et al 2001, Buxbaum et al 2004) but the underlying evidence for this disparity and its relationship with functional outcome is far from clear (please refer to the findings from the literature review chapter two). Theoretically, both ambiguity and uncertainty about the clinical importance of differences associated with HI could result in reduced priority for rehabilitation of severe stroke and HI affected patients. As witnessed by the author of this thesis, the patients often *slipped through the net* when other pressures were also present in the work place e.g. time constraints, limited professional resources (e.g. more than two persons required to assist with early sitting balance and posture training) and shorter duration of in-patient stroke unit care (Langhorne et al 2011, Walker et al 2012 and 13). Furthermore, the paucity of relevant evidence-based reviews in this area had not helped to clarify the role of HI in functional rehabilitation practice.

Taking everything into account including the paucity of research, the reported poor outcomes of HI+ patients with associated adverse rehabilitation and recovery implications and the observations from personal clinical practice, a new study was planned to address relevant questions and bridge respective gaps in the literature.

1.2 Organisation of thesis

There are seven chapters in this thesis. The remaining chapters are briefly described.

Chapter two contains an in-depth critical narrative literature review of 13 studies which compared the functional outcome of RHS patients with and without HI from acute to chronic (up to one year since stroke). Results and findings from the review formed the basis for the research question addressed in the study.

Chapter three presents the methods used to answer the research question and is divided into five sections. Section one presents an overview of the design followed by section two which contains assessment details including a critical evaluation of the measurement tools employed in the design. Section three describes the data collection methods. Section four offers a detailed, statistical data analysis plan. This includes the rationale for the use of multi-level modelling methods (MLM) to evaluate the relationship between HI and functional change. Essential information on MLM is provided, including approaches to data analysis and modelling techniques. Section five summarises the main ethical issues arising from the PhD project and their management by the researcher.

Chapter four presents the initial results. This includes an evaluation of clinical, patient and care process factors associated with functional outcome by group (HI±) and potential implications.

Chapter five offers a detailed description of the multi-level modelling (MLM) undertaken to answer the research question. Given the volume of MLM results obtained and complexity of their interpretation, they are briefly commented on in text. This maybe unconventional but it is intended to assist the reader who is less familiar with statistics understand and follow the MLM results and implications. Key findings are summarised at the end of the chapter.

Chapter six offers an in-depth interpretation of the findings in relation to the research question and context of stroke rehabilitation. This is followed by a critical evaluation of the study. The chapter concludes by highlighting important implications as a result of the findings and makes suggestions for future research and practice in the field.

Chapter seven draws the overall project together, highlighting the unique contributions to knowledge and clinical practice.

Chapter 2 – Literature Review

Chapter Two

Literature Review

2.0. Introduction

The adverse impact of hemi-inattention (HI) on the recovery of function after stroke, its perplexing behavioural presentation, and assessment and treatment challenges were highlighted in the previous chapter.

Chapter two offers a narrative, critical review of past studies in the field, which evaluated the relationship between HI status and functional ability after stroke. The length of follow-up time after stroke was not fixed so as not to narrow the choice of studies available. The layout is as follows;

The literature search is described first followed by the critical review of 13 studies, sub-grouped by the number of follow-up observations (one or more) in order to facilitate comparison of the results from similarly designed studies. A summary of the findings is followed by the research question, aims and objectives of the PhD study which conclude the chapter.

2.1. Type of review

The section contains the rationale behind the choice of a narrative versus systematic type of review both of which are found in the stroke literature.

Systematic reviews tend to be synonymous with highly advocated evidence-based practice (Quinn et al 2009, Langhorne et al 2010, Hammersley 2001). They are appropriate for answering specific research questions e.g. on the effectiveness of specific HI interventions. They are valued for their rigorous application of scientific strategies in the synthesis, assembly and critical appraisal of relevant studies (Hammersley 2001, Higgins and Green 2008). That being said, systematic reviews have been criticized for their preferential regard to randomised controlled trials (RCT) over other forms of research design and their rigid selection criteria (Whitlock et al 2008, Murphy et al 2009).

In comparison, narrative reviews are broader in scope and “lay out the most recent and best knowledge of various aspects of a problem” (Dijkers, 2009:427). They are considered more appropriate when a diversity of research methods are used in the studies (rather than focusing only on randomised controlled trials), where studies have used different outcome measures and/or non-equivalent samples (Dijkers 2009) and when studies are of relatively poor methodological quality (Pai et al 2003). Narrative reviews have been criticized for the lack of rigorous methodology and subjectivity of judgement by the researcher compared to systematic reviews. This is thought to increase the risk of bias in the reports (Bowling and Ebrahim 2005).

Since previous reviews (Jehkonen et al 2006) had indicated considerable heterogeneity in design and methods of past studies in the field, the stringent criteria imposed by a systematic review was likely to result in exclusion of relevant studies on the subject. Furthermore, the intention was not to evaluate specific interventions as customary in systematic reviews (Greenhalgh 1997, Garg et al 2008). Consequently a narrative critical review was undertaken which incorporated important features of systematic reviews that are designed to minimise researcher bias were followed (e.g. a methodological checklist to assist with the review of selected studies was drawn up and included). To further improve the quality of narrative reviews, Dijker (2009) recommended the inclusion of a detailed search strategy together with a referenced basis for judgements made. This recommendation was also followed.

2.2. Literature search

2.2.1. Literature search strategy

To inform the design and implementation of the study, an in-depth literature search was conducted for studies published from 1995 to August 2013 (later updated to August 2015) on the databases MEDLINE, AMED, CINAHL, PsycINFO and COCHRANE systematic reviews.

Data-base subject-headings were not sufficiently specific, therefore key words were searched under known headings for the umbrella term ‘neglect’. This increased specificity and the probability of capturing potentially relevant studies. For each database, three separate searches were conducted as presented in Table 2.1. The results were then combined in a fourth search to yield the number of citations as follows; AMED (70), CINAHL (86), MEDLINE (102), PsycINFO (57). Once duplicated publications were removed the number was reduced to a total of 185. In addition, four relevant systematic reviews were found (Bowen et al 1999, Bowen and Lincoln 2006, Jehkonen et al 2006, Bowen et al 2013).

Table 2.1 Literature search in databases; AMED, CINAHL, MEDLINE and PsycINFO

Search	Terms used
1	‘Right hemisphere dysfunction’ & ‘stroke’ OR ‘CVA’ OR ‘Cerebro-Vascular Accident’ OR ‘Brain Attack’
2	‘spatial’ OR ‘visual’ OR ‘unilateral’ OR ‘personal’ OR ‘extrapersonal’ OR ‘motor’ OR ‘sensory’ OR ‘hemi’ OR ‘representational’ AND ‘neglect’ OR ‘inattention’ OR hemi-inattention
3	‘Activities of daily living (ADL)’ OR ‘function’ OR ‘functional outcome’ OR ‘functional ability’ OR ‘functional recovery’
4	Combined terms in search 1, 2 & 3

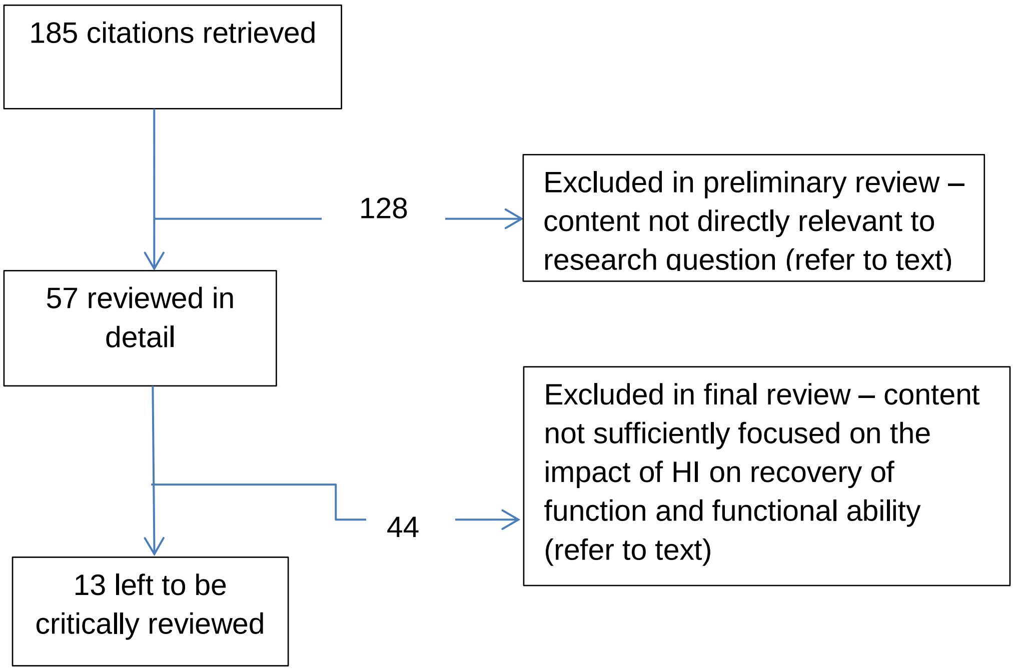
As evident from Table 2.1/search 1, the term “right hemisphere dysfunction” was used as a filter to increase the likelihood of homogeneous samples in the retrieved studies since the focus is on HI in right hemisphere stroke (for reasons given in section 1.1.2. in chapter one). This decision is supported by findings from a rare review of 26 studies from 1996-2005 undertaken by Jehkonen et al (2006) in the area of Neglect and functional outcomes. The authors reported that the results from mixed patient samples (right and left stroke) were more inconsistent than those from right hemisphere damage only. Therefore homogeneity of the sample is very important in this type of research in order to minimise the potential confounding effects of left hemisphere damage. Statistical sources also emphasise the importance of homogenous sampling in associative studies to enhance generalisation and application of findings in the researched population (Field 2009, Moons et al 2009, Royston et al 2009).

2.3. Results from the literature search

The search results are presented in the flow diagram in Figure 2.1. The abstracts of 185 publications were preliminarily reviewed by the author. Those studies which did not explicitly include data on functional change in ability were excluded (e.g. Nijboer et al 2013). In addition, studies focused on dyspraxia (e.g. Kwon et al 2011) or visual field cuts (e.g. Suter 2007) and neuro-anatomically correlates of ‘neglect’ (e.g. Gottlieb et al 1998, Karnath et al 2001 and 2002, Doricchi et al 2005) were also excluded.

After the separation process, 57 publications were retained for careful review of the content, during which further selection criteria were applied (next section).

Diagram 2.1 Flow diagram of literature search



2.3.1. Selection criteria

Retained for the final critical review were 12 studies which evaluated functional ability (with or without specific HI intervention, including Activities of Daily Living (ADL), in adult patient cohorts (>18 years old) and RHS patient samples. They had to have compared patient groups with or without (HI±) and were written or translated into the English language. The only exception to the criteria was a study by Nijboer et al (2013) in which an advanced statistical method of data analysis (Random Coefficient Analysis) had been used to analyse the data. Although they included both RHS and LHS patients in the sample, it was important to compare the results with those from the other 12 studies, who had used more traditional statistical methods (e.g. Analysis of Variance and co-variance) to analyse their data. <u>In total 13 studies were critically reviewed.</u>

Excluded from the final critical review were studies involving children or young adults (≤18 years)(n=19) who recruited heterogeneous samples i.e. mixture of

RHS and LHS and/or in which data analysis was not grouped by HI+/HI- (e.g. Pedersen et al 1997, Paolucci et al 2000) or clearly lacked a group comparative design (e.g. Kwakkel et al 2006 and Vossel et al 2013) or provided limited data on functional group differences (e.g. Viken et al (2012) or was not coherently translated into English (e.g. Karakaya and Uyanik (2003) – Turkish publication). As a result, a total of 44 publications were excluded but some of their evidence was later used in discussing the selected 13 publications for final critical review.

The studies are reviewed under two broad section headings aimed at comparing similar designs as much as possible; section one includes serial designs with one follow-up observation (generally discharge from in-patient care facility) and section two includes studies with more than one follow-up (including community setting). This sub-division clearly showed the information that could be obtained from different designs and was later used to inform the PhD project design.

Review of the 13 individual studies was guided by a checklist (described next) which ensured parity and thoroughness of the review process. Where relevant, findings are also discussed in relation to later studies and reviews, to aid synthesis of evidence and identification of common limitations in the field of research.

2.3.2. Description of ***review checklist***

With respect to Table 2.2, the questions were compiled from guidance tools developed to assess the quality of cohort reviews (Critical Appraisal Skills Programme – CASP-UK 2010).

Questions 1 to 9 refer to the internal and external validity of the research study.

Table 2.2 Critical review checklist

Internal & external validity	
1.	Is there definition of functional outcome and HI/Neglect?
2.	Is there a description of the design including setting/s, frequency of observations & time to first observation?
3.	Are the selection criteria clearly described?
4.	Has the stroke been confirmed (e.g. CT scan, MRI, neurological examination)
5.	Is the sample representative of the researched population?
6.	How has HI been identified and measured (standardised test battery, single tests)
7.	Where other factors besides HI measured? If so how (measurement tool?)
8.	How was functional ability/outcome measured - is tool standardised?
9.	What was the attrition rate - Loss to follow-up & death?
Statistical validity	
10.	What was the sample size analysed (percentage of HI+/- patients known)?
11.	Where important confounding factors adjusted for (age, neurological severity, time)
12.	Type of statistical analysis undertaken?
13.	Do the results make sense? (Are they valid & useful?)
14.	Strength & limitations of study?

Abbreviations – CT=computer tomography, MRI=magnetic resonance imaging

The contents in Table 2.2 were adapted from the Critical Appraisal Skills Programme – CASP-UK 2010)

Questions 10 to 13 refer to statistical validity e.g. failure to take into account the impact of established confounders in the design (e.g. initial stroke severity) which would complicate interpretation of results from regression models. Question 14 highlights the strength and limitations of each study according to the reviewer's opinion. It is intended to be objective and informative so that the lessons learned could be used to enhance future designs.

A natural progression from question 14 of the checklist was to grade the methodological quality of individual studies. A simple four grade scale known as Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Guyatt et al 2008) was used, which is described below.

*Description of the **GRADE** scale*

Grade A (high), assigned to well-performed RCTs or observational studies with consistent results and/or strong effects i.e. valid and reliable results.

Grade B (moderate), assigned to trials with serious flaws in the design i.e. the estimated effect is likely to be considerably different than the true effect.

Grade C (low), assigned to studies with serious limitations in which the true effect is likely to be very different than the estimated effect e.g. through failure to include relevant confounding factors in the design.

Grade D is very low and assigned to case studies or expert opinion in which any estimated effect is very uncertain and highly unlikely to reflect the true effect.

2.4. Critical review of the studies

Serial design with <u>one</u> follow-up observation point

There are 8 international studies in this section characterised by data collection at baseline and one other follow-up assessment (both variable in time since stroke) of the same patients i.e. one sample.

Findings from individual studies are presented chronologically in Table 2.3, followed by a detailed discussion of each paper in turn. For consistency, the term HI is synonymously used with ‘Neglect’ terminology found in different studies. The assigned quality grade is shown in column 1 of Table 2.3. A key abbreviation code is included below to assist the reader switch efficiently between tables/text.

List of abbreviations in Tables 2.3 and 2.4

Assessment Tools		Other abbreviations	
BBS	Berg Balance Scale	ADL	Activities of daily living
BI	Barthel Index	ANOVA	Analysis of variance
BIT	Behaviour Inattention Test	CT	Cat Scan
CMSA	Chedoke-McMaster Impairment Inventory	DV	Dependent variable
CNS	Canadian Neurological scale	f/up	follow-up
FIM	Functional Instrumental Measure	IADL	Instrumental activities of daily living
GDS	General Depression Scale	IV	Independent variable
LCT	Letter Cancellation Test	LHS	Left hemisphere stroke
LOTCA	Lowenstein Occupational therapy cognitive assessment	LOS	Length of in-patient stay
MEAMS	Middlesex Elderly Assessment of Mental State	OT	Occupational therapy
MI	Mobility Index	PT	Physiotherapy
MMSE	Folstein Mini-mental test	RCT	Randomised control trial
PASS	Postural Assessment Scale For Stroke	RHS	Right hemisphere stroke
RIC-FAS	Rehabilitation institute of Chicago functional assessment scale for comprehension and written expression	resp.	Respectively
RKE	Rabideau kitchen evaluation	SD	Standard deviation
RMI	Rivermead Mobility Index	USN	Unilateral spatial neglect
SART	Sustained & divided auditory attention Test	VN	visual neglect
TFT	Thumb finding test	VSN	Visual spatial neglect

Table 2.3 Critical evaluation of serial studies with one follow-up observation point

Source	Aims & Design	Assessment/Tools	Data Analysis	Results/Findings	Study Strengths	Study limitation
Kalra et al 1997 UK GRADE C	<u>*Aim*</u> RCT to determine whether poor outcome in patients with visual neglect (VN) was due to greater stroke severity or non-specialist management <u>*Setting*</u> - Acute, Stroke unit <u>*Sample*</u> (47 HI+, 99 HI-) <u>*Mean age*</u> 77 (SD=8) <u>*Time*</u> *to 1st obs.* 1-2 weeks post stroke onset <u>*Follow-up*</u> at discharge *Before & after controlled* <u>*intervention*</u> (conventional vs. spatio-motor cueing & early emphasis on restoration of function)	VN assessed by Line bisection supplemented by functional observation at admission <u>1a Outcome</u> BI (scale 0 to 20) & Thumb finding test <u>2nd Outcome</u> Mortality Discharge-destination LOS Therapy intensity	Median statistic Chi squared test, Mann Whitney U, t-test Multiple linear regression (n=146), DV=BI at admission <u>Modelled IVs</u> Age, gender, muscle power, balance, proprioception, cognition, pre-stroke ADL status, HI level	Patients with or without visual neglect (VN) had similar destination, slightly lower median BI scores at admission & discharge (4 vs 5 & 16 vs 14) resp. Greater LOS/days (64 HI+ vs 36 HI) & therapy input/hrs. PT (30 HI+ vs. 19 HI-) & OT (18 HI+ vs. 10 HI-) HI negatively associated with admission BI [β= -0.17, p=0.011, R^2=0.16] All other IV's not associated with DV	Confirmed stroke Clear selection criteria Validated ADL assessment Statistically modelled variety of factors associated with ADL besides HI Reported attrition due to death (n=3 extended stroke, 1pulmonary embolus, 1 myocardial infarction) Intention to treat analysis Corrected for small sample size	Wrongly labelled as RCT Recruited only patients with Partial Anterior Circulation Infarct of moderate stroke severity with potential for rehabilitation Line bisection does not distinguish between VN & other sub-types BI version excluded psycho-social dysfunction & cognitive measure Different patient LOS so exposure to therapy uncontrolled Did not model outcome data at discharge No community f/up or sensitivity analysis

Source	Aims & Design	Assessment/Tools	Data Analysis	Results/Findings	Study Strengths	Study Limitations
Ring et al 1997 Israel GRADE C	*Aim* To measure function & determine gain between admission & discharge *Design* - Prospective comparative *Setting* - Acute General Rehabilitation facility *Sample* (28 HI+, 56 HI-) *Mean age* 60.8 *Time to 1st observation* was 29 days (± 17) *Follow-up* at discharge	BIT at admission to detect 'neglect' 1[a] Outcome FIM 2nd Outcomes LOTCA Type and site of lesion LOS Discharge destination	t-test Chi square test Repeated measures ANOVA Multiple linear regression with FIM gain (DV) Modelled IV's LOS, admission FIM, age, gender, risk factors (not clear which)	FIM admission score, LOS & age predicted functional gain [β= -0.034, 0.13, 0.49, p=0.011, 0.03, 0.05] respectively 24/28 patients with HI discharged home after considerably longer period of rehab & LOS/days (137 HI+ vs. 102 HI- days) Total FIM gain HI+ 33 vs. HI- 21 units	Confirmed stroke by CT scan Validated functional ability scale & test battery for detection of HI Statistically adjusted for age & gender Clear distinction between RHS & LHS, lesion site and type Reported attrition due to death (n=1)	Selection criteria not clear what behavioural, severe comorbidity & cardio-pulmonary conditions were excluded. Variable obs. time-point No community f/up Not adjusted for differences in stroke severity or time since stroke No sensitivity analysis No data on cognitive function from LOTCA published

Source	Aims & Design	Assessment/Tools	Data Analysis	Results/Findings	Study Strengths	Study Limitations
Paolucci et al 2001 Italy GRADE **C**	*Aim* Assess influence of unilateral spatial neglect (USN) on rehabilitation outcome Matched by Age (69 ± 10) & stroke onset admission time (38 ± 17 days) *Setting* – Acute, In-patient rehabilitation hospital *Sample* - (89HI+, 89HI-) *Time to 1st observation (38± 17 days)* *Follow-up* at discharge *Intervention;* special training in visual scanning, reading & copying script, line drawings, dot matrix & description of scene 5hrs/week for 8 weeks	USN detection - Letter cancellation, line bisection, sentence reading & Wundt-Jastrow area illusion test at admission 1a Outcome BI (0 to 100) 2nd outcome LOS Rate of gain & amount of progress Other RMI CNS Hamilton Depression Rating scale	8 Multiple linear regression (forward stepwise) 6 logistic regressions 5 DV's, CNS, BI, RMI, LOS, Rate of gain & amount of progress Modelled IV's Admission CNS, gender, type of lesion, hypertension, diabetes, heart disease, unilateral spatial neglect, depression, epileptic seizures post-stroke, family support, education level, discharge destination	USN was a negative prognostic factor. USN patient group had low ADL & mobility outcomes at discharge (~ 50% less mean scores). HI+ had longer LOS/days (117± 61 vs. 81±38), ↑rate of discharge to institution (18% vs. 5%), ↑ discharge continence rates (21% vs. 5%). USN, stroke severity, heart disease & type of lesion appear to be important explanatory variables in the acute phase (~3 months)	Confirmed stroke (CT scan) Validated tools BI supplemented by data from RMI Screened for depression & neurological severity Reported attrition, (9% HI-, 6.7% HI+) Modelled broader range of factors e.g. psych-social factors & comorbidity Adjusted for stroke severity in some models	Probable patient overlap with earlier sample (Paolucci et al 1996) Probably excluded severe stroke included (mean CNS =7) Highly variable T0 observations Complicated paper to follow due to large number of factors & combinations modelled Did not measure cognition which is strongly associated with USN (neglect) Not adjusted for or modelled age which is associated with USN High variability in LOS & exposure to in-patient care likely source of bias No information on handling of missing data

Source	Aims & Design	Assessment /Tools	Data Analysis	Results/Findings	Study Strengths	Study Limitations
Buxbaum et al 2004 Italy & USA GRADE **D**	*Aim - Assess* occurrence of subtypes & related deficits in RHS. *Design* - cross-section *Setting* - Acute & community *Sample* - 623 RHS recruited from 4 rehab hospitals in Philadelphia & 2 in Italy. 268 met selection criteria 166 consented; 86 had acute & 80 chronic lesions, (88 HI+, 78HI-) *Mean age* -Acute 66, range (37 to 89)Chronic 67, range (33 to 88) *Time to 1st & only observation* - Acute (5-41) & chronic (94-1272) days.	**Personal & Peri-personal** Bells test & 4 Behavioural Inattention (BIT) sub-tests (letter cancellation, picture scan, menu reading & line bisection) **Motor & perceptual** neglect measured by response latencies in two stimulus & response tasks **Motor & Sensory exam** visual fields & extinction by means of confrontation method. **Sustained & divided auditory attention Test** (SART) **Anosognosia** 5 questions adapted from Cutting's questionnaire 1a Outcome FIM Family Burden Scale	Chi square test Mann Whitney U test Correlation tests Repeated measures ANOVA Regression analyses	Neglect severity significantly explained FIM scores & carer burden but not lesion size. Similar rate of gain in HI± but lower FIM scores in HI+ (estimates not reported in paper) Acute patient lesions were not restricted to cortical areas. Variation in associated deficits but higher frequencies in HI+ Variation in occurrence of HI sub-types	Attempted to document frequency of various HI subtypes and related deficits Included burden of care assessment Acknowledged significant limitations in sensitivity and specificity of tests used to identify neglect sub-types & anosognosia Also acknowledged lack of statistical adjustment for multiple tests	Significant heterogeneity in sample & variation in time to 1st observation complicate interpretation of results. Recruited patients deemed to benefit from rehabilitation i.e. Excluded severe attention and cognitive deficits, previous stroke or neurological disorder & dementia Combined analysis of patients from different culture and health care systems – can be strength but also weakness. Inter-rater reliability not performed FIM mean scores not directly reported

Source	Aims & Design	Assessment/Tools	Data Analysis	Results/Findings	Study Strengths	Study Limitations
Gillen et al 2005 USA GRADE **D**	*Aim* - Examine the relationship between left unilateral spatial neglect (USN) and rehabilitation outcomes in RHS patients *Design* - Retrospective *Setting* - Acute in-patient rehabilitation hospital *Sample* -(50HI+ 125HI-) *Mean age 72 (SD=11.0)* *Time to 1st observation* was 15 ± 10 days *Follow-up* observation at discharge	'USN' assessed by Letter cancellation test (LCT) at admission 1[a] Outcome FIM Other Cognistat at admission Geriatric Depression Scale (GDS) at admission LOS	Univariate correlation Multivariate regression analyses (n=98) FIM discharge scores (DV) regressed on FIM admission & USN	Longer mean LOS in HI+ 31 vs 25 in HI-. HI+ progressed at slower rate. Mean admission FIM score 50 (SD=16) vs 69 in HI- (SD=16) Greater cognitive impairment in HI+ ($p<0.001$), higher GDS scores & depression levels ($p<0.01$) 'USN' predicted social-cognitive domain (β= -0.29, $p< 0.001$.	Included depression and cognitive function. Used validated measures Modelled rate of progress (change in FIM score/LOS)	106/281eligible patients excluded due to poor visual acuity. Perceptual deficits & difficulty completing LCT at 1st observation Depression assessed probably too early when patients are likely to be depressed due to stroke event No FIM or cognitive discharge score reported .

Source	Aims & Design	Assessment/Tools	Data Analysis	Results/Findings	Study Strengths	Study Limitations
Odell et al 2005 USA GRADE **D**	*Aim – To* document selected functional outcomes at the termination of in-patient treatment *Design* - Retrospective *Setting* - Acute in-patient rehabilitation hospital *Sample* - (60HI+ 41HI-) *Mean age* 70 years *Range* (40 to 99) *Time to 1st observation not known* *Follow-up* observation at discharge	No formal assessment of HI (relied on mention of condition in medical records) 1a Outcome FIM scores at admission & discharge 2nd Outcome Amount & efficiency of gain, LOS Discharge placement	Mann Whitney-U test Regression analysis Modelled IV's 12 predictor variables made up of initial motor score, cognitive items plus age, gender, previous neurological episodes, no. of comorbidities, lesion site & presence/absence of HI	Admission, discharge FIM median HI+ (57 & 88), HI- (66 & 104); similar gains in motor ~ 24 units, cognitive domains HI+ (3.5), HI- (2). 1 unit gain in FIM cognitive scores by in HI± groups When modelled, functional outcome was predicted by age, memory, problem solving & motor function Mean LOS, HI± 29 vs. 22 (3 to 75) days; >75% home discharge Therapy sessions HI± 61 vs. 27 (range 1 to 194)	Transformed data by means of Rasch method to increase accuracy of estimates Adjusted for variation in age Recorded number of comorbidities & therapy sessions. Categorised descriptive statistics by age range [40 to 92]; younger age group were less impaired & made highest gains overall.	Highly selective criteria i.e. included only patients referred to speech therapy (reduces generalisation of findings) Stroke severity not known No formal assessment of HI Variable follow-up observation point Limitations of retrospective studies e.g. reliability & accuracy of data cannot be checked, consistency of assessment methods & data collection cannot be guaranteed. Missing data not reported

Source	Aims & Design	Assessment/Tools	Data Analysis	Results/Findings	Study Strengths	Study Limitations
Di Monaco et al 2011 Italy GRADE **C**	*Aim* - To investigate the relationship between severity of unilateral spatial neglect (USN) & functional recovery in ADL after a RHS *Design* - Prospective *Setting* - Acute in-patient, physical medicine & rehabilitation hospital *Sample* - (54HI+53HI-) *Mean age* 70 (range 63 to 80) *Time to 1st observation was 23 days post-stroke onset* *Follow-up* observation 80 days post-stroke onset	Detection of USN - BIT at admission only & Diller's test (cancellation task) 1a Outcome Admission & discharge FIM scores Other BI prior stroke by anamnesis Mini-Mental (MMSE) LOS	Data analysis on 107/131 Bivariate correlation FIM x BIT scores Mann Whitney U for group differences Chi square test 3 multiple regressions 3 DV's = discharge FIM, FIM efficiency & effectiveness Modelled IV's Age, MMSE score, time to 1st observation, gender, education, BI , FIM admission & discharge	Admission, discharge FIM median HI+ (45 & 91), HI- (55 & 110) but > 30 units of variation within each group at all times MMSE median group score (HI+ 24, HI- 27). FIM admission best predicted FIM discharge score. Model explained 49% of variance in DV; of these 'USN' explained 5%; FIM 44%. High variability in & LOS (37 to 72 days)	Reported missing data (n=5) Statistically adjusted for age, gender, education level, time to 1st observation &FIM admission Transformed FIM scores to ~ normal distribution Recognised limitations of the study i.e. assessing limited no. factors associated with HI & function & limitations of BIT in distinguishing between sensory motor HI, visual-spatial & motor Modelled education level	Excluded 19 with severe stroke No intention to treat analysis – possible bias towards milder stroke severity (MMSE scores at admission indicate mild cognitive impairment) FIM cognitive score not provided to compare with MMSE No adjustment for stroke severity or carer status Different patient exposure to in-patient care likely source of bias

Source	Aims & Design	Assessment/Tools	Data Analysis	Results/Findings	Study Strengths	Study Limitations
Timbeck et al 2013 Canada GRADE **D**	_Aim_ - Evaluate effect of visuo-spatial neglect (VSN) on functional outcome & discharge destination in RHS _Design_ - Prospective _Setting_ - Stroke rehabilitation programme _Sample_ - (6HI+10HI-) _Mean age_ 76 (SD=10) _Time to 1st observation was 7 days from admission to rehabilitation_ _Follow-up_ observation prior to discharge	VSN detected by BIT 1ª Outcome FIM Other MMSE Berg balance scale (BBS) CMSA LOS	MANOVA to compare between VSN± patients DV – age, time to 1st observation, LOS. MMSE, admission-discharge FIM, BBS & CMSA Independent t-tests for univariate analyses & Fisher's exact for categorical variables	VSN+ (n=6) tended towards supported living FIM admission-discharge score; HI+ 60 & 73, HI- 86 & 102 units High SD in both groups at all FIM observations ~ 20 admission, 28 discharge LOS average VSN+ 48, VSN- 38 days Differences in BBS within groups (SD=16), between groups; HI+ scored 12 & 22 vs. 28 & 41 BBS units in HI- at admission & discharge resp.	Included balance measure Supplemented motor activity on the FIM scale with another impairment measure Evaluated multivariate effect by Pillai's trace (ensure robustness against non-normal distributions & heterogeneity of variance particularly with small samples & groups) Acknowledged significant study limitations	Very small sample unlikely to be fully representative of RHS has implications for study power & validity of results Tight selection criteria excluded patients with chronic co-morbidity (not clear what), English as 2nd language & cognitive impairment – has implication for generalisation of results Not accounted for changes due to spontaneous recovery effects occurring in average 28 days (SD 19.23) delay in starting rehabilitation programme. This has implications for findings & conclusions based on results. No adjustment for multiple testing especially on a small sample

Study 1

Title - The Influence of visual neglect on stroke rehabilitation **(Kalra et al 1997)**

Kalra et al (1997) conducted one of the first intervention studies in the UK. The authors prospectively evaluated the effects of visual neglect on functional outcome at discharge in a consecutive stroke patient sample (n=150), with reported comparable pathology and motor severity treated in a stroke unit. A randomized study was subsequently undertaken in 50 of the patients with visual neglect (VN) to evaluate the effectiveness of spatial cueing during motor activity on functional outcome and use of therapy resources.

The authors reported similar rates and amount of progress in the overall functional ability in both patient groups (HI±) as measured by the Barthel Index (BI); discharge (10 BI units) but the HI+ patient group had longer duration of in-patient rehabilitation (LOS) and more therapy than HI-. Discharge destination rates were similar, 33% of both HI± groups were discharged to institutional care either residential or nursing home. These results suggest that longer, intensive and targeted training in spatial cueing may improve the functional outcome of HI+ patients in line with that of HI-, and possibly increases the chances of a home discharge. However, the findings apply only to patients with Partial Anterior Circulation Infarct of moderate stroke severity (recruited in view of their perceived potential for rehabilitation). This limits generalisation to a wider RHS patient population.

An important point concerns the interpretation of results obtained from standardised pen and paper tasks commonly used to assess HI (referred to as “visual neglect” in Kalra et al 1997). Results obtained by assessment methods which involve writing such as cancelling out targets are potentially confounded by spatial, motor and perceptual neglect sub-types since, all three skills are required for the writing activity itself i.e. performance is not just a question of vision and VN as inferred by Kalra et al (1997) in their study which is somewhat misleading. Moreover the writing hand must cross the mid-line with respect to the body's spatial frame of reference, which has additional spatial-motor implications in terms of processing speed and direction of movement trajectory. This was clearly shown by findings from McIntosh et al (2010) who found that the trajectory of the hand was unbalanced by visual disturbances attributed to HI - findings which supported those by Parton et al (2006) and Russel et al (2010). Concerns about the misleading interpretations of results from pen and paper assessment methods for HI were made by other reviewers (Plummer et al 2003, Bailey et al 2004, Menon & Korner-Bitensky 2004, Singh-Curry and Husain 2010), who similarly argued that cancellation (writing) tasks cannot reliably distinguish between visual, motor and spatial HI in clinical settings. To increase accuracy and interpretation of the results, significant limitations of assessment methods for HI should be acknowledged.

Estimates from regression models

Statistical modelling results from Kalra et al (1997) showed that HI was responsible for 16% of the variance in the dependent variable (admission BI) when it was regressed with age, gender, muscle power, balance, proprioception, cognition and ADL status (prior to stroke) in the same model. This estimate suggests that **HI** is probably related to early functional ability following stroke. However, the potential confounding effect of individual stroke severity was not accounted for and the correlation of HI with cognitive ability is not known. Statistical sources advise that high inter-correlations of more than 0.8 known as **multicollinearity** are problematic as they distort the analysis and the results (Field 2009, Walker and Almond 2010). It is not clear how cognitive ability was assessed but based on the results and data available, informed judgements about the reliability of HI estimates cannot be made.

Although **muscle strength** is a key component of balance which is necessary for the successful performance of ADL tasks (as in sitting and standing activity), it was not significantly related to admission BI scores in Kalra et al (1997). This result is supported by findings from predictive studies which indicated that overall balance contributed more to ADL outcome than graded muscle strength in the leg (Kollen et al 2005, Kwakkel et al 2006). A recent subject review also found that balance training improved functional performance (Lubetzky-vilnai and Karin 2010). Together these findings suggest that balance skills are of specific relevance to the relationship between HI and functional outcome, since they may be functional determinants of ADL performance.

Age was not related to outcome in the analysis undertaken by Kalra et al (1997). However, the result is difficult to interpret as it may be confounded by the highly specific patient sample (with good rehabilitative potential characterised by insignificant co-morbidity and moderate **stroke severity**) reported in the study. The impact of *age* reached predictive importance when co-morbid factors such as heart disease and diabetes were included in other predictive models (Black – Schaffer and Winston 2004, Fischer et al 2006). In addition, Gottesman et al (2008) found that advancing age in patients with acute RHS significantly increased the odds of “neglect” and its severity, independent of initial stroke severity. These results suggest an interaction between age and

HI which may be of considerable importance given supporting evidence for increase in stroke risk factors and age related co-morbidity - an issue not shown to be predictive by Kalra et al (1997). Overall, findings from other stroke studies (e.g. by Sacco et al 2008, Sandercock et al 2012) tended to be inconsistent. However, it is possible that the effect of age varies on an individual basis depending on patient's characteristics and heath condition at the time. This possibility will be borne in mind in subsequent studies in this review.

Stroke severity was not modelled in Kalra et al (1997) probably due to the selectivity of the sample which consisted of patients with Partial Anterior Circulation Infarct (PACI) of moderate severity. However, stroke severity is an established confounder and predictor of functional outcomes including mortality in the first month after stroke (Smith et al 2011). Saver and Altman (2012) reported that 75% of the variance in the Modified Rankin Disability Scale (DV) was explained by stroke severity at three months post-onset. Based on the evidence, both age and stroke severity, either together or independently exert important influences on functional outcome, probably quite irrespective of HI status – which should be accounted for statistically in associative models.

In support of results from Kalra et al (1997), **gender** was not associated with discharge (Functional Instrumental Measure) FIM scores in studies by Reid et al (2008) and Ones et al (2009). However, the importance of gender has been disputed by Rundek (2007) and Gargano et al (2008). It is possible that gender exerts important influences under specific circumstances e.g. when caring for a stroke survivor in the community. This possibility is borne in mind but at this point in the review, there is insufficient information to make a decision on the relevance of gender to functional ability and HI status.

In light of the discussion and apparent weaknesses in methodology, Kalra et al (1997) was assigned a C on the GRADE scale.

Study 2

Title - Functional measures of first-stroke rehabilitation inpatients: Usefulness of the functional independence measure (FIM) total score with a clinical rationale **(Ring et al 1997)**

In a prospective study undertaken in Israel, Ring et al (1997) investigated the usefulness of the FIM total score in measuring functional ability in a sample of RHS patients with first stroke (n=151); 84 patients were subsequently divided into two groups (HI±), their FIM scores were compared at admission and discharge including rate of gain from a neurological rehabilitation ward. Their lesion site, LOS and discharge destination outcome were also recorded.

Ring et al (1997) reported that the total FIM gain in the HI+ group exceeded that in HI- by 12 units but it was over a relatively longer period of in-patient rehabilitation (137 versus 102 days); yet the mean discharge FIM score was 17 units lower in HI+ group indicating higher residual dysfunction. These results do not corroborate those from Kalra et al (1997), who found no difference two months after stroke onset, using the short BI scale (0 to 20 units) (Mahoney and Barthel 1965). The discrepancy in scores may reflect geographical and contextual differences e.g. patients in Israel may expect to stay longer in hospital and return to the community to be looked after by a close knit family when compared to the UK. Besides there is always a possibility that the quality, quantity and content of therapeutic care provided in rehabilitation hospitals in Israel differs from care in the UK in a stroke specific unit as defined by (Intercollegiate Stroke Working Party - ISWP 2012).

Direct comparison between Ring et al (1997) and Kalra et al (1997) is limited by the use of different assessment tools (FIM vs. BI and BIT vs. line-bisection). In comparison to the BI scale, the FIM has a finely grained interval (18 to 126) and grade (0 to 7) scale, which is likely to be more sensitive and precise in detecting small changes in function (although more time consuming and complicated to administer). Coverage of ADL tasks as defined in the ICF (World Health Organisation - WHO 2001) is broader in the FIM, which includes social interaction and cognitive function not covered in the original BI (Mahoney 1965) used in Kalra et al (1997) albeit assessment of cognitive components is included in a modified BI version by Prosiegel et al (1996).

Comparison was also limited between samples from both studies e.g. mean age differed by 17 years and time to 1st observation differed by 15 days. Both factors would be expected to impact on results. Furthermore, Ring et al (1997) used a standardised test battery (BIT) to assess HI which represents an improvement from reliance on a single line-bisection test by Kalra and colleagues. Experts in the field strongly recommend an assessment test battery because it increases the chances of picking up HI sub-types (Menon & Korner-Bitensky 2004, Jehkonen et al 2006, Maxton et al 2013).

Estimates from regression models

Regression results from Ring et al (1997) indicated that **LOS, age** and **FIM admission** score were related to functional gain (DV) but **gender, risk factors** and **HI** showed no statistically significant relationships in the same model. However, HI was entered as a dichotomised categorical variable in the regression analysis which may have resulted in important loss of information by collapsing the original scores into two, a binary variable. This measurement level may in part explain the conflicting results obtained in both studies (Ring et al 1997, Kalra et al 1997). Where possible, statistical sources recommend the use of original levels of measurement which tend to preserve information and precision of estimates better than dichotomised scores (Twisk 2006, Cheng et al 2009, Royston et al 2009). Given that HI is present on a wide continuum of severity (0 to 146 on the BIT), it would make sense to include it as a continuous variable and/or undertake sensitivity analysis aimed at validating the results (Thabane et al 2013).

In contrast with data from Kalra et al (1997)***, age*** significantly contributed 0.49 FIM units per year which is considerable given that average age was 60 years. **LOS** significantly affected gain which tends to suggest that greater exposure to therapy in the acute phase was beneficial to outcome. However, it is also possible that people who need more therapy need to stay longer.

Admission FIM score showed a statistically significant (p=0.01) negative relationship in that the lower the functional ability at admission the higher the overall gain at discharge. This data is consistent with findings from a recent systematic review of early (≤ 2 weeks post onset) ADL predictors of stroke recovery 3 months after stroke by Veerbeek et al (2011). Veerbeek and colleagues found strong evidence in favour of age, stroke severity, arm paresis and walking ability but also cautioned that prediction of outcomes in stroke was methodologically weak – presumably due to the extent of variation between and within patients. In summary, early functional ability (≤ 2 weeks post onset) and LOS may be important indicators of functional outcome (3 months after stroke).

In light of the discussion and limitations in design, the study by Ring et al (1997) was assigned C on the GRADE scale.

Study 3

***Title - The role of unilateral spatial neglect (USN) in rehabilitation of right brain–damaged ischemic stroke patients: a matched Comparison* (Paolucci et al 2001)**

Paolucci et al (2001) evaluated the influence of unilateral spatial neglect (USN) on the rehabilitation outcome of RHS patients (n=178) as assessed by the modified BI scale (0 to 100 max. independence) at admission and discharge from an acute in-patient hospital in Italy. The design consisted of a matched comparison between two patient groups (89 HI+/ & 89 HI-) and a USN targeted intervention, which consisted of 40 hours training in visual scanning, reading and copying script, line drawing, dot matrix and description of scenic pictures.

Technically the term ‘USN’ is misleading in this study. For reasons explained in study one (Kalra et al (1997), it is not possible to differentiate reliably and accurately between USN and other sub-types of neglect/HI (e.g. motor, visual, sensory) by means of assessment measures consisting of pen and paper cancellation and line bi-section tasks (Plummer et al 2003, Menon & Korner-Bitensky 2004).

Paolucci and colleagues reported 50% lower mean outcome scores in ADL and mobility as measured by the BI and Rivermead Mobility Index (RMI) for the HI+ group, despite special training and a longer period of rehabilitation; (117 versus 81 days in HI+, HI- groups respectively). Consistent with findings from Ring et al (1997), Paolucci et al (2001) reported high rates of institutional care in the HI+ when compared to HI- group (18% vs. 5%). This finding is consistent with similar rates of continence dysfunction reported by Paolucci et al (2001) in the HI+ (21%) versus (5%) HI-, groups.

Based on the reported BI scores at admission (mean 38, +/- 17 days since stroke) HI+ patients were functionally more impaired as a group than neurologically indicated by the mean Canadian neurological scale (Cote et al 1989) (CNS) score of 7, which equates to moderate stroke severity. However, it is possible that HI+ patients were more depressed a month into their stroke and consequently less motivated to improve. To rule out this possibility and treat clinical depression appropriately, NICE stroke guidelines (ISWP 2012) recommend the inclusion of a depression screen (not included in Paolucci et al 2001). An alternative explanation could be that the use of a finely graded BI scale (0 to 100) enabled the detection of smaller differences between HI± groups leading to a larger 50% discrepancy between them. The sensitivity of functional scales to change is an important psychometric property which can substantially impact on outcome (Salter et al 2007, Quinn et al 2009). In addition, there is preliminary evidence that the recovery pattern for ADL tasks differs for different tasks (Nijboer et al 2013). This data is not available for comparison between HI± groups in Paolucci et al (2001). Further, time to 1^{st} observation was ≥ 38 days (since stroke) which implies that intervention effects are likely to be confounded with spontaneous (natural) recovery effects in Paolucci et al (2001).

An increasing number of neuro-imaging studies and reviews on brain re-organisation after stroke have found evidence of neuronal sprouting and new connectivity approximately (~) 10 days and up to ~ four weeks after stroke - which were correlated with amelioration in motor function in initially more motor impaired patients (Rehme et al 2011, Grefkes and Fink 2011, Takeuchi and Izumi 2013). Therefore, in relationship studies evaluating cause and effect it is becoming important that baseline measurements are taken as early as possible (ideally within the first week of stroke) to minimise the confounding effects of spontaneous neurological recovery on function. That being said, there is no clear demarcation between when neurological recovery subsides and functional recovery (largely driven by rehabilitation) begins but substantial variation exists across individuals (Dobkin 2007, Dimyan and Cohen 2011, Takeuchi & Izumi 2013). Overall, this relatively ‘new’ knowledge and information highlights the importance of evidence-based future research designs, which take into account the importance of time (since stroke) in stroke functional recovery because this is at least in part dependent on the extent of neurological recovery and therefore functional reorganisation in the recovering brain.

Interpretation of continence data in Paolucci et al (2001) is complicated by the omission of an appropriate cognitive measure in their design. The high incontinence rates reported in HI+ patients could also be explained by lower (cognitive) awareness levels (rather than HI), which are positively associated with functional recovery, drive and motivation in the stroke and HI literature; Livneh (2009), Prigatano (2009), Kortte & Hillis (2009), Vossel et al (2013). This example highlights the importance of including multiple factors associated with HI in regression analysis so that modelling results are easier to interpret.

E*stimates from regression models*

In the study by Paolucci et al (2001), thirteen potential explanatory factors were modelled in 14 regressions involving 5 different DVs (refer to table 2.3 for detail). The results indicated that **HI, stroke severity, heart disease and type of lesion** had significant negative relationships with functional gain, which supports findings from earlier studies in the review. HI predicted 0.33 BI units less per unit increase in overall neglect score derived from several single neglect/HI tests as opposed to a standardised battery of tests. **Family support, education level** and **discharge destination** did not show significant relationships with functional gain. However, the results have to be interpreted with caution because the potential confounding effect of **age** and stroke severity was not included in the models. Further, due to the large number of factors modelled, multicollinearity issues (high correlation (>0.8) between two predictor variables in the same model) could have distorted the results. There is no mention of this potential threat in the data provided.

Another point is the total reliance on stepwise (forward) regression techniques to select factors for the final models. Statistical sources caution against over-reliance on this technique and advise that it may result in pre-mature exclusion of important variables because the researcher has no control on the selection process (Tabachnick and Fidell 2007, Field 2009, Cheng et al 2010). Instead, they recommend that sound theoretical and clinical justification be used to guide factor selection.

In light of the discussion and highlighted methodological limitations an overall C was assigned on the GRADE scale for the study by Paolucci et al (2001).

Study 4

***Title - Hemispatial neglect: Subtypes, neuroanatomy, and disability* (Buxbaum et al 2004)**

The stated aim of this study (Buxbaum et al 2004) was to assess the occurrence of hemi-spatial neglect sub-types and related deficits of attention and anosognosia (denial of illness state) and the neuro-anatomic substrates of neglect in patients with right hemisphere stroke (RHS) in rehabilitation settings.

Functional ability was measured by the FIM. Both in and out-patients who had sustained an RHS within the previous three years were eligible to participate; 623 were recruited from 4 rehabilitation hospital and surrounding areas; two in Italy and two in the USA. Of the 623, selection criteria were met by 268 patients of whom 166 consented; 86 had acute and 80 chronic lesions. The final sample was divided into two groups; 88 HI+, 78HI-.

With reference to data in study 4/table 2.3, Buxbaum et al (2004) reported that 62% of HI+ patients did not exhibit **motor or perceptual** HI and 54% had neither **personal nor peri-personal** sub-types, 21% had a mixture and 79% had one sub-type. The HI+ group had higher frequencies of **visual field defects** (~ 35% versus 1%), **visual extinction** (30% versus 14%), **tactile sensory loss** (40% versus 11%) and **tactile extinction** (28% versus 22%). **Anosognosia** was significantly more common in acute and chronic HI+ ($p<0.0001$) compared to HI-.

In relation to functional ability, the authors reported that the HI+ patient group had a lower mean **FIM score** but similar rate of gain to HI- group which corroborates with reports from Ring et al (1997) and Paolucci et al (2001). Unfortunately, actual figures were not published in the paper but the results support current knowledge in that (i) HI is a heterogeneous disorder which can dissociate into different sub-types, (ii) HI frequently co-exists with other conditions and (iii) importantly suggest that poor functional ability in HI+ patients is partly due to the higher frequency of conditions associated with HI found in the HI+ group, rather than the presence of HI itself. However there are methodological limitations which need to be considered when interpreting the results.

The sample was specifically recruited for its rehabilitation potential, therefore it unlikely to be fully representative of RHS patients and stroke severity levels. It is also unclear as to why only 166 patients consented out of an eligible 268. This raises further concern in terms of representation and generalisation of the results - especially if the lack of consent was linked to the rigorous assessment protocol, which may have put potential participants off.

The sample is heterogeneous with respect to age and time elapsed post-stroke (up to 3 years). As already explained in the review of Paolucci et al (2001), differences in time to 1st observation is a confounder of results which was unaccounted for in subsequent regression analysis. Furthermore, five sub-groups had ≤ 5 patients in them which again questions, the representativeness of these sub-samples. In addition, no statistical adjustment for multiple testing was undertaken. Taken together, all the factors mentioned increase the probability of a type I error (finding significant differences when they do not exist), which was partly acknowledged by the authors.

Epidemiological estimates on the frequency of HI/neglect sub-types are difficult to find in the literature, probably because of the assessment challenges posed by fragmentation of HI into sub-types and an unpredictable course of recovery (Appelros et al 2004, Viken et al 2012, Nijboer 2013). This lack of predictability is supported by the detection of HI three years post-stroke in chronic patients in Buxbaum et al (2004). Assuming that the estimates from Buxbaum et al (2004) are fairly accurate, this means that 1/5 of the patients with ‘good’ rehabilitation potential have a mixture of HI sub-types and 1/3 have visual field defects e.g. hemianopia. Consequently, there may be implications for interpretation of the results from other studies in the field.

The cause and classification of sensory extinction is debated in the literature as follows. Based on clinical observation, Becker and Karnath (2007) and Vossel et al (2011) argued that sensory extinction is a sub-type of HI. Brozzoli et al (2006) and Chechlacz et al (2013) claim that the phenomena is a separate pathological entity (independent of HI). Both **visual & sensory defects** have implications for function and are not easily distinguishable from HI, hence the debate.

The discrepancy in anosognosia scores between HI± groups in Buxbaum et al (2004) makes sense considering the relatively higher levels of sensory dysfunction reported in patients with HI, supported by findings from Paolucci et al 2001. In other words, patients are unlikely to be aware of what they do not experience visually and/or feel (in a tactile sense). Notwithstanding limitations of the study by Buxbaum et al (2004), it seems that anosognosia levels probably moderate the effect of HI on functional ability. This statement is further supported by research findings from Fotopoulou et al (2009), Garbarini et al (2012 and 2013) who showed that interpretation of reality in anosognostic patients with HI was dependent on the presence or absence of a visual stimulus (distractor) compared to patients without HI.

There were no data on the **cognitive components** assessed but Buxbaum et al (2004) but the authors reported significant negative correlations (associations) between average neglect percentile and (i) **sustained attention (**response time) ($r = -0.49$, $p<0.0001$), (ii) **sensory-motor speed** ($r = -0.47$, $p<0.0001$)**.** Both correlations suggest an inverse relationship between HI (neglect), attention levels and sensory-motor processing speed. A growing body of evidence from brain imaging and behavioural studies supports longer reaction-response time to perceptual/attention stimuli in RHS/HI+ patients when compared to normal controls (Husain & Rorden 2003, Chica et al 2011, Finke et al 2012). Although correlation is not causation, the results from Buxbaum et al (2004) provide supportive evidence that both components of executive function are likely to be important in terms of functional performance in patients with HI. To this end, observation has indicated that HI+ patients often required longer task-completion time and had difficulty finishing simple tasks (e.g. washing and dressing) due to reduced focus and attention to detail compared to HI- patients (Karnath & Rorden 2003, Parton et al 2004).

Buxbaum & colleagues acknowledged that their assessment tools may have lacked sensitivity to HI sub-types. In their defence, the choice of assessment tools available was severely limited in 2004 and is still limited at the time of writing, partly because it remains difficult in day to day practice to isolate HI sub-types (Vahlberg & Hellstrom 2008, Singh-Curry & Husain 2010, Ting et al 2011). As pointed out earlier, test batteries provide an overall score of HI severity which is better than nothing. However, pending the development of practical and clinically appropriate tools, a trade-off has to be reached between practicality, clinical appropriateness of tests and psychometric properties (Chen et al 2012, Maxton et al 2013).

E*stimates from regression models*

Results from two separate regressions carried out by Buxbaum et al (2004) indicated that **severity of HI** was significantly negatively related to functional outcome (DV) and carer burden (DV) when both were independently regressed on **lesion size** as the only predictor variable (IV) in the models. In a separate analysis, there was weak indication that **lesion location** determined the development of acute vs. chronic HI (> 3 months post stroke onset). This may have implications for specific support services of HI+ patients in the community. The results also suggested that **carers of HI+ patients** experienced increased burden as a result of residual HI. However, none of the models explained more than 15% to 24% of the total variance in the DV's respectively which tends to suggest that lesion location and caring factors although important probably possess limited predictive ability. It is also possible that the data in models evaluated by Buxbaum et al (2004) is not sufficiently representative of the variation in the HI± population seen in everyday practice (only patients deemed to benefit from rehabilitation were recruited). Further, important predictors such as age and stroke severity were not always included in the models, which has implications for the appropriateness and interpretation of modelling results (Tabachnik and Fidell 2007, Field 2009).

Overall the study design (Buxbaum et al 2004) reinforces some of the points made in earlier discussions (Kalra et al 1997, Ring et al 1997, Paolucci et al 2001) that the choice of factors and type of data collected statistically determine the complexity of models that can be evaluated, their accuracy and ease of interpretation of the results. This was taken into account in the PhD design. Following on from this discussion and the considerable flaws highlighted in the design, an overall D on the GRADE scale was assigned to the study.

Study 5

Title - Unilateral spatial neglect: Relation to rehabilitation outcomes in patients with right hemisphere stroke **(Gillen et al 2005)**

Gillen et al (2005) retrospectively examined the relationship between unilateral spatial neglect (USN) and rehabilitation outcomes in RHS patients (n=175) selected from an in-patient rehabilitation hospital database over a five year period. The patients were assessed at admission by means of a letter cancellation task (LCT) and comparatively grouped according to USN status (50HI+ and 125HI-). Admission cognitive function and depression were recorded by the Cognistat (Kiernan et al 1987) and General Depression Scale (Yesavage et al 1983)(GDS) respectively. Functional outcome was assessed by the FIM. A sub-sample of 45 HI+ and 53 HI- were subsequently matched according to admission FIM score (27 to 82) and their data modelled.

The findings from Gillen et al (2005) corroborate those from reviewed studies by Ring et al (1997), Paolucci et al (2001) and Buxbaum et al (2004) in that patients with HI tended to progress at slower rates, had lower mean admission FIM scores (HI+ 50 versus HI- 69), increased cognitive dysfunction ($p<0.001$) and higher depression levels ($p<0.01$) when compared to patients without HI. The FIM mean discharge score by group was not published but the overall score was (93.41±21.96).

This study had considerable limitations which may have impacted on results. The sample was probably not fully representative of RHS patients, since 38% of those eligible for recruitment were excluded (reasons given were poor visual acuity, perceptual deficits & difficulty completing LCT at 1st observation). This suggests that patients with severe stroke were most likely excluded. Identification of USN (HI) relied only on one test instead of the recommended test-battery by experts in the field (Menon and Korner-Bitensky 2004, Jehkonen et al 2006, Lopes et al 2007). Therefore a proportion of HI+ patients could have been missed and/or misclassified which increases the risk of bias in the study.

Significant differences between HI± groups were reported at admission on the FIM and Cognistat scores but not at discharge. This means that the rate of progress and magnitude of differences between HI± groups could not be calculated at discharge. The inclusion of a depression screen (GDS) was an identified strength and helped with the interpretation of the results. Based on the GDS scores, both groups were clinically depressed but patients with HI were on average significantly more depressed than HI- ($p<0.01$). However, the patients could have been assessed too soon after the stroke (within two weeks). In which case, they are likely to be depressed anyway by the recent stroke event, although this general likelihood does not explain the significant difference between HI± groups. Since no discharge scores were available, the change in GDS could not be calculated.

E*stimates from regression models*

It is noted that only data from the matched sub-sample (n=98) was subsequently modelled. **FIM admission scores** and USN predicted negative change in the **social-cognitive** domain ($\beta = -0.29$, $p< 0.001$) of the FIM discharge scores which were the designated DV. **FIM-motor function** showed a negative relationship which tended towards significance ($\beta = -0.15$, $p= 0.08$), indicating that the HI+ group were worse off compared to HI-. This result supports earlier findings from Ring et al (1997) in that admission functional levels predicted discharge outcome. It is noted that although the FIM was used in both Ring et al (1997) and Gillen et al (2005), the estimated effect size of HI differed considerably ($\beta = -0.034$ versus -0.29) probably due to the different predictor variables included in the models e.g. Ring et al (1997) included age which is also a potential confounder. Data collected by means of different assessment measures of HI (line bi-section in Kalra et al 1997 and line cancellation in Gillen et al 2005) could have also contributed to the differences in the reported effect size (USN). As previously discussed in study four, the choice of factors in a model and the quality of data available have implications for regression analysis and coefficient estimates obtained (Tabachnik and Fidell 2007, Field 2009). In light of the discussion and limitations highlighted an overall D was assigned on the GRADE scale with respect to Gillen et al (2005).

Study 6

Title – Functional outcomes in patients with right hemisphere brain damage **(Odell et al 2005)**

Odell et al (2005) retrospectively evaluated the impact of social-cognitive factors on functional outcome in RHS patients (n=101) referred to speech therapy from an in-patient rehabilitation hospital. The patients were comparatively grouped by HI status depending on whether neglect was mentioned or not in their records; 60HI+ and 41HI- were assessed by the FIM at admission and discharge. Their LOS was recorded.

Odell et al (2005) reported that the total FIM gain in the HI+ group was 7 units and the mean discharge score was 16 FIM units less compared to the HI- group. This indicates higher residual dysfunction in HI+ patients at discharge point, which was supported by findings from Gillen et al (2005). Odell and colleagues reported that more than 75% of HI± patients returned home which supports findings by Kalra et al (1997), Ring et al (1997), and Paolucci et al (2001). However, the mean LOS was much shorter (~30 days for both groups) compared to the latter three studies just cited. The differences probably reflected differences in local culture and health practices in stroke service provision in different countries (USA compared to UK, Israel or Italy). In Odell et al (2005) discharge destination outcome was predicted by advanced age, single marital status and lower admission FIM motor scores.

The authors reported that HI+ patients received more than double the intensity of speech therapy during the same in-patient period (~30 days) but neither HI+ nor HI- patients showed progress in social-interaction, language comprehension and expression, memory and problem solving on the FIM scale. The results are puzzling considering that the patients were specifically selected for their assumed rehabilitation potential. One interpretation could be that, both HI± patients lacked language specific cognitive skills. Another possibility is that the FIM was not sufficiently sensitive to small changes in cognitive/executive function. It would have been useful to know the severity of both the stroke and HI in the sample. Compared to other study samples the percentage of patients with HI was relatively high. This may be linked to the assessment time chosen and methods used to identify HI which were both unknown entities and probably a source of bias in the study.

E*stimates from regression models*

Multiple regression results indicated significant relationships between discharge FIM scores (DV), **age and initial (starting) FIM scores** (in memory, problem solving and motor function) when they were included as IV's in the same model with **gender**, **previous neurological** episodes, **number of comorbidities, lesion site** and **HI status**. In the same model, HI status was not identified as an important predictor which supports findings from Kalra et al (1997) but not from Paolucci et al (2001), Gillen et al (2005) and Buxbaum et al (2004). The predicted importance of cognitive-social factors (as measured by the FIM scale in all three studies) contradicted findings by Buxbaum et al (2004) but supported those from Gillen et al (2005). Moreover, the predicted importance of initial functional ability (initial FIM scores) contradicted findings by Gillen et al (2005) but supported those by Ring et al (1997). In light of so many conflicting findings, it is difficult to draw firm conclusions about the predictive or explanatory importance of respective factors in relation to functional ability.

Regression estimates from Odell et al (2005) are likely to be imprecise because of fundamental flaws in the design e.g. patients were grouped as HI± based on mention of the presence of HI in the patients' medical documents. This seems to be a very unreliable method of grouping compared to diagnostic assessments for HI. Improving the quality of the data by Rasch transformation method is not going to correct fundamental flaws in design.

Variation in the combination of factors in different models across studies reviewed so far could also explain the conflicting findings on the relationship of HI with functional change between studies reviewed so far. Together both points (patient grouping methods and model-factor specifications) reinforce the need to interpret findings within the context and quality of individual studies.

In light of the discussion and highlighted limitations in design, the study by Odell et al (2005) was awarded a D on the GRADE scale.

Study 7

Title - Severity of unilateral spatial neglect (USN) is an independent predictor of functional outcome after acute inpatient rehabilitation in individuals with right hemispheric stroke **(Di Monaco et al 2011)**

Di Monaco et al (2011) prospectively evaluated the relationship between severity of USN and ADL after RHS in a sample (n=131) patients recruited from an acute in-patient physical medicine and rehabilitation hospital in Italy, over an 18 month period. The patients were divided into two comparative groups based on the presence/absence of USN at admission. USN was assessed by the both parts of the BIT; the conventional part which consists of six pen and paper based tasks and the functional section which consists of nine subtests – picture scanning, telephone dial, menu reading, article reading, telling and setting the time, coin sorting, address and sentence copying, map navigation and card sorting. Admission and discharge functional ability were assessed by the FIM. Other admission assessments consisted of Diller’s Test (cancellation task) (Diller and Weinberg 1976), pre-admission BI by anamnesis from patients and carers and the Mini-Mental test (MMSE) (Folstein et al 1975) which measures overall cognitive ability.

Similar to reviewed studies so far (e.g. Kalra et al 1997, Paolucci et al 2001, Buxbaum et al 2004), Di Monaco et al (2011) excluded 24 patients from the original sample; 19 because they were too severely affected by stroke to continue with rehabilitation and 5 had missing data leaving n=107 in the study. This suggests a non-representative RHS sample which limits generalization of findings to the selected portion of the RHS patient population.

Di Monaco et al (2011) found substantial variation (>30 FIM units) within individual (HI±) groups and reported a lower median FIM score for patients with HI compared to without HI (admission-discharge FIM median HI+ (45 & 91), HI- (55 & 110) respectively). These results suggest that patients within the same HI+ or HI- group had very different abilities, which is likely to be an important source of variance in itself. Too much ‘within group’ variation would make it difficult to find statistically significant differences between groups and interpret the results. Di Monaco et al (2011) did not offer an explanation for the large variation identified between HI± groups. However, it is unlikely that the disparity is associated with differences in time to first observation (which varied by ~ 23 days) and was reportedly as adjusted for in the regression analysis. The source of variation is puzzling considering that the sample did not include severely stroke impaired patients and all 107 patients in the sample scored at least 24 points on the MMSE scale (indicating no significant cognitive impairment at admission). Taking everything into account, it is likely that this variation is not related to measured differences but to unmeasured patient characteristics e.g. psycho-social as in attitudes to health and motivation. Whilst other explanations may come to light from subsequent modelling results, the point is that they are difficult to interpret because of large variation within and between groups.

E*stimates from regression models*

Three multiple regressions were carried out with discharge FIM, FIM efficiency (change over time) and FIM effectiveness as DV's on separate occasions. The IV's included in each model were **age, MMSE score, time to 1st observation, gender, education, previous BI and FIM admission score** and **USN score.** Consistent with findings by Ring et al (1997), discharge FIM scores were best predicted by admission FIM scores. **USN** (HI) was a relatively weak predictor explaining no more than 5% of the total variance (45%) in discharge FIM scores. The finding that **cognitive ability** was not of predictive importance made sense because all MMSE scores were within the same (normal) range.

The lack of predictive importance of **education** and **previous BI** is consistent with findings by Paolucci et al (2001). **Age** was not predictive in Di Monaco et al (2011), which tended to support the notion that the influence of age increases when other factors such as co-morbidity and stroke severity are also taken into account (they were not specifically included in the study by Di Monaco et al 2011). It is also noted that **gender** and **time to 1st observation** made no significant contribution to functional outcome.

The study by Di Monaco et al (2011) was graded a C in view of substantial flaws in the design e.g. USN was only assessed at admission which precluded comparison of BIT scores at discharge. Without evidence of change in BIT scores, the claim that admission USN was a predictor is not well substantiated - especially when USN predicted only 5% of the total variance (45%) in the discharge FIM.

Study 8

Title - The effect of visuospatial neglect (VSN) on functional outcome and discharge destination: an exploratory study **(Timbeck et al 2013)**

Timbeck et al (2013) prospectively compared the effect of visuo-spatial neglect (VSN) on functional independence as assessed by the FIM and discharge destination in a sample of 16 RHS patients (6HI+ and 10HI-) RHS recruited from a stroke rehabilitation programme in Canada. Other assessments included the MMSE, Berg Balance Scale (BBS) (Berg 1989) and Chedoke McMaster Impairment Inventory (CMSA) (Morland et al 1983) which measures of neurological impairment. The patients were assessed at admission and discharge to the rehabilitation programme.

The authors reported relatively large differences in HI± group scores at admission and discharge in the order of; mean 26 and 30 FIM units respectively. However, the results may have been biased by the small sample size. The most important contribution of this study was in the area of **balance.**

The results indicated that HI+ patients had poorer balance and higher levels of neurological impairment when compared to HI- patients (~20 unit difference on the BBS at admission and also at discharge from the programme). The findings support evidence from recent systematic reviews that motor skills (balance and posture) are positively associated with functional independence levels post-stroke (Lubetzky-Vilnai & Kartin 2010, An & Shaughnessy 2011). Timbeck et al (2013) reported that HI+ patients tended to go into supported living which is not surprising, given previous evidence of cognitive and motor limitations. However, this has to be counterbalanced by the small sample size which severely limits generalisation of the findings to the RHS population. Given the limitations of the study, Timbeck et al (2013) was graded a D on the GRADE scale.

2.4.1. Summary of the findings from (studies 1 – 8)

The eight studies reviewed so far used varying terminology (e.g. unilateral spatial neglect, visual-spatial neglect, spatial and hemi-spatial neglect) to describe a collection of signs and symptoms thought to be associated with 'Neglect/HI' sub-types. The use of various terms is both confusing and misleading because conventional pen and paper tasks (such as the BIT sub-tests) cannot reliably distinguish between sensory, motor, visual, spatial and representation HI sub-types (Bowen et al 1999, Plummer et al 2003, Menon & Korner-Bitensky 2004). The reason being that, all these components are used to different extents in the same pen and paper task used for assessment purposes. Consequently, the scores obtained from pen and paper tests (e.g. line or letter cancellation, drawing and copying figures) are likely to be confounded and cannot be attributed with confidence to specific sub-types of HI (Neglect) - as would appear from the descriptive terminology used by the reviewed studies. Moreover, the inherent interdependency of sensory and motor aspects of movement makes it impossible to separate out the two components during routine clinical assessment situations. The same applies to visual and spatial components which makes it difficult to attribute cause or effect to a specific component. Pending the development of HI/Neglect sub-type specific measurement tools, it would be more accurate to regard the overall score from pen and paper tests as a measure of the severity of the condition rather than its potential sub-types (Wilson et al 1987, Halligan et al 1991, Mark 2003).

Notwithstanding the confusion with terminology, all eight studies found that as a group, patients with HI tended to score lower than without HI on overall functional scales, as assessed by the FIM or BI at admission and discharge in the acute phase (~ three months after stroke onset). The rate of progress (change in FIM/BI scores/LOS) varied across studies; albeit patients with HI progressed at similar or slightly lower rates than patients without HI. As a group, patients with HI tended to have longer in-patient stays and more intensive rehabilitation, although benefits were not always evident (e.g. Paolucci et al 2001). Higher levels of sensory-motor and cognitive-perceptual dysfunction were found in patients with HI, which predisposed the HI+ group to increased risk of discharge to an institution.

The presence of HI at baseline predicted functional outcome (DV) independently or with other factors (IVs) in five out of seven studies modelled data by means of multivariate regression analysis (Ring et al 1997, Paolucci et al 2001, Buxbaum et al 2004, Gillen et al 2005, Di Marco et al 2011). However, results from modelling analyses are difficult to interpret both within individual studies and also across studies due to substantial differences in design. For example, there was lack of consistency between evaluated models, time to 1st observation was poorly defined, sample representation varied and tended to exclude severe stroke, recruitment occurred from characteristically different settings in culturally and geographically different countries, assessment tools and discharge point from the treatment facility varied across studies.

As a result of all the flaws and limitations described summarised above the reviewed studies were awarded a C (low) or D (very low) quality grade on the GRADE scale (Guyatt et al 2008). This also implies that it is difficult to infer causality from the regression results in the five studies. Consequently, the importance of initial HI status in relation to functional outcome within the acute rehabilitation phase (up to ~ 3 months post-stroke onset) is not known with confidence. This has implications for prognosis e.g. the level of recovery expected at and beyond discharge point, treatment priorities and therapy focus on targeting factors which are likely to result in enhanced functional outcome.

2.5. Critical review

Studies with serial design and multiple follow-up observations

Five relevant international studies that had a serial design with more than one follow-up observation were identified; the longest was up to one year post-stroke onset. Findings from individual studies are presented chronologically in Table 2.4. For consistency, HI is synonymously used with Neglect terminology found in different studies. The assigned quality grade is shown in column 1/Table 2.4. Please refer to the abbreviation list in the beginning of section 2.4, (p. 23) to help with efficient switching between tables and text.

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Table 2.4 Critical evaluation of five studies with serial design and multiple follow-up observations

Source	Aims & Design	Assessment tools	Data analysis	Results/ Findings	Study Strengths	Study limitations
Paolucci et al 1996 Italy GRADE **D**	*Aim* - to test whether specific neglect training improved hemi-spatial neglect & functional outcome Prospective design Setting - Community rehabilitation facility *Sample* n=59 RHS (23HI+, 36HI-) *Mean age* 65 (SD=13) *Time to 1st observation* was 2 to 6 months post-stroke onset *Follow-up* at 2 & 4 months whilst in rehab facility *Intervention;* 40 hours *of* visual scanning, auditory cueing, reading, copying, line drawing, picture description	HI assessed once at admission to rehabilitation facility by means of Letter cancellation, line bisection, sentence reading & Wundt-Jastrow area illusion test at admission BI (0 to 100) RMI CNS Lesion size	3 ANOVA's for differences between 3 groups in BI, RMI & CNS scores by assessment time-points 4 ANOVA's for differences in HI tests by assessment time-point 1 ANOVA difference in lesion size by group (n=3)	Specific HI training improved functional ability of HI+ group but gains not maintained by end of study Similar magnitude of difference between HI+/- patients in mean functional ability & mean RMI (1st, 2nd & 3rd observation = 20%, 30% & 30% respectively). No group difference in lesion size	Screened for stroke severity but data not reported Standardised assessment tools Test-battery used to assess HI Used RMI to supplement information on functional ability not provided by BI scale e.g. walking outside house Community follow-up	No radiologic confirmation of stroke Excluded patients over 78, multiple lesions, haemorrhage or chronic CNS pathologies Small intervention HI+ group sizes (n=11 12) Stroke severity not known No fixed assessment time-points Not adjusted for multiple testing. Not accounted for the effect of time since stroke Attrition not reported

Source	Aims & Design	Assessment tools	Data analysis	Results/ Findings	Study Strengths	Study Limitations
Katz et al 1999 Israel GRADE **D**	_Aim_ - To evaluate impact of unilateral spatial neglect (USN) on functional outcome in long term Prospective, repeated measures design _Setting_ – Acute, General Rehabilitation Hospital _Sample_ n=40 RHS(19HI+, 21HI-) _Mean age_ 57 (SD=10) _Time to 1st observation_ was ~30 days _Follow-up_ at discharge, 6/12 after discharge, up to 1 year post-stroke onset No intervention but HI+ patients received special attention & care for HI	BIT at admission & discharge only FIM LOTCA cognitive assessment at admission & discharge only) Rabideau kitchen evaluation (RKE), which is an IADL measure (not included at admission)	t-test Chi squared test Repeated measures ANOVA Multiple linear-regression – FIM (DV), modelled stepwise - IV's BIT score, sitting balance, thinking operations (not defined) & tactile sensation	USN was major predictor of functional outcome from admission to follow-up. Despite special attention given to HI+ group, they had higher disability levels, slower improvement rate Most progress occurred within the in-patient facility Longer LOS/days for HI+ (119+/-49) vs (78+/-52) for HI- 39/40 patients were discharged home, 1 patient with HI discharged to NH. HI+ needed high levels of support at home compared to HI- HI could be predicted from pen & paper tests alone (no advantage in giving functional sub-section)	Confirmed stroke by CT scan Standardised assessment tools Long term follow-up 2/4 fixed observation points Modelled also cognitive, IADL score, tactile factors, sitting balance Reported therapy time 45 to 60 minutes. of OT & PT/patient Tracked recovery of function up to a year post-onset	Small sample size & mean age (younger) limit generalisation Excluded severe stroke & psychiatric disorders not clear which, restricted inclusion to 1st stroke only with no comorbidities. Inconsistent assessment protocol (BIT not repeated at follow-up) to assess recovery. No attrition reported At risk of low statistical power for regression analysis Observations from same patients not independent – invalidates regression assumption No statistical adjustment of confounding factors FIM is a multi-disciplinary tool, how was this completed in the community?

Source	Aims & Design	Assessment tools	Data analysis	Results/ Findings	Study Strengths	Study Limitations
Cherney et al 2001 USA GRADE **D**	*Aim* To evaluate relationships between unilateral spatial neglect (USN) & cognitive-communicative functional outcomes in RHS Prospective, repeated measures design *Setting* - Acute rehabilitation facility *Convenience sample* n=52 RHS (36HI+, 16HI-) *Mean age* 66 (SD=14.0) *Time to 1st observation* at facility was 33+/-68 days after stroke *Follow-up* at discharge & 3 months post-discharge	BIT at admission FIM Rehabilitation institute of Chicago functional assessment scale for comprehension and written expression (RIC-FAS) LOS	ANOVA Mann Whitney U Pearson's coefficient of correlation	Statistically significant differences were found in overall FIM and motor sub-score but not cognitive score. HI+ patients scored 10 FIM units (8%) less at each observation point. High correlation between pen & paper tests and behavioural section on BIT (r=0.89) Moderate correlation (r=0.51) between FIM & BIT scores at 1st & 2nd observation points which weakened by 3rd (r=0.36) LOS/days for HI+ vs HI- (38+/- 9 vs 31+/- 10). No impact of HI severity on LOS reported.	Evaluated cognitive function & communication (not previously included) Reported attrition (n=4) due to incomplete documentation at discharge & (n=12) lost to 3 month follow-up.	Small sample size for sub-group analysis by HI severity Highly variable time to 1st observation Stroke severity not known No fixed observation point – limits comparison of results No intention to treat analysis FIM scores at 3 month follow-up obtained by telephone interview - reliability of data?

Source	Aims & Design	Assessment tools	Data analysis	Results/ Findings	Study Strengths	Study Limitations
Stein et al 2009 UK GRADE **D**	*Aim* To compare & evaluate basic functional mobility in patients with and without visual neglect Prospective, repeated measure design *Setting* Acute inpatient rehabilitation & community rehabilitation *Sample* *n=28 RHS* (14HI+, 14HI-) *Mean age* 76 (SD=11) *Time to 1st observation was 7 to 28 days post-stroke onset* *Follow-up* observation at discharge & 4 weeks post-discharge	BIT BI (0 to 20) EMI. MEAMS (cognitive screen) PASS (balance/posture scale), LOS Discharge destination Continence status Carer status	Mann Whitney U test Kruskal Wallis Wilcoxon matched pairs Bonferroni correction for multiple testing	Mean LOS/days was 79 & 52 for HI+/- respectively 7 HI+ discharged home vs. 12 HI-. HI+ increased risk for institution discharge. Mean difference of 7 BI units (35%) at discharge (p=0.013). Patients with mild HI and independent mobility tended to be discharged home. Relationship between carer presence & discharge destination was not clear.	Data spanned acute and early community phase Included range of severity of HI Included separate measure of posture relevant to functional mobility Included data on discharge destination & continence status Reported number of deaths (n=3) &outliers (n=4) Corrected for multiple testing to minimise type 1 error	BIT, MEAMS, BI were not assessed post-discharge, therefore unable to track change especially in functional mobility Possibility that differences observed between patients could be due to type 1 & II errors largely due to small sample size No correlation statistics to study association of factors with functional mobility No fixed observation points limits comparison to other studies

Source	Aims & Design	Assessment tools	Data analysis	Results/ Findings	Study Strengths	Study Limitations
Nijboer et al 2013 Holland GRADE **D**	*Aim* To specify the relationship between neglect and recovery of different domains of ADL. Prospective, repeated measures design *Setting* 4 Dutch in-patient rehabilitation centres in the period April 2000–July 2002 *Sample - selected from a larger Dutch stroke database* *n=318 (RHS + LHS) patients. Excluded n=134, left 53 HI+ & 131 HI-* *Mean age* 57 (SD=11) *Time to 1st observation was 55 to 63; SD 20 &30 days resp. post-stroke onset* *Follow-up* 6, 12, 36 months post-discharge	Single pen & paper; Letter cancellation task (LCT) FIM BI (0 to 20) Motoricity Index (MI) Depression (CES-D) Sensory deficits (TFT) Mini-mental state (MMSE)	184 records used Mann Whitney U test for demographic group comparison Random co-efficient regression analysis Modelled FIM domains as DV's against IV's neglect status at admission, time, MI, TFT, CES-D, BI, neglect status x time Modelled FIM overall score (DV) against IV's neglect severity (for neglect patients only)	Group differences At baseline, for self-care, transfers & locomotion HI+ scored -4, -3 & -2 FIM units when compared to HI- reps. Difference HI+/- groups decreased by ~ 1.7 FIM unit less at 6, 12 & 36 months resp. No difference was found for sphincter control & cognitive function. Significant -ve relationship found between **severity of neglect** & self-care & transfers. No relationship with sphincter control or locomotion or cognition. +ve relationship with time but no interaction between time x FIM domains	Random coefficient analysis method increases precision of estimates Long term follow-up up to 3 years post onset. Employed specific measures for sensory &, motor deficits which increase respective assessment accuracy. Adjusted for the effect of time and corrected for admission motor, sensory, dependence in ADL as measured by BI & depression	Mixed pathology (RHS + LHS) limit application of findings. n=134 excluded; 100 unable to do LCT & 34 had sub-arachnoid haemorrhage. Further, assessment of HI relied on 1 cancellation task – implications for identification of all patients with HI, accuracy & interpretation of results. Highly selective sample - young, mild-moderately disabled. Mean 57 years - has implications for generalizability of findings. ~2 months delay in time to 1st observation has implications for results & system bias

Study 9

Title - Facilitatory effect of neglect rehabilitation on the recovery of left hemiplegic stroke patients: a cross-over study **(Paolucci et al 1996)**

Paolucci et al (1996) undertook a cross-over intervention study for HI between two groups of patients with HI and a third comparative group without HI. They assessed whether specific HI training improved hemi-spatial neglect (HSN) & functional outcome over a period of 10 months post stroke (estimated by the author of the thesis from data published by Paolucci and colleagues). The sample consisted of 23 HI+, 36 HI- (RHS) patients recruited from a community rehabilitation setting in Italy. HSN was assessed by a letter cancellation and line-bisection task, sentence reading and Wundt Jastrow (area illusion test). Rehabilitation outcome was assessed at baseline (2 to 6 months since stroke) by the BI scale (0 to 100) and the Rivermead Mobility Index (RMI) (Collen et al 1991). Baseline neurological severity was assessed by the Canadian Neurological Scale (CNS) and lesion size was also recorded. The intervention consisted of 40 hours of visual scanning, auditory cueing, reading and copying, line drawing and picture description. Follow-up was at 2 and 4 months whilst in the rehabilitation facility.

The authors reported an improvement of 10 BI units during the intervention phase in each of the two groups with HI but neither group maintained gains up to 10 months post stroke, at which time HI+ patients were significantly behind the comparative group of patients without HI by 20 BI units. A similar difference was observed on the mobility index. These results suggest that trends observed in HI+ patients for lower scores persist beyond the acute phase – in this case, at least up to 10 months after stroke. Paolucci et al (1996) was one of the 1st studies to follow up patients beyond discharge and the data gathered highlights the advantages of longer follow-up studies in capturing progress trends compared to earlier reviewed studies (1-8) with much shorter duration and less follow-up. The ‘take home’ message from Paolucci et al (1996) is that community (delayed) intervention was not effective in elevating functional ability in HI+ patients because improvement was not maintained once specific training was withdrawn in both of the groups with HI.

Although this finding was supported by similar reports by Mark (2003) and Cochrane reviews by Bowen & Lincoln (2007, updated in 2013), there were important limitations in Paolucci et al (1996) which may have affected the accuracy and precision of results. Time to 1st observation varied by 2 to 6 months since stroke which meant that there was no fixed (reference) time-point with which to compare subsequent data. Consequently the results are likely to be biased towards patients in the acute phase because at two months, the patients’ rate and amount of functional recovery are considerably faster than at six months when recovery in ADL tasks tends to plateau (Kwakkel et al 2006, Langhorne et al 2011). Therefore, the change in BI and RMI are expected to be substantially larger between 2 -10 than 6 -10 months.

Furthermore, the data is generated by the same patient throughout the study and has similar characteristics. Therefore, it is likely to be self or auto-correlated which increases the risk of bias in the results. ANOVA method of analysis does not account for this type of bias (auto-correlation), it treats every observation as though it were independent (Tabachnik and Fidell 2007, Field 2009). There is no statistical adjustment for multiple testing which may further compromise accuracy of the results and inferences made.

If anything, the flaws in the design reinforce the message that time is an important confounding factor as it independently influences functional outcome especially with time-variant factors such as HI (Kollen et al 2005, Kwakkel et al 2006, Nijboer et al 2013). Whilst longitudinal studies offer much needed continuity and visibly show recovery trends and patterns, the design is crucial to their outcome. In light of the limitations discussed, the study by Paolucci et al (1996) was graded a D on the GRADE scale.

Study 10

***Title - Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect* (USN) (Katz et al 1999)**

Katz et al (1999) undertook a prospective, comparative study between two RHS patient groups (HI±) to evaluate the impact of USN on rehabilitation outcome in the first year after stroke. The sample (19 HI+, 21 HI-) was recruited from an acute general rehabilitation hospital in Israel. The patients were observed at admission, discharge, 6 and 12 months (presumably since stroke). The BIT and the Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) (Katz et al 1989) were used to assess USN and cognitive ability respectively, at admission and discharge, the Rabideau Kitchen scale (RKE) (Neistadt 1992) assessed food preparation skills at follow-up points and the FIM assessed functional ability at all four observation time-points. No intervention was included but the HI+ group received special attention and care for HI e.g. patients were encouraged to scan affected space.

The authors reported substantial variation (8 to 23 FIM units) within both HI± groups and disparity in mean FIM group scores; HI+ 80.0, 97.0, 102.0 vs. HI- 105.0, 121.0, 122.0 respectively at baseline, discharge and post-discharge (6 up to 12 months). Similar trends were reported in cognitive function (perception, visuo-motor organisation, thinking and planning) up to discharge (mean LOS/days HI+ 119, HI- 78) and the RKE between discharge and follow-up. In a nutshell, these results support progress trends reported in Paolucci et al (1996) and more recent functional recovery trends reported in relevant generic stroke reviews by Craig et al (2011) and Langhorne et al (2011). This is reassuring given the geographical and likely cultural differences between Israel and Italy. However the size of disparity reported by Katz et al (1999) is likely to be a rough estimate when the limitations of the study are taken into account. These are described below.

The mean age in their sample was 57, which is relatively young compared to other samples (typically ≥ 65 years). The age difference is relevant because some past studies have found that younger patients tended to progress faster (Buxbaum et al 2004, Gottesman et al 2008). Therefore, generalisation of the results from Katz et al (1999) is limited to younger populations. Furthermore, the BIT scores provided suggested that patients with severe HI (USN) (and probably severe stroke) were not represented in their sample. Both factors detract from the value and application of the findings. There are also issues with variation in time to 1st observation, the implications of which were discussed in section 2.4 (Paolucci et al 2001, Buxbaum et al 2004, Di Monaco et al 2011). In addition, the lack of a consistent assessment protocol has repercussions for internal validity (e.g. the BIT should be repeated throughout the study to assess recovery of USN/HI). Attrition was not reported; given that the starting sample size was already small, there are statistical implications for study power and increased risk of type 1 error.

E*stimates from regression models*

Katz et al (1999) found that **HI** predicted outcome up to one year post stroke onset - when FIM scores were regressed on the following factors in the same model; **sitting balance, proprioception, cognitive ability, visuo-motor abilities**, **tactile sensation, BIT scores** and extent of **voluntary movement**. There was weak indication that **sitting balance and cognitive abilities** were predictive, although it is not clear what aspects of cognition were assessed (global or higher executive function). As explained in the previous reviewed study (Paolucci et al 1996), the data is likely to be auto-correlated. This would invalidate the assumption of independent observations in regression analysis and leads to potentially inflated p-values (Singer and Willet 2003, Snijders and Busker 2012). Therefore modelling results have to be interpreted with caution. That being said, compared to models evaluated in studies reviewed so far, the model by Katz et al (1999) explained larger amounts of variance (70% compared to < 50%) in the DV (follow-up FIM scores). This is a positive point because the prediction may be more stable. However, it does not negate the issue of likely imprecision due to auto-correlation bias which is not accounted for by ordinary multivariate regression analysis or ANOVA methods (Twisk 2006). Considering that there was no adjustment for important confounding factors such as age, stroke severity and time which could change the results if included, Katz et al (1999) was graded a D on the GRADE scale.

Study 11

Title - Recovery of functional status after right hemisphere stroke: relationship with unilateral neglect **(Cherney et al 2001)**

Cherney et al (2001) prospectively evaluated the relationship between unilateral spatial neglect (USN) & cognitive-communicative function, LOS and overall functional outcome in a sample of (n=52) RHS patients recruited from an acute rehabilitation facility in the USA. The study duration was between four to six months post-stroke (estimated from baseline and LOS data). The patients were assessed by the BIT at baseline (median 12.5 days) and comparatively grouped by their HI status (36 HI+, 16 HI). Functional ability was assessed by the FIM at baseline and follow-up points; discharge and 3 months post-discharge. Cognitive-communicative function was assessed by the Rehabilitation Institute of Chicago Functional Assessment Scale for comprehension and written expression (RIC-FAS) at follow-up (discharge and 3 months post-discharge).

The proportion of HI+ patients in the sample was twice as many when compared to other longitudinal studies (e.g. Katz et al 1999) even when the same diagnostic measure was used (BIT); albeit time to 1st observation varied by 68 days in Cherney et al (2001) compared to Katz et al (1999). This variation probably contributes to the discrepancy in findings but also indicates lack of homogeneity in sample characteristics across both studies. Cherney et al (2001) reported the reason for the delayed 1st observation (68 days) was largely due to two outliers who were tested very late compared to the other patients. This is plausible but would also give rise to differential bias in baseline assessment time since stroke, which is associated with amount and rate of functional outcome (Kollen et al 2005, Kwakkel et al 2006).

In Cherney et al (2001), correlation of FIM and BIT scores suggested a moderately strong negative association between HI and functional ability in the first 6 weeks (calculated from LOS) which weakened thereafter (r=0.51, 0.36 respectively). Since all three observation points were relatively variable in time, it is difficult to specify the study duration which is problematic when interpreting the results. Nevertheless, the results do not support findings by Katz et al (1999) that HI is a major predictor of functional ability in the first year post-stroke. However, the study by Katz et al (1999) was possibly underpowered which may have increased the chances of a type 1 error (finding a significant difference when there is none). In addition, auto-correlation is likely to be problematic in both studies (Cherney et al 2001 and Katz et al 1999) because it was not accounted for by the statistical analysis methods employed at the time (ANOVA and multiple linear regression). As pointed out earlier, this can give rise to inflated significance values which in turn may lead to inaccurate conclusions.

The possibility that the observed differences in FIM scores (over time) are due to confounding variables e.g. stroke severity and the impact of time since stroke instead of HI status cannot be ruled out in Cherney et al (2001) (or indeed in Katz et al 1999), since these factors were not included in the design. Therefore these results need verification in future study designs which account for the differences in stroke severity and time since stroke.

The lack of significant difference between HI± patients on the FIM-cognitive sub-section is not surprising given that the FIM has shown bias towards motor domains (Ottenbacher et al 1996, Van Der Putten et al 1999, Cohen et al 2000). An alternative explanation for the lack of disparity could be that there was little change in cognitive function within or between individuals in the sample irrespective of grouping. Furthermore, if the FIM-cognitive scores between e.g. discharge and post-discharge are the same (which is possible), then correlation results would be artificially high but such a correlation is not meaningful because the patient has not improved or deteriorated – they were just stable.

Of note in this study (Cherney et al 2001) is the high correlation reported between the conventional (pen and paper tests) and behavioural section of the BIT (r=0.89) (the BIT is described in the methods - chapter 3). This finding suggests that the behavioural section adds very little new information over and above that provided by the conventional section alone. The information is useful to know because it would shorten the BIT assessment time considerably without compromising results. Assessment time is relevant to RHS patients especially those who have limited focus and concentration.

To summarise, in view of the design limitations highlighted in this account, a D grade was assigned to Cherney et al (2001) on the GRADE scale.

Study 12

***Title - Impact of visual-spatial neglect (VSN) on stroke functional outcomes, discharge destination and maintenance of improvement post-discharge* (Stein et al 2009)**

Stein et al (2009) compared the differences in functional ability of 28 RHS patients to ascertain the potential impact of admission VSN on discharge destination, functional outcome and early community mobility (after 4 weeks post discharge). The patients were recruited from a stroke unit in the UK and grouped by HI status (14 HI+, 14 HI-) although not purposely matched. HI was assessed and diagnosed by the BIT at baseline (up to 4 weeks post stroke onset), functional ability and mobility were assessed by the BI (0 to 20), the Elderly Mobility Scale (EMS) (Smith et al 1994) and the Postural Scale for Stroke (PASS) (Benaim et al 1999) at baseline and follow-up (discharge and posit-discharge). Cognitive ability was assessed by the Middlesex Elderly Assessment of Mental State (MEAMS) (Golding 1989) at admission and discharge only.

The authors reported that all patients (apart from 3 deceased during the study) showed positive improvement trends in the BI, PASS, EMI and MEAMS between admission and discharge which tended to statistically significance both within and between groups. At discharge, HI severity was less but considerable indicating significant residual HI which may have impacted on community functional mobility levels. In line with findings from Katz et al (1999) and Paolucci et al (2001), the HI+ group (in Stein et al 2009) scored less than HI- on all scales indicating greater residual impairment. An increased tendency towards low continence levels and discharge to nursing institution care (7HI+ versus 1 HI-) was reported. In Stein et al (2009), overall differences between HI± patients were more marked due to the inclusion of patients with severe stroke and inherent greater functional impairment, including increased HI severity (Appelros et al 2003 & 2007, Kerkhoff & Rossetti 2006). However, the small sample size could have biased the results.

Significant improvement was found in balance and posture (functional) abilities over time since stroke especially in HI+ patients not living in institutions. This result supports previous findings that motor skills are of predictive importance particularly in the acute phase (Meins et al 2001, Kollen et al 2005).

Due to the small sample size, it was not possible to model relationships between functional ability, HI and other covariates which could not be studied in depth. That is, no causation could be attributed to any of the factors studied from the results.

In regard to the design, the assessment protocol was not consistently repeated which meant that useful data on functional change and recovery patterns was not collected. In addition, the study duration varied between individual participants because all three observation points were not fixed in time. This should be a priority feature in future serial designs - to have at least baseline and last follow-up point relatively fixed in time so that the study duration is clear and consistent across patients. This would enhance comparison of results between studies even with minor differences in the design. Since the effect of time elapsed since stroke could not be statistically adjusted for the risk of bias is unacceptably high.

The definition of function was limited to items found on the short version of the BI (0-20), which does not include communication, cognitive and social-interaction items. Therefore, despite its practicality in acute and community settings, this BI version is not particularly suited for measurement of functional ability in its broadest sense (WHO 2001). In view of the limitations highlighted, the study by Stein et al (2009) was assigned a D on the GRADE scale.

Study 13

Title - Predicting functional outcome after stroke: the influence of neglect on basic activities of daily living **(Nijboer et al 2013).**

This study is specifically included in the review because it employed random coefficient analysis - an advanced statistical data analysis method and as such represents a departure from ordinary multivariate regression and ANOVA methods employed so far in the reviewed studies (1-12). However, it should be noted that the sample is generic (a mixture of RHS and LHS) instead of only RHS which has important implications for the generalisation of findings.

According to Twisk (2004), Random Coefficient Analysis (RCA) is also known as multilevel analysis (MLM) (Goldstein 1995). However, statistic terminology can be confusing in that, it is not clear whether RCA is the same as Random Effects Analysis listed by Diez Roux (2002) in a glossary for multilevel analysis and by Peacock and Peacock (2011) in the Handbook of Medical Statistics. Twisk (2004) writes that the basic idea behind RCA in longitudinal, serial studies is that regression coefficients are allowed to differ across subjects to accommodate individual variation which is then accounted for in the multilevel-modelling process. This increases the precision of regression coefficient estimates obtained by RCA which in turn enhances the results (Twisk 2004, Snijders 2005). Therefore, in this respect the use of RCA was an identified strength in the study by Nijboer et al (2013) which is critically reviewed below.

Nijboer et al (2013) aimed to specify the relationship between visuo-spatial neglect (VSN) and recovery of FIM-ADL domains in order to assist with early stroke management, set suitable rehabilitation goals, enable discharge planning and psycho-education. The original sample (n=318) was selected from a larger database (Fu-Pro-stroke) collected from four Dutch rehabilitation in-patient centres from 2000 to 2002. Inclusion criteria were met by 184/318 patients who were subsequently recruited. VSN was diagnosed and measured by a single letter cancellation task (LCT) wherein the patients were grouped accordingly into two (VSN±). Both groups were assessed at baseline (week 1 of admission to rehabilitation centre) and followed-up at 6, 12 and 36 months. Baseline Motricity Index (MI), depression levels and BI were also recorded.

In regard to group differences, Nijboer et al (2013) found similar trends as in past reviewed studies in that HI+ patients were initially more impaired in sensory-motor function (see Cherney et al 2001, Buxbaum et al 2004) and dependent in ADL tasks (Gillen et al 2005, Di Monaco et al 2011) when compared to HI- patients. The HI+ group were more depressed which supports the need to screen for depression in future studies. In addition, Nijboer and colleagues found that patients younger than 55 years achieved 67% of the maximum possible improvement compared with only 50% for patients above 55 years ($p<0.001$) which supports the predictive role of age on functional recovery (Black-Schafe and Winston 2004).

In relation to modelling and RCA results, Nijboer et al (2013) found that the HI+ group scored lower than HI-; ~ 4, 3 and 2 FIM units for **self-care, transfers** and **locomotion** respectively. All group differences decreased by ~ 1 FIM unit with each subsequent measurement but remained statistically significant even when the effect of time after stroke, admission motor, sensory, dependence in ADL (BI score) and depression were adjusted for. No group differences were found for **cognition** and **bladder** control. Consequently, Nijboer and colleagues concluded that the recovery patterns of VSN± groups differed between different ADL tasks.

In a 2nd (RCA) model, Nijboer et al (2013) found a negative, significant relationship between **VSN severity levels**, **self-care and transfers** but not with **bladder control, cognition** and **locomotion**. They found no interaction between **VSN severity and time.** These results suggested that the contribution of VSN severity differs by type of ADL task, which is plausible because the set of skills required for self-care are quite different than those required for locomotion. Example, self-care occurs within peri-personal (near) space and locomotion within extra-personal (far) space with respect to the body (refer to diagram 1 in the Introductory Chapter). However, in terms of causality, these RCA results do not support an absolute (important) VSN contribution to functional change. Neither do they support an ‘independent’ predictive role of VSN as reported by Katz et al (1999), Paolucci et al (2001) and Gillen et al (2005) because one would expect a ‘powerful’ predictor to be a reliable one under a given set of circumstances (Moons et al 2009, Royston et al 2009).

According to the results obtained by Nijboer et al (2013), VSN status is unlikely to be a reliable predictor of functional change across all aspects of ADL function and stroke/HI severity but of negative influential importance in aspects of self-care (i.e. eating, grooming, bathing, dressing (upper/lower body) and toileting), and transfers (i.e. bed/chair/wheelchair,toilet, bath/shower). It is clear that more research would be needed in this area in order to validate the results on a more representative and homogenous sample of RHS patients only.

That being said, there were important limitations in the design which undermine the reliability and accuracy of the results obtained by Nijboer et al (2013). It seems clinically odd that VSN severity is related to transfers but not locomotion and is related to self-care but not cognition (given the cognitive demands of self-care tasks). One possible explanation is that both groups (with and without VSN/HI) were not cognitively impaired at baseline (supported by a normal range (>24) MMSE score). Another explanation is that LCT was measuring other forms of HI than VSN which may not impact on locomotion (this being a more automated activity) but could impact on transfers because these are less automated and conducted in close body proximity. Given that the recovery pattern of VSN was quadratic (non-linear) (Nijboer et al 2013), one would expect an interaction with time but this is difficult to identify with a small number of patients in the HI+ group (n=53). The lack of a statistically significant relationship between **age and VSN** reported by Nijboer and colleagues is understandable because their sample had a low comorbid risk which tends to support earlier findings from Kalra et al (1997); that the predictive importance of age increases with co-morbidity.

Nijboer et al (2013) acknowledged some of the limitations in their study in that all patients received inpatient rehabilitation after hospitalization (a mean of 56 days, SD=30 since stroke). Their patients were relatively young (mean 57 years, SD 10.00) and moderately disabled with low comorbidity (as inferred from a pre-stroke BI score of 18 or more). In addition, the proportion of patients with VSN in the final sample was relatively low 29% (53 HI+ v.s.131 HI-) compared to other studies who recruited at least a month after stroke (Paolucci et al 1996, Katz et al 1999, Cherney et al 2001). The low frequency rate is probably explained by the inclusion of LHS patients in the sample but also significant delay to 1st assessment (mean 56 days) and the fact that VSN was only diagnosed by a single line cancellation test versus a test battery such as the BIT - which increases the likelihood of picking up HI+ patients (Jehkonen et al 2006, Lopes et al 2007). Furthermore, 100 of the 134 patients initially excluded were unable to complete the LCT which would suggest that patients with severe cognitive impairment were most likely excluded. All these factors affect sample representation which impacts on the generalizability of findings and possibly accuracy of the results, which need to be interpreted with caution.

It is also not clear why the 1st follow-up point was 6 months apart from baseline with potential loss of important data in between. Given that recovery of ADL skills and HI reach peak levels around 3 months after stroke (Duncan and Lai 1997, Kwakkel et al 2006, Nijboer et al 2011), it seems logical to have at least one follow-up point between baseline and 6 months.

Nijboer and colleagues provided scant detail on model structure and specification. From the text, it can be deduced that group differences were modelled as a categorical term (with VSN=1, without VSN=0) and only single level regression was undertaken which presumably corresponds to within patient variation (Snijders 2005, Cheng et al 2010) although this is not clear from the text. It is also not evident whether time was modelled as a continuous, linear term or quadratic or a categorical variable; current evidence supports a quadratic pattern of functional recovery and HI in the six months after stroke (Duncan et al 2000, Kollen et al 2005, Langhorne et al 2011, Nijboer et al 2013). This detail is not reported therefore it is difficult to make an informed judgement on model specification.

In summary, no firm conclusions on the relationship between VSN (HI) and improvement in ADL tasks can be made from the data and results obtained in Nijboer et al (2013). Nevertheless, urgent validation is warranted in future research studies with serial design and multilevel method of analysis because this method can account for considerable variation in the data typical of patients with RHS (with and without HI).

2.5.1. Summary of findings from (studies 9-13)

All five studies found differences between HI± patient groups in overall functional ability and motor components as assessed by the FIM or BI up to three years after stroke. In general, the duration of time since stroke was unclear due to considerable variability around baseline and follow-up observation time-point which blurred the beginning and the end of all five studies (e.g. in Stein et al (2009) 4 weeks post-discharge was the last observation point but this was relative to discharge point which was also variable). In hindsight, both the first and last observation points should be relatively fixed for all patients so that there is at least some consistency needed for comparison of the results across patients. This would also promote wider application of the findings.

In line with the previous point, the independent effect of 'time since stroke' should be estimated in future models so that it can be accounted for. The HI+ group tended to show lower outcomes than HI- group in the rate and amount of functional recovery, balance and posture skills, continence levels, rate of institution care, self-care, transfers and locomotion but less disparity between groups was observed in cognitive components. Conflicting findings were made in regard to the explanatory importance of continence status, the overall rate of progress and institution care (see studies 10, 12 and 13). However, this is not surprising due to the heterogeneity in respective study designs. Example, in Nijboer et al (2013) the patients were relatively young, less functionally impaired and of mixed stroke pathology (RHS+LHS) compared to the other four studies in this section. Substantial differences in sample characteristics are likely to impact differently on rates of continence, progress and institutional care across studies.

Only two of the studies undertook regression analysis and both concluded that HI was an adverse prognostic predictor of functional ability up to a year (Katz et al 1999) and three years post stroke onset (Nijboer et al 2013). However, the reported size effect varied significantly in that HI predicted more than 10% of the DV in Katz et al (1999) but prediction was more variable in Nijboer et al (2013) (as measured by the FIM in both studies). Consequently the relationship of early HI status with functional change (time since stroke) remains unclear.

To sum up, the same flaws in research methodology found in the 1st eight serial studies (with one follow-up point) were also evident in studies with multiple follow-up points e.g. important differences in sample characteristics, strict selection criteria with a tendency to exclude patients with severe stroke, substantial variation in diagnostic methods and assessment tools for HI, confusion in the interpretation of the results from test batteries which give an overall score of the intensity of HI but not individual sub-types. In addition, the inherent dependency of multiple measures with the same tool from the same patient over time, together with the hierarchical data structure, presented statistical challenges which could not be adequately overcome by traditional methods of regression analysis (due to under-estimation of associated standard error). The only study (Nijboer et al 2013) which employed more advanced statistical methods (RCA) had significant methodological limitations marked by lack of descriptive detail on the procedure and analysis carried out.

Together, all the factors highlighted substantially undermine the results obtained from statistical models in this section and the quality of evidence available from characteristic, serial studies included in the current review.

2.6. Quality of the reviewed studies

The quality of studies in this review were rated using the GRADE scale. Based on their strengths and limitations four received a C (low) and nine a D (very low) grade. Low methodological quality in studies on the effectiveness of HI interventions has also been reported by Paci et al (2010), who reviewed 18 RCT's by means of - the Physiotherapy Evidence Database (PEDro) scale (Moseley et al 2002) – accordingly the quality was rated low when the official cut-off score of 5 was used. Paci et al (2010) did point out that the PEDro scale penalises for expectations which cannot be realistically met in neglect/HI research. For example, they refer to the difficulties in blinding patients and staff in neglect conditions and recruiting a large enough sample size for RCT's. They report that the recruitment process is fraught with problems especially in longitudinal designs, where the attrition rate is higher the longer the duration of the study.

2.7. Overall summary and conclusion

Despite significant disparity in findings between the 13 critically reviewed studies, there is substantial evidence that patients diagnosed with HI after stroke (~ 1 to 8 weeks) tend to underscore those without HI on global functioning assessment tools such as the BI and the FIM. Compared to their counterparts, HI+ patients score significantly less on motor components but attain comparable scores on cognitive and social domains in the acute phase (~

3 months after stroke). However, these results need to be validated by means of specific motor and cognitive measures other than sub-scales of the FIM which was frequently employed in past designs.

Initial functioning levels were lower in patients with HI, which is indicative of greater stroke severity, and conversely higher levels of physical and cognitive impairment relative to patients without HI. Data from community follow-up studies was also to be scarce. Probably, this reflects the practical difficulties and added financial cost incurred in sustaining serial, longitudinal research across acute and community research settings - wherein professional and resource consumption are expected to be very high. Nevertheless, the paucity of information implies that the impact of HI on functional ability, the value of longer-term rehabilitation and the impact of caring for a patient with HI in the community are relatively unknown in the longer term (> 3 months).

This review highlighted the importance of choosing strategic observation points consistent with the average natural tendencies for change in the amount and rate of progress pattern with time since stroke. The beginning and end of the study for all participants should be relatively fixed to enhance consistency in the data e.g. baseline measurement within 7 days of stoke onset. Enhanced or targeted HI intervention in the form of compensatory techniques was provided in four studies (Kalra et al 1997, Paolucci et al 1996, Katz et al 1999, Paolucci et al 2001). Based on their results functional gains tended not to be maintained after the cessation of treatment among HI+ patients. However, the findings need to be validated in more robust research studies which include community follow-up in the design.

In regard to the relationship of HI with functional change, the findings were varied and inconsistent, both when HI was modelled on its own or with other potential explanatory factors e.g. cognitive and motor function. This is not entirely surprising, given the significant differences and design limitations across studies included in the current review.

Table 2.5

Type of predictors modelled by nine of the reviewed studies, results and prediction direction

Evaluated predictor factors	Study identification according to reviewed order in text								
	1	2	3	4	5	6	7	10	13
Age (-ve)	x	Y	-	-	-	y	x	-	x
Attention sustained (+ve)	-	-	-	y	-	-	-	-	-
Balance (+ve)	x	-	-	-	-	-	-	y	-
Carer burden[3]	-	-	-	y	-	-	-	-	-
Cognition (+ve)	x	-	-	-	-	-	x	y	-
Continence (-ve)									x
Dis/destination	-	-	x	-	-	-	-	-	-
Educational level	-	-	x	-	-	-	x	-	-
Family support	-	-	x	-	-	-	-	-	-
FIM cog/social (+ve)	-	-	-	-	y	-	-	-	x
FIM motor[4]	-	-	-	-	x	-	x	-	y, y, x
Gender	x	X	-	-	-	x	x	-	-
Heart disease (-ve)	-	-	y	-	-	-	-	-	-
HI levels [1] (-ve)	y	X	y	y	y	x	y	y	y
Initial function (+ve)	-	Y	-		y	y	-	-	-
Lesion site	-	-	-	y		x	-	-	-
Lesion type	-	-	y	-	-	-	-	-	-
LOS (+ve)	-	Y	-	-	-	-	-	-	-
Muscle strength	x	-	-	-	-	-	-	-	-
Perception	x	-	-	-	-	-	-	x	-
Pre-stroke function	x	-	x	-	-	-	x	-	-
Processing speed (+ve)	-	-	-	y	-	-	-	-	-
Risk factors[2]	-	X	-	-	-	x	-	-	-
Stroke severity (-ve)	-	-	y	-	-	-	-	-	-
Tactile sensation	-	-	-	-	-	-	-	x	-
Time to 1st obs[5]	-	-	-	-	-	-	x	-	-

"y" = predictive, "x" = not predictive, "-" = not modelled, [1]Gillen and Katz found HI to be an independent predictor, i.e. explained >10% of the outcome, [2] predictive in the presence of age, [3] Higher burden in HI+ group, [5] time to 1st observations (23 days since stroke), [4] positive predictors self-care & transfers, negative for locomotion

Study key: (1) Kalra et al 1997, (2) Ring et al 1997, (3) Paolucci et al 2001, (4) Buxbaum et al 2004, (5) Gillen et al 2005, (6) Odell et al 2005, (7) Di Monaco et al 2011, (10) Katz et al 1999, (13) Nijboer et al 2013.

Table 2.5 summarises the modelling results (predictive versus non-predictive at α=0.05, 95% CI) from nine studies which evaluated the impact of HI and other predictor variables on functional ability by means of multivariate regression modelling and random coefficient analysis in Nijboer et al (2013). Overall the majority of predictor factors were modelled twice and often yielded contradictory results (e.g. FIM cognitive and FIM motor sub-scales, age, balance and lesion site); some were modelled only once. Based on the modelling results in table 5.2 and the reviewed quality of the studies, no firm conclusion could be inferred on the predictive strength or explanatory contribution of HI status to functional ability over time since stroke either independently or with other factors. Subsequently, its relationship with functional change remains unknown in the literature. In addition, this status quo is not helped by findings from isolated past studies that anosognosia (denial of illness state) is a more powerful predictor of functional outcome when modelled with HI (Gialanella and Mattioli 1992, Pedersen et al 1996, Jehkonen et al 2001, Vossel et al 2012). Anosognosia frequently occurs with HI; 47% and 57% were reported by Hartman-Maeir et al (2003) and Berti et al (2005) respectively. This finding was supported by one of the reviewed studies (Buxbaum et al 2004) but anosognosia was not modelled with HI in the same study.

In order to improve consistency of modelled results in HI studies, important confounding factors such as time since stroke, stroke severity and age should be included in future designs so that their effect can be accounted for. To this end, stroke severity and time since stroke were rarely included in the evaluated models. Furthermore, data analysis methods have to be optimised so that the hierarchical structure is preserved and the inherent dependency in the data is accounted for. The only study to use advanced methods of data analysis was Nijboer et al (2013). In their case, the random coefficient analysis allowed for variations in the natural progress pattern over time, which also increases stability and accuracy of regression coefficient estimates (Singer and Willet 2003, Twisk 2006, Snijders and Bosker 2012). However, there were significant limitations in the design by Nijboer et al (2013) which precludes reliable conclusions from their findings. The limitations included a generic stroke sample which would tend to dilute the effects of HI in a non-homogenous (RHS) population and initiation of the study after prolonged in-patient care (55 to 63 days) of relatively young (mean 57 years) and moderately abled patients with low risk of co-morbidity. In relation to this subject, patients with severe stroke tended to be excluded from the 13 reviewed studies. Future studies need to include a full stroke severity range and also HI to enhance consistency and generalizability of the findings.

Another reason for disparity across findings was differences in the diagnostic tools used to assess and measure HI. In particular, the erroneous assumption that pen and paper tasks such as those included in the BIT are sensitive to specific types of HI (such as visual-spatial). Pending the availability of more specific tools, future studies should acknowledge the shortcomings of assessments for HI and follow the recommended assessment guidelines i.e. a standardised battery of tests which provides an overall profile and severity level (Jehkonen et al 2006, Lopes et al 2007, Singh-Curry & Husain 2010).

To summarise, a new project was undertaken to bridge existing knowledge gaps and study limitations as illustrated in this chapter. The aim of this PhD project was to estimate the magnitude of differences between HI±

groups and assess the impact of early HI status on functional ability over time under various modelled conditions described in the Methods Chapter (3).

Specifically, the design of the PhD study followed the recommendations and guidelines highlighted from this critical literature review in order to enhance weaker aspects found in past designs. These included sample size and selection criteria, position and number of observation points and time to 1st observation (since stroke). The choice of factors to be measured and modelled was guided by indicative findings from past studies and the stroke literature. However, the aim of this study was not to isolate the smallest combination of factors possible that would predict a future outcome, in as much as to understand by studying in depth the associative relationship of early HI status with change in functional ability over time. Therefore, important potential confounding factors (stroke severity, age and time since stroke) were selected for inclusion in the present study. As per expert recommendation and findings from the review, a standardised test battery for HI was used for identification and assessment purposes and standardised tools were used to assess functional components evaluated in the study. Statistical data analysis was optimised by means of multilevel modelling methods appropriate for the design and the research question (which are further justified in the next chapter).

The research question was:

"What is the relationship between early***** HI status (HI±) and functional change in the 1st six months after right hemisphere stroke?"

*****(within 7 days since stroke)

2.8. Aims and objectives of the PhD study

The main aim of the PhD project was to inform the evidence-base supporting early predictive factors of functional ability in RHS patients; more specifically the likely predictive and explanatory importance of HI in relation to progress (functional change) of RHS patients in the first six months after stroke. The reason for the 6 month duration being practicality (as in time constraints imposed by the PhD) but also the known stroke recovery trend which tends to slow down in terms of measureable change after six months post stroke onset (Kwakkel et al 2004, Langhorne et al 2011).

The research objectives were;

1. To measure and compare the overall functional outcomes of patients with and without HI in the first six months since stroke.
2. To measure and compare the outcomes of patients with and without HI on clinical, patient and care process factors (e.g. cognitive function, self-efficacy and continence status) also associated with HI and/or functional ability in the first six months after stroke.
3. To study in depth the dynamic relationship between early HI status and functional progress (change over time) when other factors, (identified in research objective two) are also taken into account.

The research objectives are further elaborated on in chapter three which contains information in relation to planning, design and implementation of the research project.

Chapter 3 – Methods

Chapter Three

Methods

3.0. Introduction

This chapter describes in detail the design and data collection methods used in this PhD project to address the research question and objectives identified in the previous chapter. For convenience, they are restated;

Research question

"What is the relationship between early ***** *HI status (HI±) and functional change in the 1st six months after right hemisphere stroke?"*

******(within 7 days since stroke)*

Research Objectives

1. To measure and compare the overall functional outcomes of HI± patients at various time points in the first six months after stroke.
2. To measure and compare the outcomes of HI± patient groups on i) clinical, ii) patient and iii) care process factors (e.g. motor function, continence status, nutrition) associated with HI and functional ability in the first six months after stroke. These factors are specified in Table 3.1 (page 100) under these three main categories BUT the grouping assigned is purely for ease of description and to aid clarity.
3. To study in depth the dynamic relationship between early HI status and functional recovery (change over time); when other factors (identified in research objective two) were also taken into account. This is important because HI is only one of several motor and cognitive-behavioural impairments which usually accompany the sequel of RHS stroke. The use of multi-level modelling results will enable a more comprehensive

answer of the research question than gained in past studies in which fewer factors were considered.

The **contents** of this chapter are organised in five sections:

Section one contains details of the study design, the population studied, selection criteria, identification of the primary and secondary outcomes, sample size and specification of observation time-points.

Section two contains measurement details including the rationale behind the assessment tools specifically employed in the study.

Section three Handling of missing data and extreme values.

Section four contains statistical information on the data analysis procedures undertaken to answer the research question and objectives. This includes a basic description of multilevel modelling principles and techniques used to model the data collected for the study.

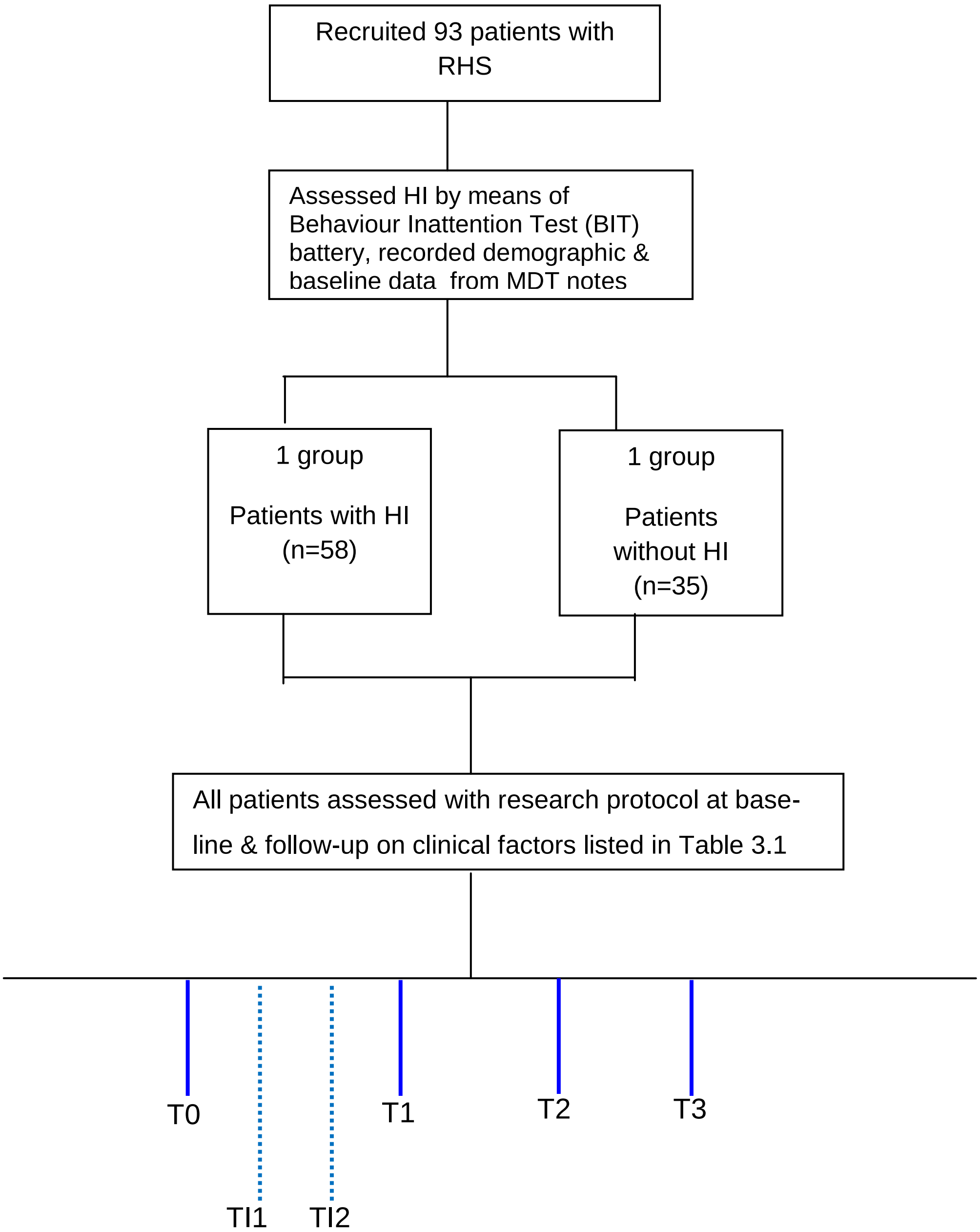
Section five highlights the main ethical issues arising from the study and how these were managed by the researcher.

3.1. Section one *– Study Design*

Overview of the design

This section presents an overview of the design which is illustrated in Diagram 3.1 and discussed in the text. A cohort of patients with RHS (n=93) was recruited within seven days after stroke (T0 – time-point 0) by the researcher from two stroke units and followed up at discharge (T1 – time-point 1), then again at 6 weeks (45 days) into community living, including residential and nursing institutions (T2 – time-point 2), and finally at 6 months post-stroke onset (T3 – time-point 3).

Diagram 3.1 Overview of the design



Abbreviation key: HI+ and HI- (with & without hemi-inattention respectively), T0 = baseline (assessment within 7 days since stroke for all patients), T1 = discharge (naturally time-variable for each patient; range (4 to 182 days), T2 = 45 days post-discharge (approximately 6 weeks), also time variable (T1 dependent), T3 = 6 months since stroke for all patients. TI1 & TI2 = interim observation points for patients affected by severe stroke positioned at 30 and 60 days between T0-T1 (see comments in text).

Those patients who were severely affected by stroke were also followed up at interim observation periods (TI1 & TI2) positioned 30 and 60 days since stroke (see justification of the design/section 3.1.1) between admission and discharge. The researcher assessed all 93 patients at baseline and follow-up (T0 to T3) with a pre-determined research assessment protocol and extracted relevant demographic and care process data from multi-disciplinary team records (e.g. initial stroke severity, carer status, nutrition and continence statuses, lesion type and site). The assessment protocol consisted of validated measurement tools which assessed specific clinical and patient factors, such as HI levels, self-efficacy, cognitive function, motor function and overall functional ability level. A complete list of factors is available in Table 3.1 (page 100); they are discussed later in this section.

The subjects were grouped into two according to the presence or absence of clinically significant HI severity levels as diagnosed by the Behaviour Inattention Test (BIT) (Wilson et al 1987) conventional section described in section 3.2.2.2. The cut-off score for clinically abnormal versus normal HI levels on the BIT scale is 129; the range is 0 to 146 and the higher the score the less severe the HI (Wilson et al 1987). Fifty-eight patients scored 0 to 128 and were allocated to the HI+ group (with HI), 35 patients scored 129 to 146 and were assigned to the HI- group (without HI). Thirty-three patients (23 HI+ & 10 HI-) spent over 30 days on the stroke unit, consequently they were at high risk of developing abnormal levels of anxiety and depression (Robinson 2003). As per NICE stroke guidelines (2013), these 33 patients were assessed with The Hospital and Depression (HADS) scale so that the potential impact of anxiety and depression on the results could be ruled out or accounted for. The study duration was six months for all participants.

Further justification of the design follows in subsequent sections.

3.1.1. *Study population*

The study population consisted of a cohort (n=93) of RHS patients (58 HI+, 35 HI-), 18 years or older with first or subsequent stroke, of haemorrhage or thrombotic origin. The sample was recruited from two in-patient stroke units although formal approval was initially secured from three stroke units. This reduction in the number of units from which recruitment could be made had implications for sample size and duration of recruitment which are further discussed in subsequent chapters. Recruitment took place over 17 months during which eligible patients with a range of mild to very severe stroke were recruited. Further details on demographics are included in Chapter four.

3.1.2. Sample size estimation

Required sample size was estimated from that in previous stroke studies by Kwakkel et al (2006) (n=101), Ekstam et al (2007) (n=34) and Nijboer et al (2013) (n=184), all of whom <u>employed a serial design and mixed (MLM) methods of data analysis as in this PhD study</u> (refer to Appendix A for more detail on each study). The study by Ekstam et al (2007) was the closest match in terms of the research question, objectives and statistical model variant. Ekstam and colleagues reported clinical and statistically significant findings relevant to functional ability in a heterogeneous elderly stroke patient sample (n=34) over a one year follow-up period. Ekstam et al (2007) found that cognitive awareness of disability was related to ADL motor ($p<0.001$), cognitive ability ($p<0.001$) and time since stroke (linear $p<0.001$, quadratic $p<0.0034$).

These findings suggested that their sample size was sufficiently powered to detect significant changes in function over time.

In addition, required sample size was informed by computer simulation findings published by Bell et al (2010). The authors researched the impact of small cluster size in two level models with binary and continuous predictors in 5,760 different simulated modelling conditions. Bell and colleagues reported that a minimum of 30 units per level sufficiently controlled for type 1 error when less than six predictors were included and still achieved a statistical power of 0.8, 0.05 significance level and, 95% confidence interval (CI). These findings support those from previous computer simulations by Mass and Hox (2004) and the sample size used in Ekstam et al (2007).

Based on all the evidence available and the observation that the disparity between HI± groups tended to be large and statistically significant in past reviewed studies (e.g. Cherney et al 2001, Di Monaco et al 2011 and Nijboer et al 2013) - the sample size in Ekstam et al (2007) was increased to 60 (30 HI+, 30 HI-) to increase likelihood of detecting group differences. Another 20% extra were added to account for attrition rate in serial longitudinal studies (Di Carlo et al 2003). This gave a minimum required sample size of 72; 36 HI+, 36 HI- which was deemed feasible to recruit over one year, assuming 100% occupancy of participating stroke units at the time of recruitment. In terms of power, the larger the sample the better, so up to 100 participants was desirable.

3.1.3. Selection criteria

In contrast to past designs, patients with severe and very severe stroke were included which enhanced representation of the sampled population and generalisation of important findings.

Inclusion criteria

- Diagnosis of first or consecutive RHS stroke confirmed by magnetic resonance imaging (MRI) or computerized axial tomography (CAT) scan.
- In line with research ethics, eligible patients needed to be able to provide formal written consent prior to enrollment in the study. For severely affected patients the enrollment period was extended up to one month since stroke which coincided with interim observation point (TI1). If able to consent, they were then enrolled and assessed with the research protocol. All 93 patients provided written consent by TI1 (please also see Ethical Issues in section 3.5).
- Patients were independent with ADL tasks prior to stroke, including with assistance of family or residential home care community support services. This was important to maintain sample homogeneity and reduce sources of bias. Prior dependency would likely imply other variables such as dementia and physical frailty which might have affected assessments and also consent.
- Patients needed to have daily English language conversation skills to follow the assessment process.

Exclusion criteria

- Patients with sub-arachnoid hemorrhage, brain tumor, actively receiving treatment for cancers e.g. radio- or chemo- therapy when the stroke occurred), advanced renal failure (as in needing dialysis at the time of stroke), significant visual field loss e.g. due to macular degeneration which would interfere with formal assessment. These factors were likely to confound results by accentuating stroke symptomology which would threaten sample homogeneity.

- Patients previously living in nursing institutions who were bed or chair bound prior to the stroke as this would have confound the results by introducing limitations on functional measures which had nothing to do with stroke.

3.1.4. Frequency of observation points

In line with the requirements of the research question, a serial, comparative group design was justified in order to measure change in progress (within and between) patient groups (HI±) over time. This was important because it allowed different sources of variance to be identified, thereby increasing insight into the data and the extent to which the research question could be answered.

Baseline measures

As per recommendations in the literature review (Ch.2), baseline measures (T0) were taken as early as practically possible, working single-handedly i.e. within seven days since stroke for all but five severely impaired patients who were fully assessed 1st time at TI1 (refer to interim observation points). This minimised the potential confounding effect of spontaneous recovery on functional gain (Kwakkel et al 2004, Bayona et al 2005, Hermann and Chopp 2012).

Follow-up observation points

The number and frequency of follow-up observations was based on (quadratic) stroke functional recovery trends identified in the literature review (Jorgensen et al 1995, Kwakkel et al 2004 and 2006, Langhorne et al 2011). On average, significant functional change was likely to occur during the first 6-12 weeks since stroke, followed by a gradual tapering off around the six month period (albeit considerable variation was expected according to Langhorne et al 2011, Craig et al 2011 and further supported by reports from past reviewed studies (Katz et al 1999, Cherney et al 2001, Stein et al 2009).

Therefore to best capture natural variation patterns in functional ability, follow-up was conducted at discharge (T1) (which is an individual time-variant; range 4 to 182 days), six week post-discharge (T2) which marked the next prominent change in the functional recovery pattern, and six months (T3) since stroke. T3 was fixed for all the patients. Another pertinent reason for the choice of follow-up assessment points is the fact that the research question required comparison of groups at key time-points. It also marked the end of the research for two reasons – PhD time constraints, resources and a tendency for a natural plateau (slowing down) of functional recovery albeit with considerable individual variation around this point (Craig et al 2011, Korner-Bitensky 2012).

Interim time-points

In addition to the standard time-points (T0 to T3), severely cognitive impaired patients who could not be thoroughly assessed with the research protocol at baseline (e.g. due to fluctuating levels of alertness) and were also likely to need longer stroke unit care than milder patients were specifically assessed at interim time-points set at 30 and 60 days since stroke (TI1 & TI2). This complex but important modification in the design allowed for recruitment and retention of an all-inclusive stroke severity sample but also for the fact that some patients were exposed to longer stroke unit context of care which may have impacted on their outcome e.g. the amount of therapeutic intervention received which was a potential predictor variable. It also captured more of the individual variation in progress patterns for severely impaired patients; details of which are relatively unknown but relevant to the research question (in terms of explaining associative-functional relationships in the data).

The researcher acknowledges that in past studies variation in assessment time was statistically problematic and limited comparison of the results across studies. However, advanced statistics such as multi-level modelling methods have now made it possible to model natural, individual population variation across time without necessarily jeopardising validiy of the results. For this and other reason discussed later on in the chapter, multilevel modelling methods were incorporated within the design. At this point, it is also worth stating that variation in assessment times was not only consistent with the pragmatic nature of the research but also accommodated ‘real world’ situations. These imposed different demands on the data collection process such as, knowing sufficiently ahead when the patient was likely to be discharged and the destination (home versus intermediate or institution care) – factors which are not easily predictable in stroke (Rittman et al 2004, Cott et al 2007, Portelli et al 2005, Ilse et al 2008, Stein et al 2009, Cowman et al 2010).

3.1.5. Rationale for the inclusion of specific factors in the design

Based on the results and indications from the literature review (Ch.2), 19 factors listed in Table 3.1 were included in the design – their inclusion was further supported by the author’s clinical experience and observations in the field (Stein et al 2009).

For convenience, the 19 factors were grouped under three headings (clinical, patient and care-process) in order to facilitate clarity of description. However, it is acknowledged that factors such as continence or nutrition status could easily be grouped under clinical, patient or care-process due to the degree of overlap between groups.

Table 3.1 Factors evaluated in the PhD study (new ones are in italics).

Clinical	**Patient**	**Care process**
Stroke severity	Age	*Nutrition status*
Lesion site	Gender	*Continence status*
Lesion type	*T0/HI status*	Duration of in-patient stay (LOS)
Motor (balance and posture)	*Self-efficacy*	Discharge destination
Basic cognition	*Denial of illness*	
Time post-stroke	*T0/Carer status*	
Executive function – *task processing speed*	Overall functional ability	
Number of pre-recorded face to face therapist patient contacts		
N.B. Factors not measured or modelled in past critically reviewed studies but measured in this study are in italics in the highlighted cells.		

The following 10 factors were included in past studies but for reasons discussed in Ch.2/Table 2.5 are in need of revalidation and so incorporated into this study.

1. Age
2. Gender
3. Stroke severity,
4. Lesion site
5. Lesion type,
6. Motor skills (balance & postural),
7. Cognitive ability (global)
8. Duration of in-patient stay
9. Overall functional ability
10. Discharge destination (home or intermediate or institution care)

The other nine factors were new additions; these are shown in italics in highlighted cells/Table 3.1 and are further defined in text.

1. *Baseline HI status* (which is the subject of interest in this PhD project)

2. *Nutrition status*
3. *Continence status*
4. *Carer status*
5. *Higher executive function (component - task processing speed)*
6. *Self-efficacy levels*
7. *Denial status*
8. *Number of pre-recorded face to face therapy contacts*
9. *Time since stroke*.

Time showed an independent predictive positive relationship with functional ability in the acute phase (≤ 3 months since stroke) in studies by Kollen et al (2005) and Kwakkel et al (2006).

Poor nutrition was reportedly negatively associated with functional outcome in generic stroke and RHS/HI+ patient samples (Choy and Bhalla 1996, Dennis et al 2005, Saxena et al 2007, Theurer et al 2008). These findings are corroborated with clinical observations of inadequate nutrition intake in patients with HI documented by Robertson and Halligan (1999), Mark (2003) and Parton et al (2004). Together with the tendency for reduced insight and awareness in RHS patients (Cherney 2006, Besharati et al 2014), poor nutrition was expected to increase the risk of malnutrition and potential impact on functional recovery - hence it made sense to group nutrition status under 'care process'. Its effect was modelled along with other factors in the study.

Continence status was not modelled in RHS homogeneous past patient samples despite its established negative predictive influence on functional independence (Pettersen et al 2002, Harari et al 2003, Meijer et al 2003). The care process is one of several documented factors which are thought to contribute to increased susceptibility of stroke patients to continence dysfunction (Wagg et al 2005, Poisson et al 2010, National Sentinel Stroke Audit ISWP 2012); hence it was grouped under care-process in Table 3.1. Continence status (bladder and bowel) were modelled in this PhD study.

Self-efficacy conceptually refers to the individual's perceived ability to cope with unprecedented life changing events such as stroke and their confidence in reaching valued goals (Bandura 1977). Findings from systematic reviews support a positive association between functional change and self-efficacy levels over time (Marks et al 2005, Jones and Riazi 2011). Korpershoek et al (2011) in their review reported a positive association between self-efficacy levels and mobility, activities of daily living and quality of life and a negative association with depression. Given the reduced awareness and insight reported in RHS patients (Katz et al 2001, Cherney 2006), self-efficacy was relevant to the study, it was modelled with other factors.

Anosognosia is an umbrella term applied to partial or complete lack of awareness, and is synonymously used with denial of illness (Orfei et al 2007, Jenkinson et al 2010). In this study "denial status" denotes the condition, which was reportedly positively associated with RHS and HI in past studies and reviews (Katz et al 2001, Cherney 2006, Telford et al 2006, Buxbaum et al 2004, Barrett et al 2006, Livneh 2009). Based on the strength of evidence in the literature, denial status was included and modelled in the MLM analysis.

Amount of therapy - The number of physiotherapy, occupational and speech/language therapy (face to face) contacts pre-recorded by therapists and their assistants in the MDT notes was counted at discharge. The data was analysed and modelled as a potential explanatory factor of functional change.

Its inclusion was supported by evidence of a positive correlation with functional outcome in results by Bode et al (2004), Kwakkel et al (2004), Grasel and Biehler (2005). That being said, the optimal amount, quality and intensity needed for effective rehabilitation gains are debated in the literature (RCP 2012). The general consensus is that quality and quantity (frequency and amount) of therapy are important (Young and Forster 2007, Karges and Smallfield 2009, Foley et al 2012, Wang et al 2013). However, in the current study it was not practical or realistic to extract additional information (e.g. to do with therapy quality) from the in-patient and community data available to the researcher (Issues with data collection are discussed in Ch.6).

Carer status refers to the availability versus absence of an informal carer identified by discharge. Conflicting evidence supported the inclusion of this factor in the design in that past studies report both a positive and negative association of carer status with functional outcome (Norris et al 1990, Glass et al 1993**,** Kwakkel et al 1996, Gottlieb et al 2001, Buxbaum et al 2004). However, whether carer status expedites change in functional ability over time and its relative important in HI conditions remains unknown. Carer status was modelled in the study and grouped under patient factors.

3.1.6. Specification of the primary and secondary outcomes

In line with requirements of the research question, the primary outcome was change in functional ability between T0 and T3. Functional ability was conceptually defined as relevant activities of daily living (ADL) recognised by the International Classification of Functioning and Disability known as the ICF (WHO 2001). ADL include (but are not limited) to mobility e.g. ambulation, toileting, dressing, eating and drinking, problem solving, communication and social interaction. Functional ability was assessed by a validated scale - The Extended Barthel Index (EBI) (Prosiegel et al 1996) evaluated in section 3.2.

Similar to past designs from critically reviewed studies (e.g. Kalra et al 1997 and Paolucci et al 2001), the secondary outcomes were mortality between T0 and T3 and discharge destination outcome i.e. community residence (home or institution - nursing or residential).

3.2. Section two – *Data recording and assessment tools*

This section covers data recording methods and assessment tools. For convenience, psychometric data (e.g. reliability and validity of specific tools) are tabulated in Appendix A and referred to in text.

3.2.1. Data recording methods

Two methods were employed by the researcher - formal patient assessment by means of validated measurement tools and data extraction (pre-recorded by MDT professionals e.g. neurologist, nursing, dietician, physiotherapist and occupational therapist). Relevant formal approval was secured from the East Kent Hospitals Trust and South East Research Ethics Committee – the letter of approval is included in Appendix E, and further details of the ethics process is presented in section 3.5. Data collection details are summarised in Table 3.2 and further discussed in text.

With reference to Table 3.2 (p.105), factors assessed (measured) by the researcher are coded (**M),** data sourced from MDT documents coded **(E)** and assessment tools rated by patients are coded **(PR).** In addition**,** the frequency of observations is colour coded: coded **green** are observations taken at (T0, T1, T2 and T3), coded **yellow** at T0 only, **brown** at T1 and **grey** at (30 days since stroke).

Table 3.2 - Frequency of data recording, measuring tools and abbreviations by individual factor.

Clinical factors	Tool identification and Assessment method	Abbreviation & frequency of observation
Stroke type & lesion	M	x1
Stroke severity	National Institute of Health Stroke scale (E)	x1
Co-morbidity	(for description of sample purposes) (E)	x1
Functional ability	Extended Barthel Index (M)	4 x EBI
Hemi-inattention	Behavioural Inattention test (M)	4 x BIT
Postural control	Postural Assessment scale for Stroke (M)	4 x PASS
Global cognitive ability	Middlesex Elderly Assessment of Mental State (M)	4 x MEAMS
Cognitive/executive	Trail Making test (M)	4 x TMT
Therapy contacts	Number of contacts in MDT & community notes (E)	x 4
Patient factors		
Age & gender	E	x1
Informal carer status	E	x 1
Self-efficacy	General Self-efficacy Scale (PR)	4 x GSE
Denial of illness/status	Set of questions (interview) (M)	x 4
Anxiety & depression	Hospital Anxiety & Depression Scale (PR)	x1 HADS
Care/process factors		
Length in-patient stay	Calculated from MDT record (E)	x 1
Continence	Assessed &/or extracted as part of the EBI (M/ E)	x 4
Nutrition	Malnutrition Universal Screening Tool MUST (E)	x 1MUST
Discharge destination	E	x 1

Colour code:

T0 T1 T0, T1, T2, T3 screened once at 30 days since stroke, for those patients receiving stroke unit rehabilitation at the time.

Abbreviations: T0 = baseline, T1 = discharge, T2 = 6 weeks post discharge, T3 = 6 months since stroke, E = Extracted from MDT notes by researcher, M = measured by researcher, PR = patient rated. N.B. Patient assessments coded green were repeated at interim time-points TI1 &/or TI2 for patients with prolonged stroke unit rehabilitation due to e.g. severe stroke impairment.

From Table 3.2, it can be observed that the researcher formally measured <u>seven factors</u> (coded **M**) at T0, T1, T2 & T3 for all 93 patients. In addition, 21 patients were measured with the whole protocol at interim observation point one (TI1) and 14 at interim observation points one and two (TI1, TI2) - which for clarity are omitted from Table 3.2. The researcher also assessed 33 patients (23 HI+, 10 HI-) who were at risk of increased anxiety and depression levels due to relatively long in-patient stays (> 30 days) on the stroke unit (Aben et al 2003, Robinson 2003). Data for another nine factors was extracted from MDT documents by the researcher (coded **E**). Data from two patient rated **(PR)** assessments (the GSE and HADS) was collected by the researcher as part of the research protocol.

The rationale for the choice of assessment tools employed in the design follows in the next section

3.2.2 Selection of assessment tools – general considerations

The success of this PhD project depended heavily on the validity of assessment tools and their administration method. Where possible, selected assessment tools conformed to the minimum psychometric criteria (appropriateness, reliability, validity and response to change) recommended in the literature (WHO 2001, Barak and Duncan 2006, McDowell 2006, National Clinical Guidelines for Stroke ISWP 2008 and 2012, Salter et al 2010). The combined guidelines and recommendations drawn upon in this study are presented in Table 3.3 (p.107); they were used to critically review individual tools in section 3.2.3.

In addition, there were important practical requirements that underscored the selection of assessment tools. That is, the tools had to be feasible such that effort and disruption to clinical staff, stroke unit routines, patient and relatives in the community was kept to a minimum. For example, any equipment required had to be easy to transport and set-up at different settings. Practicality and judgement were informed on relevant clinical experience of the researcher in the field (as described in Chapter one).

Table 3.3 Literature recommendations - minimum psychometric tool requirements

Criterion	Definition	Standard
Appropriateness	Overall suitability/match of the tool to the intended purpose and ease of use (Barak and Duncan 2006).	Accurate reflection of the factor being measured – in this case change in e.g. overall functional ability in the first six months after stroke.
Reliability	According to Barak and Duncan (2006), it is the proportion of the score that genuinely contains information about the attribute of interest versus measurement error i.e. the larger the error the less reliable the instrument. *Conventionally evaluated in 3 ways* - Test re-test & inter-observer (rater) & internal consistency.	Recommended tests and scales (Fitzpatrick et al 1998, Andresen et al 2000, Walker and Almond 2010) - Scale for coefficient α (Cronbach's α), test/retest and inter-rater reliability is 0.8+ is good, 0.7 to 0.79 is acceptable, 0.6* to 0.69 is weak, < 0.6 unacceptable *acceptable levels of agreement vary +0.1 between cited researchers.
Validity	Capacity of an instrument to measure what it is intended to and presumed to measure (Barak and Duncan 2006). Many types of validity were referred to in the literature e.g. face, content, discriminative, convergent and predictive (McDowell 2006, Salter et al 2010). Construct and predictive validity are mostly researched. .	Concurrent validity – correlation tests interpreted as 0.8+ is good, 0.7 to 0.79 is acceptable, 0.6* to 0.69 is weak, < 0.6 unacceptable (Walker & Almond 2010)
Responsiveness to change	Responsiveness refers to sensitivity to changes within patients over time (Salter et al 2005, McDowell 2006); an essential property to the success of the study which needed to capture change within and between patient groups (HI+/-) over time.	Evaluated according to recommendations by Barak and Duncan (2006) and Almond and Walker (2010) -. correlation with other scores, change scores and standardised effect sizes; <0.5 = small; 0.5 – 0.8 = moderate ≥0.8 = large
Floor and ceiling effects	Floor and ceiling effects were important since they indicated upper and lower limits beyond which change was no longer detectable by the measure. This would have implications for the interpretation of results especially in very mild and severe patients.	Conventionally adequate when ≤ 20% of patients were reported to have reached the minimum (floor) or maximum (ceiling) score of the measuring tool under evaluation (Salter et al 2010).
Precision	Number of gradations within the measurement. E.g. Yes/no response versus a 64 point scale	Depends on the precision required – the finer the better for evaluation and prediction purposes.

From an ethical perspective, acceptability of the assessment task to the patient was important to minimise the likelihood of associated burden or fatigue setting in especially in patients with severe stroke who were at increased risk. Therefore cognitive difficulty levels, attention and concentration were taken into consideration in the decision making process. Theoretically, such considerations also facilitate assessment completion and minimise the prospect of missing data. From the researcher's perspective, fatigue, ease of scoring system, interpretation, availability and cost of purchasing new assessment tools were taken into account.

This next section offers a review of the evidence that supported the inclusion of specific tools in the design. For convenience, the scale, range and additional information on individual tools are tabulated and placed in Appendix C.

3.2.2.1.

Assessment of functional ability (primary outcome) by the: Extended Barthel Index (EBI) - authors Prosiegel et al (1996).

Description - The EBI scale range is 0 to 64; 0 is the lowest and 64 the highest level of functional ability attainable. It consists of 16 items (15 derived from the Functional Instrumental Measure (FIM): 10 assess ADL activity limitations in eating, drinking, dressing, bathing, wheelchair to bed transfer, locomotion, stairs, toilet, bladder and bowel control; four assess aspects of cognitive functioning, namely problem solving, orientation, memory and learning; and two assess communication and social interaction. The patient demonstrated the skills which were rated by the researcher on an ordinal scale from 0 to 4, depending on the level of assistance required and individual task completion time (see instructions in Appendix B). Continence status on the EBI was rated by the researcher from observation and nursing records taken on a 24-hour basis.

Historically, the EBI was developed to address practical and theoretical limitations in the construct validity of its predecessor Barthel Index versions (e.g. Mahoney and Barthel 1965 and Granger et al 1981) and the FIM (Granger et al 1986); both scales were used in past reviewed studies (e.g. Paolucci et al 1996, Kalra et al 1997, Stein et al 2009).

Traditionally, the BI versions cited tend to be used in stroke clinical research trials, especially in the UK, despite well documented, significant limitations and bias towards physical (as opposed to cognitive and social-communicative) measurement of function and reduced sensitivity to change with time since stroke (Duncan et al 2000, McDowell 2006, Salter et al 2010). That being said, the EBI is a validated measure (refer to pychometric properties further on) and has been used in continental stroke studies largely because of its greater coverage and assessment of core functional components (including cognitive, social and communication) not assessed by predecessor BI verions, easier scoring method, reduced training time compared to the FIM and standardisation of time taken to compete functional tasks (not accounted for in previous BI versions and the FIM) (Proseigel et al 1996, Marolf et al 1996, Jansa et al 2004, Mcdowell 2006, Latham et al 2009). Therefore it was more soothed for use in the current study - considering its aims and broader ICF definition of function (WHO 2001) than the FIM or popular versions of the BI. That being said, participatory measures such as The Frenchay Activities Index (FAI) (Holbrook and Skilbeck 1983) were inappropriate because they do not assess activities typically undertaken in the acute stroke recovery phase (first 3 to 6 months) which are the focus of the current PhD study.

In addition, the EBI was found to be a suitable tool for use in community settings up to one year after stroke and sensitive to change over time (Keller et al 2003, Harscher et al 2006, Geschwinder et al 2007 and Schuster et al 2012) - both features were important requirments of all assessment tools used in the design of the PhD study and especially the primary outcome measure of the dependent variable (change in functional ability over time).

Like all existing functional overall scales, the EBI has some limitations, the most important being the lack of established cut-off values for low, moderate and high functioning patients. For this reason, percentiles (25^{th}, 50^{th} and 75^{th}) were used in this study for descriptive purposes. Another limitation is that initial training is required (Latham et al 2009) (although less in comparison to the FIM). The EBI is not a comprehensive measure of participatory activity (but this is not the focus of the study). Lastly, comparison of results with past studies which used the BI or FIM maybe limited. Although not a limitation as such, considerable observation and assessment time are required to complete the EBI scale especially in patients with severe stroke and/or cognitive impairment. That is, completion time depended on the level and type of impairments present at assessment time which ranged from ~30 to 120 minutes (over several observations).

Psychometric properties - Jansa et al (2004) conducted factor analysis on pooled EBI data from 33 stroke patients taken at three observations. Their findings indicated a reliable, two dimensional scale (cognitive-communication and physical) in terms of internal consistency, with Cronbach's α as: 0.897, 0.934 and 0.948 at 1, 3 and 6 weeks after stroke respectively. These values are well within the recommended guidelines (see Table 3.3). Their results were supported by those from Jorger et al (2001) who assessed a larger sample (n=743) of neurological patients with the EBI, at two time-points (admission to and discharge from) rehabilitation centres in Switzerland. Since the EBI is not unidimensional the summation of individual scores into a total score may misrepresent the patient's true functional ability, which was taken into consideration when interpreting results. Findings from factor analysis by Jansa et al (2004) indicated that the EBI was more weighted towards physical (eigenvalue 8.24) than cognitive-social-communicative (eigenvalue 2.75) which was also taken into account when interpreting the results.

Concurrent validity of the EBI was supported against the Fugl-Meyer Motor Impairment scale ($p = 0.1$ to 0.001) and Self-Assessment scale ($p < 0.001$) (Jansa et al 2004). Weimar et al (2002) reported ceiling effects in the EBI scale for very high functioning neurological patients (n=4262) over a one-year follow-up period. However, this was surprising given the duration of time post-stroke and initial high functioning levels. To this end, Jansa and colleagues reported no ceiling effect in the first six weeks. Given the six-month duration of this PhD project, ceiling effects were unlikely to pose a major problem. In fact, the EBI showed acceptable floor and ceiling effects in the current study that were well within the conventional 20% cut-off acceptable limit in the literature (Mc Dowell 2006, Salter et al 2010). See also the discussion chapter (Ch6)/critical evaluation section 6.3.2.4.

Compared to the BI, the EBI showed greater responsiveness to change in the first six weeks (Jansa et al 2004) and 100 days after stroke (Weimar et al 2002). Marolf et al (1996) reported comparable responsiveness to change between the EBI and FIM, in 100 patients recovering from multiple sclerosis over a four week rehabilitation period; 29% & 32% changed their EBI and FIM score (improved) whereas 4% & 7% deteriorated on the measures respectively. Overall, the data suggested that sensitivity to change was in line with that of other functional rating scales frequently used in stroke research.

3.2.2.2.

Assessment of Hemi-inattention (HI levels) by the: Behavioral Inattention Test (BIT) authors Wilson et al (1997).

Description - The BIT (conventional section) measures HI severity on a continuum scale from the most profound (0) to least (146) level; 129 is the cut-off point between impaired (0 to 128) and healthy HI levels (129 to 146). The BIT battery consists of six pen and paper subtests: line crossing, letter cancellation, star cancellation, figure and shape copying, line-bisection, and representational drawing. The patient was required to cross out targets, bisect lines, copy figures and shapes and draw familiar objects from memory. The BIT is not a timed test. The percentage error of missed targets in the overall score provides a measure of HI severity (Stone et al 1987). Completion time depended on severity of impairments at assessment time ~ 15 to 30 minutes.

The BIT has been extensively used in stroke research on HI including six of the critically reviewed studies (e.g. Ring et al 1997, Stein et al 2009, Di Monaco et al 2011). Other assessment batteries were considered e.g. Catherine Bergago scale (CBS) (Azouvi et al 2003) and computerized virtual reality environment tests (Jannink et al 2008), however these were not practical to use in both acute and community settings and not appropriate for severely cognitively impaired patients recruited erly on in the PhD study. In comparison, the BIT was more feasible and practical to administer to severely ill patients in bed and in the community and was therefore the assessment of choice.

That being said, like all other assessments for HI, the BIT has some limitations. The most important being that it does not assess personal or extra-personal neglect and is not standardized with respect to time taken to compete individual tasks. This is a potential source of bias which was taken into account when interpreting the results. Another limitation is that it cannot differentiate between different forms of neglect/HI e.g. sensory-motor-spatial-perceptual because they are inherently used to varying degrees by the pen and paper tasks within the BIT (Plummer et al 2003, Singh-Curry and Husain 2010, Goedert et al 2012). This means that the results obtained from the BIT are diagnostic with respect to the presence/absence of HI but cannot be attributed to specific types of neglect – instead provide an overall severity index of the HI condition in different individuals.

Psychometric properties - Wilson et al (1987) and Halligan et al (1991) reported excellent test-retest (r = 0.83 & 0.89), intra-rater reliability (r = 0.99) and internal consistency (r=0.832) using Pearson correlation coefficient (r). Their results were recently supported by findings from Goedert et al (2012), who conducted factorial analysis on BIT data from 51 RHS patients (average age 70 years, 22 days post-stroke). Goedert and colleagues reported excellent reliability (α = 0.93), however the patient selection criteria were vague (stroke severity was not published). This would have enhanced interpretation of the results.

Construct validity - Hartman-Maier and Katz (1995) and Cassidy et al (1998) reported good convergent validity (r=0.77) with the ADL checklist and BI at one month after stroke (r = 0.642) respectively. The report was supported by regression results from Goedert et al (2012) indicating a significant relationship between BIT and BI scores (p<0.0001) when age and time since stroke were adjusted for. Concurrent validity with the CBS was insufficiently supported probably due to the small sample size (n=17) and highly selective sample of patients with mild HI (Luukkainen-Markkula et al 2011).

Linear regression results from Jehkonen et al (2000) supported HI as a predictor of poor functional outcomes in 50 RHS patients assessed by the BIT, 10 days since stroke. The result accounted for 73%, 64% and 61% of the total variance of the FAI (dependent variable) at 3, 6 and 12 months respectively. However, the sample was not representative of severe stroke patients and the data analysis methods did not account for auto-correlation arising from multiple observations taken from the same person. Potentially this may have affected significance levels and interpretation of the results from Jehkonen et al (2000) (Singer and Willett 2003, Snijders and Bosker 2012).

Responsiveness to change in the BIT was demonstrated in reviewed studies by Katz et al (1999), Stein et al (2009). Jehkonen et al (2000) reported that after six months since stroke the rate of change gradually diminished. However, there were significant design and methodological issues (e.g. poor sample representation and tight selection criteria) associated with studies by Katz et al (1999) and Stein et al (2009), which may have confounded results.

Halligan et al (1991) reported 75% sensitivity and 96% specificity in 80 patients with RHS and LHS, which were supported by results from Lindell et al (2007) and Lopes et al (2007). Floor and ceiling effects for the BIT were not reported in the literature. To conclude, the evidence presented indicated that the BIT was a validated measurement tool suitable for use in this PhD study.

3.2.2.3.

Assessment of motor skills by the Postural assessment scale for stroke (PASS)

*a*uthors - Benaim et al (1999)

Description – the PASS scale range is 0 to 36. The lower the score the poorer the balance and posture control skills. It consists of 12 tasks which assess static and dynamic balance both of which facilitate functional tasks e.g. lying to sitting to standing and reaching (see details in PASS profile Appendix B). These skills were demonstrated by the patient who was graded by the researcher on a 0 to 3 point ordinal scale. The PASS lacks published cut-off scores for mild, moderate or severe postural control. However based on experience of the measure, a score of 30 to 36 implies that the patient has standing balance and is ambulant for short distances (~5 meters on smooth level). The PASS took ~15 to 30 minutes to complete depending on the ability of the patient at time of assessment.

The PASS was developed specifically for use with stroke patients irrespective of their balance control i.e. it is sensitive to severe impairment. Previous researcher experience with the PASS indicated that the tool was feasible to use across both acute and community research settings although for safety reasons, assistance of one other person was required for assessment of severely impaired patients.

Psychometric properties – Mao et al (2002) compared properties of the PASS, Berg balance (BBS) and Fugl-Meyer Assessment Modified Balance Scale (FMA-B) in 128 patients at 14, 30, 90 and 180 days since stroke. The authors reported internal consistency (Cronbach's α as: range = 0.94-0.96), inter-rater reliability for the total score (Intra Class Correlation coefficient (ICC) = 0.97, 95% CI 0.95-0.98). Criterion (predictive) validity was reported as Spearman's ρ correlation coefficient (α=0.86-0.90), concurrent validity between PASS and FMA-B as (α=0.95-0.97), PASS and BBS (α= 0.92-0.95) at all time-points, and convergent validity between PASS and the BI as (α=0.88-0.92) across the 180 days. These results were well within the recommended figures for reliability and validity in the literature (refer to Table 3.3). However data for the four observations came from the same individuals, which would artificially inflate significance levels due to auto-correlation between observations. Further, only data from 80/128 patients was available for analysis at 180 days after stroke which may have affected the accuracy and interpretation of the results. However, the results from Mao et al (2002) were later partly supported by correlation results from short term studies (within 3 months after stroke): Chien et al (2007), Persson et al. (2011) and Yu et al (2012) reported that PASS scores predicted discharge BI scores, based on simple linear regression results (see Appendix C for details).

Mao et al (2002) examined responsiveness to change using Wilcoxon matched-pairs signed-rank tests. Their results indicated good responsiveness in relation to the PASS up to 90 days post-stroke which gradually reduced between the 90 to 180 days. The reported effect size was large (0.89) between 14-30 days, moderate (0.64) between 30-90 days and low (0.31) between 90-180 days after stroke. These results also suggested that the PASS was more responsive to change in moderate to severe than mild stroke. Results from Mao et al (2002) supported those by the PASS authors (Benaim et al 1999) which were further supported by results from Wang et al (2004).

More recently, Yu et al (2012) reported a relationship between PASS and BI at admission-discharge from acute rehabilitation based on estimates from simple linear regression analysis (R^2 = 0.20, p<0.001). Mao et al (2002) and Wang et al (2005) reported different proportions of patients reaching ceiling effects in their studies of the same duration - 180 days since stroke (17.5% and 30%) respectively. This discrepancy is probably explained in part by the exclusion of 71.8% (685/954) severely stroke impaired patients from the study by Wang et al (2005) which would have left more of the mild to moderately severe patients in their sample; hence the high rate of ceiling effect reported. Since this PhD study recruited severely impaired patients, ceiling effects were well within acceptable limits for the PASS (see critical evaluation/measurement section in the discussion chapter).

3.2.2.4.

Assessment of cognitive function by the Middlesex Elderly Assessment of Mental State (MEAMS) authors – Golding et al (1989)

Description - The MEAMS scale has a range of 0 to 12; the lower the score the higher the overall cognitive dysfunction. Clinically, scores (0 to 7) indicate impairment, (8 to 9) borderline and (10 to 12) within normal range (Golding et al 1989). The MEAMS consists of 12 items, which assess orientation, short and long term memory, verbal and comprehension skills, numeracy, spatial construction skills, letter perception, two and three dimensional object discrimination and motor perseveration. As per manual instructions, patient responses were graded as pass (1) or fail (0) by the researcher. Completion time was about 15 to 20 minutes depending on the patient’s level of cognitive impairment and fatigue at assessment time.

The MEAMS was validated on an English population sample consisting of patients with Alzheimer's disease (n=40), vascular dementia (n=40) and older people with depression (n=40). It has been used in past stroke research (e.g. Shiel and Wilson 1992, Hyndman et al 2002, Hydman and Ashburn 2004, Kneebone and Lincoln 2012). The Mini-Mental State Examination (MMSE) was employed in three of the critically reviewed studies in chapter two (Di Monaco et al 2013, Nijboer et al 2013, Timbeck et al 2013) however in terms of content, the MEAMS yielded more relevant information than the MMSE e.g. the MEAMS included visual construction ability and tendency towards motor perseveration which are both associated with HI (Marotta et al 2003, Sampanis and Riddock 2013). In addition the MEAMS has two parallel versions. These were alternately used to minimise the impact of practice effects on the MEAMS scores of mild-moderately impaired patients likely to learn the test material between administrations (Collie et al 2003, Bartels et al 2010).

<u>Psychometric properties -</u> Kutlay et al (2007) validated the MEAMS by Rasch analysis methods on 155 patients (mean 59 years) with stroke (85%) and acquired brain injury; 16% were illiterate and 43% were educated at a primary level. The patients were assessed at admission (median 46 days since stroke) and discharge from acute care hospitals. Their results supported a uni-dimensional scale with a reliable internal consistency reported as Cronbach's α: 0.82, ICC was 0.8 at admission and discharge. Construct validity was good judging by the data on model fit (mean item fit 70.178; SD 1.019), concurrent validity with the FIM cognitive scale was moderate at admission and discharge (Pearsons r = 0.60 & 0.62). Convergent validity with the FIM overall scale was poor (Pearsons r = 0.19 & 0.42) however, this result is probably explained by

the higher physical weighting of the FIM scale. These results supported those by Tennant et al (2006) which were in line with the recommended ratings for good and excellent validity in Table 3.2. Kutlay et al (2007) reported an effect size of 0.42 compared to 0.2 for the FIM-cognitive sub-scale, but without indication of stroke severity in the sample it was difficult to comment on its significance. Tennant et al (2006) reported no ceiling effects in a brain injured (n=158) patient population in comparison to (n=350) of similar aged healthy subjects on the MEAMS sub-tests. In support of the findings, data from Stein et al (2009) showed a clinically significant change in scores (median 3 MEAMS units) between admission and discharge in patients with HI.

In regard to sensitivity and specificity, Cartoni and Lincoln (2005) reported that three subtests, Orientation, Naming and Unusual views had 81% sensitivity and 50% specificity for detecting problems in language, perception or memory but the MEAMS as a whole was less sensitive (52%) to overall cognitive impairment. However, the sample was small (n=30), stroke severity was not reported and the selection process was not clear. Based solely on the results from Cartoni and colleagues no conclusions could be drawn on the sensitivity of the MEAMS. Of note, the original tool authors reported clear discrimination of three patient groups (Alzheimer's disease, vascular dementia and older people with depression) in the original sample (Golding et al 1989), which was supported by results from Tennant et al (2006).

Based on the data available in the literature, the MEAMS showed the recommended validity and reliability figures (Table 3.3) and was responsive in stroke populations from different educational backgrounds. A ceiling effect was possible in mildly cognitively impaired patients, which was taken into account in the current study.

3.2.2.5.

Assessment of higher cognitive (executive) function by the: Trail Making Test (TMT) - author Reitan (1958)

Description - The TMT is a two part timed test. Evaluation involves tracking of a visual conceptual and visuo-motor task in part A and B respectively. Part A involves connecting numbers 1-25 in ascending order; and Part B involves connecting numbers and letters in an alternating and ascending fashion in the shortest time possible (see copy in Appendix B). The researcher timed the patient using a stop watch and counted the numbers and letters joined correctly. Scoring – This was standardised according to test author instructions: the maximum time allowed to complete each part is 300 seconds and the more neurologically impaired the longer the response time. Those patients who did not complete within this time were conventionally assigned 300 seconds. Normative data is available for the TMT (Tombaugh 2003) although the average group (HI±) response times were compared in this PhD study. The test took 10 minutes or less to complete and a trial run was given to patients as per manual instructions.

The executive component assessed by the TMT was cognitive-motor processing speed supported by findings in the literature review (Buxbaum et al 2004, Hussain and Rorden 2003, Smith and Schenk 2012). One of the critically reviewed studies by Buxbaum et al (2004) used a computerised timed-reaction task (SART) which was not appropriate for severe stroke impaired patients or for use in the community settings, both factors being of importance for this PhD project. In contrast, the TMT was identified as a practical and valid tool in past stroke research by Stuss et al (2001), Keller et al (2003), Chaytor et al (2006).

Originally the TMT was included as a component of the Army Individual Test Battery and is also a part of the Halstead-Reitan Neuropsychological Test Battery (Reitan and Wolfson 1993). The TMT requires a variety of mental abilities including letter and number recognition, mental flexibility, visual scanning, and motor function (Kortte et al 2002, Barker-Collo et al (2010).

<u>Psychometric properties</u> – Goldstein and Watson (1989) investigated the test-retest reliability in 150 neuropsychiatric patients including stroke. The investigators reported Pearson Correlation Coefficients for part A & B as 0.94 and 0.86 respectively in the stroke sub-group of patients. Their results were supported by Wagner et al (2011) who reported regression coefficients as 0.76 & 0.89 for part A & B respectively, albeit in patients with major depressive disorder. These results suggested that part A was probably more discriminant than part B in stroke although part B was more sensitive to cognitive flexibility than part A in studies on healthy and cognitively elderly impaired by Kortte et al (2002) and Silva et al (2009) respectively.

Sanchez-Cubillo et al (2009) validated the TMT against the WAIS digit symbol in 41 healthy elderly individuals. The authors reported that the WAIS explained 51% of the variance in TMTA and 36% in TMTB indicating a modest relationship. However, these results could not be generalised to a stroke population. Tamez et al. (2011) examined convergent/discriminant validity as part of a bigger study in 689 patients with stroke. The TMT and NIHSS were administered within 3 days since stroke. Tamez and colleagues reported a significant, positive, correlation with both TMT parts, which was significantly greater in the relationship between NIHSS ($p<0.001$) and trail A versus NIHSS and trail B ($p<0.05$). These results supported those by Sanchez-Cubillo et al (2009) in that the TMT part A was discriminative and sensitive to stroke severity – a potentially useful piece of information in the current study.

Barker-Collo et al (2010) assessed the recovery of attention span in 43 patients with acute stroke over a 6-month period by means of the TMT. The test was administered within 4 weeks, 6 weeks and 6 months since stroke. Barker-Collo and colleagues reported detectable improvements in attention at 6 weeks and 6 months since stroke. This suggested that the TMT was likely to be responsive to change in this PhD study which had a similar serial design.

Korner-Bitensky et al (1994) investigated the ability of the TMT to predict on-road driving outcomes in patients with stroke and reported ceiling effects in part A but not B. However in this case, ceiling effects are likely to be less problematic because the executive demands and skills imposed by driving would be considerably different than those for ADL function. Nevertheless in view of the reservations by Korner-Bitensky et al (1994) ceiling effects were taken into account in the interpretation of results from the current project.

Duff et al (2008) showed considerable TMT practice effects after a week interval in mild patients with stroke. However psychological test administrations were at least 4 weeks apart and therefore less influential in the PhD study. Furthermore, 70% of the PhD sample was likely to have significant cognitive impairment which would make it harder to memorise the material between tests. Overall, based on the data presented in this review the TMT was a validated measure appropriate for use with this PhD project design.

3.2.2.6.

Screening of depression and anxiety by: The Hospital, Anxiety and Depression Scale (HADS) - Authors Zigmond and Snaith (1983)

Description - The HADS scale range is 0 to 42; the higher the score the higher the distress levels; range is 0 to 7 is considered normal, 8 to 10 is borderline and 11 to 21 abnormal - applicable to both anxiety and depression scales which add up to separate totals (Zigmond and Snaith 1983, Aben et al 2002).

The HADS consists of two sub-scales each containing seven items as follows; depression: five items assess specifically anhedonia - inability to experience pleasure, and two assess appearance and feelings of slowing down. For anxiety, two items assess autonomic response - panic and butterflies in the stomach and five items assess tension and restlessness (Dunbar et al (2000) (see copy in Appendix B). As described above (refer to overview beginning of section 3.1), 35 patients in this PhD study were assessed with the HADS at 30 days since stroke whilst on the stroke units because of increased risk of depression with prolonged hospital stays (> 30 days) (Aben et al 2002, Robinson 2003). The researcher read the questions to patients who needed assistance e.g. due to poor concentration and/or fatigue. The patients rated each question on 0 to 4 scale. Completion time was 2 to 15 minutes depending on the patient's ability at assessment point.

Psychometric properties – Internal consistency was studied by Aben et al (2002) in 200 patients with stroke. The authors reported Cronbach's α as: 0.85. This was recently supported by results from Rasch analysis in Muller et al (2012) who reported (r=0.72, 0.82) in a sample (n=102) of spinal cord injury patients and Tang et al (2007) in a sample (n=100) of acute hospitalised stroke patients. In addition, Muller et al (2012) reported unidimensional sub-scales supported by Tang et al (2007) for the depression scale, which was the focus of their study. In regard to the HADS scale, this finding supported an interval level of measurement. In a review of 71 publications by Bjelland et al (2002), concurrent validity was reported as: r = 0.61 to 0.83 against the Beck Depression Inventory Montgomery and as: r = 0.62 to 0.81 against the Asberg Depression Rating Scale. These values were within recommended standards in Table 3.3. Aben et al (2002) was the only apparent study to report on the sensitivity and specificity of the HADS (one month after stroke) as per the current design. The authors reported sensitivity as 86.8% and specificity as 69.9% for detecting both major and minor depression when the cut-off score was 11. Since the HADS was only administered once in this PhD project, data on its responsiveness to change was not relevant. Overall, based on the evidence reviewed, the HADS was an appropriate screening tool with no ceiling effect reported in mild stroke conditions (Bjelland et al 2002, Salter et al 2010). This corroborates with reports of high sensitivity by Aben et al (2002).

3.2.2.7.

Assessment of self-efficacy by the: The General Self-efficacy Scale (GSE)

Authors - Jerusalem and Schwarzer (1992)

Description – The GSE consists of 10 items which assess people's belief in their abilities to cope with adverse situations such as stroke (refer to GSE items in Appendix B). Each item was rated by the patient on a 4 point scale with "1" not at all true, "2" hardly true, "3" moderately true and "4" exactly true. In the original version there was no total score, however for quantification purposes the scale was scored on a range from 10 to 40, which preserved the order of interpretation of the GSE scores by the tool authors i.e. the higher the score, the higher the self-efficacy level. The GSE took about 10 - 25 minutes to complete depending on the level of cognitive impairment, fatigue and patient tolerance at assessment time. Similar to past stroke studies (e.g. Jones et al 2004, Svensen and Teasdale 2006 and Kendall et al 2007) which employed the GSE, the language was adapted for stroke. The GSE was feasible to complete on the stroke units and in community settings.

The psychometric properties of the GSE were evaluated by Peter et al (2014) who undertook Rasch analyses methods on data from 102 spinal cord injury (SCI) patients, mean age 57 years. Their results supported previous findings by Scholz et al (2002) and Scherbaum et al (2006) which showed that the construct validity of the GSE was unidimensional and highly reliable ($r_p = 0.92$). Peter et al (2014) found no item bias by gender, age, education or lesion levels but a ceiling effect was observed in their comparative sample of healthy subjects (with SCI). In relation to the current project, ceiling effects did not necessarily generalise to stroke in whom significant cognitive-intellectual dysfunction and advanced age (>75 years) were expected to influence patient GSE scores. Response to change was not specifically studied, however data from self-efficacy intervention studies on patients with stroke by Kendall et al (2007) (n=100) and Jones et al (2009) (n=10) indicated significant change in GSE scores (~10 units, p<0.003) over a one year period when compared to baseline (~ 12 weeks post stroke onset). Overall, reviewed evidence pointed to a validated tool in other samples of patients with SCI and depression. Consideration was given to the lack of validation studies of the GSE in stroke. Relevant implications are further addressed in the Discussion Chapter.

3.2.2.8.

Assessment of denial status by: Denial questionnaire adapted from Cutting (1978).

The literature review (Ch.2) did not reveal any feasible, appropriate and validated assessment tools suitable for use in this PhD project. Example, self-rated tools such as Structured Awareness Interview (Marcel et al 2004) and Berti's self-rating questionnaire (Berti et al 1996) depended on awareness levels and executive function which were thought to be severely impaired in more than half of the subjects. Another potential limiting issue to be considered in this PhD project was likely to be poor concentration and short attention span. These challenges were also documented in other relevant critical reviews (Orfei et al 2007 and 2009, Livneh 2009, Jenkinson and Fotopoulou 2010, Cocchini et al 2012, Vocat and Vuilleumier 2013). That being said, one of the critically reviewed studies in Chapter 2 (Buxbaum et al 2004) used an adapted version of Cutting's Anosognosia Questionnaire (1978) which was also employed in the current study.

Table 3.4 Denial questionnaire

Original questions (Cutting 1978)	*Adapted questions for PhD project*
Why are you here?	Why are you here?
What is the matter with you?	How did the stroke affect you?
Is there anything wrong with your arm or leg?	Is there anything wrong with your arm or leg?
Is it weak, paralysed or numb?	Is it weak, paralysed or numb?
How does it feel?	How does it feel?

Description – The researcher rated the patient's verbal response as true or false for each of the five adapted questions in Table 3.4. If denial was elicited in at least one question than the overall assigned rating was "1" = denial present, otherwise “0” = no denial present. The questionnaire took 5 to 12 minutes to complete depending on the patient’s cognitive impairment level.

It was acknowledged that the rating for question five bordered subjectivity on the researcher’s part and that “denial state” was likely to be on a continuum versus a dichotomous scale (present or absent) (Livneh 2009, Orfei 2009). This may have resulted in loss of information, the implications of which are addressed in the Discussion Chapter.

3.2.2.9.

Assessment of neurological stroke severity by the: National Institute of Health Stroke Scale (NIHSS) - Authors Brott et al (1989)

Description - The NIHSS range is 0 to 42. The higher the score, the greater is the neurological severity. Stratification is mild (1 to 5), moderate (6 to 14), severe (15 to 24), very severe (>25) (Brott et al 1989).

The scale consists of 15 items, which assess severity of impairment in the level of consciousness, response to questions and simple commands, visual and spatial impairments, facial palsy, sensory loss, muscle weakness in upper and lower limbs, ataxia, plantar reflexes and communication. Response is graded on a 3 or 4 point scale (varying across different items), scoring guidelines are provided for each item. 0 represents no clinically significant impairment.

The researcher extracted data from the NIHSS profile completed by a trained professional (generally neurologist or a thrombolysis nurse) who would have assessed the patient at Accident and Emergency.

Psychometric properties - Brott et al (1989) reported adequate to excellent test-retest *reliability* (mean kappa = 0.66 to 0.77) in (n=24) stroke patients; correlation between the 1st and 2nd examination scores (within 24 hours) was r =

0.98. This result was supported by Meyer et al (2002) in (n=45) stroke patients who reported total NIHSS score as kappa = 0.969. Brott et al (1989), Lyden et al (1994) and Goldstein and Samsa (1997) also reported that the *test-retest, inter and intra rater reliability* did not differ significantly when administered by trained health care professionals other than neurologists (which was relevant to the current study). Fink et al. (2002) examined the *concurrent validity* of the NIHSS with lesion volumes measured by diffusion weighted imaging within 24 hours of stroke in 153 patients. Fink and colleagues reported adequate correlation with lesion (r = 0.48, right; r = 0.58, left) and hypo-perfusion volumes (r = 0.62, right & r = 0.60, left in terms of hemisphere laterality, RHS and LHS). Fink and colleagues also reported lower NIHSS scores for LHS despite substantial lesion volume which was adjusted for in the multiple regression analysis. This supported earlier observations by Woo et al (1999) and Hillis et al (2003) in that the NIHSS was biased towards more dominant LHS motor function. Millis et al (2007) examined *internal validity* by means of Rasch analyses in 380 LHS and 347 RHS within 12 hours of stroke onset. Millis and colleagues reported the existence of two uni-dimensional scales consistent with known RHS and LHS functional differences i.e. although both scales represented cerebral function, patients with RHS or LHS constituted two distinct patient populations. This finding also supported the decision to recruit an RHS homogenous patient sample in the current project. The same report by Millis et al (2007) corroborated with earlier reports by Woo et al (1999), Fink et al (2002), Hillis et al (2003) and results from factor analyses by Lyden et al (2004). Overall, the evidence supported a non-interval level of measurement in regard to the NIHSS summative score, although only ischaemic stroke patients were included in all the studies cited.

Predictive validity was studied by Schlegel et al (2003 and 2004) in the first 24 hours after stroke in 94 patients. Schlegel and colleagues reported that for each 1-point increase in NIHSS score, the likelihood of going home was significantly reduced (odds ratio = 0.79). The category of NIHSS score also predicted the next level of care i.e. an NIHSS score of ≤ 5 (mild) was strongly associated with discharge home when compared to patients in the moderate category – those with NIHSS scores 6 to 13 were nearly 5 times more likely to be discharged to rehabilitation (OR = 4.8). Patients who scored >13 were nearly 10 times more likely to require rehabilitation (OR = 9.5) and more than 100-fold more likely to be placed in a long-term nursing facility (OR = 310). The results of this study confirmed previous findings that overall, the NIHSS was a significant predictor of discharge outcome and subsequent level of care, also an important confounder of stroke functional outcomes relevant to the current project; hence its inclusion in the project design. Muir et al (1996) pointed out a possible ceiling effect in very severe stroke because of difficulties in testing these patients on scale items, the implications of which are discussed in subsequent chapters. Based on the reviewed data, the NIHSS met the recommended standards for validation in Table 3.3 and was suitable for use in this PhD study.

3.2.2.10

Assessment of Stroke type and extent of lesion

The researcher extracted relevant information from radiological reports filed in the MDT documents. Although the CT and MRI scans provided evidence for stroke the report content was not sufficiently comprehensive or clear to allow fine classification. Type (cause) of stroke was graded as (haemorrhage = 0 or infarct = 1). Extent of lesion was graded as 0, if damage was limited to brain cortex or 1, if damage involved also sub-cortical areas. Implications resulting from collapse of these lesion categories are addressed in the discussion chapter.

3.2.2.11

Nutrition status was assessed by the: Malnutrition universal screening tool (MUST) author - British Association for Parenteral and Enteral Nutrition (BAPEN)

Description – The MUST is designed to assist with the identification of adults who are underweight and at risk of malnutrition or obesity. It has five steps to be undertaken by a trained professional as follows; (1) Height and weight are measured to calculate the person's body mass index (BMI), (2) the assessor establishes whether the person has lost any weight unintentionally and (3) establishes the effect of the person's illness on their ability to eat and drink. In step (4) scores from 1st three steps are added up to assess if the person is at low = 0, moderate = 1 or high = ≥2, risk of malnutrition which in turn is used to guide the patient’s reassessment and care plan (5). BAPEN recommends routine clinical care if the risk is 0, monitor if 1 and the development of a treatment pathway if the risk is high (≥2). For stroke, a high risk is weekly assessment of hospitalised patients, follow-up at 1st out-patient appointment and whenever there is concern in care homes or rehabilitation units - National Clinical Stroke Guidelines, Recommendation 6.23.1/B (RCP 2012).

The researcher extracted from the MDT documents the level of risk on the MUST as assessed by the dietician at admission. Ideally nutrition status would have been recorded at all assessment time-points, however follow-up records were unavailable to the researcher (see also data collection method).

Psychometric properties – A recent systematic review of nutrition screening tools by Van Bokhorst-de van der Schueren et al (2014) concluded that the MUST showed moderate validity (Kappa 0.4 to 0.6) when used to screen different subgroups of adult hospitalized medical, surgical, orthopaedic and elderly patients. Further, a MUST score of ≥ 2 was likely to have fair predictive validity (OR=2 to 3 & $p<0.05$) for both LOS and mortality in adult hospitalized patients - however stroke patients were not included in the studies reviewed.

Neelemaat et al (2011) carried out a feasibility study in which five malnutrition tools including the MUST were compared in 275 adult hospitalised patients. Although the authors reported ≥70% sensitivity and specificity, 47% of the data on the MUST questionnaire were missing due to practical difficulties, such as professional time constraints and equipment malfunctioning. The BAPEN UK survey (2011) also identified considerable missing data in hospital records and assessment tools. The implications of missing data on nutrition status in this PhD study are addressed in the Discussion Chapter.

3.2.2.12

Assessment of continence status – the data was already recorded as part of the EBI profile from which it was transferred into the relevant variable (bladder or bowel control). The scoring on the EBI is in appendix B and is the same for bladder or bowel control; only that for bladder is shown in the current section.

For statistical analyses, the categories were collapsed into 0 = normal bladder or bowel control and 1 = abnormal control (all other categories). This was justified because 90% of impaired patients were graded “0” or “1” which also simplified the statistical model.

Controlling bladder

• Complete or very frequent incontinence (several times a day and unable to change continence pads unassisted) OR needs indwelling urethral catheter, supra-pubic catheter or self-catheterisation and needs assistance with managing those devices	**0**
• Partially incontinent (at most once a day) and needs assistance in changing continence pads and cleaning self	**1**
• Fully or partially incontinent but needs no assistance in changing continence pads and cleaning self OR needs indwelling urethral catheter, supra-pubic catheter or self-catheterisation, but needs no assistance with managing those devices	**3**
• Normal bladder control	**4**

3.2.2.13

Duration of stroke unit stay and amount of therapy

Duration of in-patient stay (LOS) was calculated from admission and discharge dates. The number of face-to-face therapy-patient sessions recorded by occupational therapist, physiotherapist and speech and language therapist or their assistants was extracted from MDT documents by the researcher. The data was transferred to individual respective variables so that it could be statistically analysed. It was possible that some contacts were missed if not entered in MDT documents by discharge point (see methods section 3.4 for more detail).

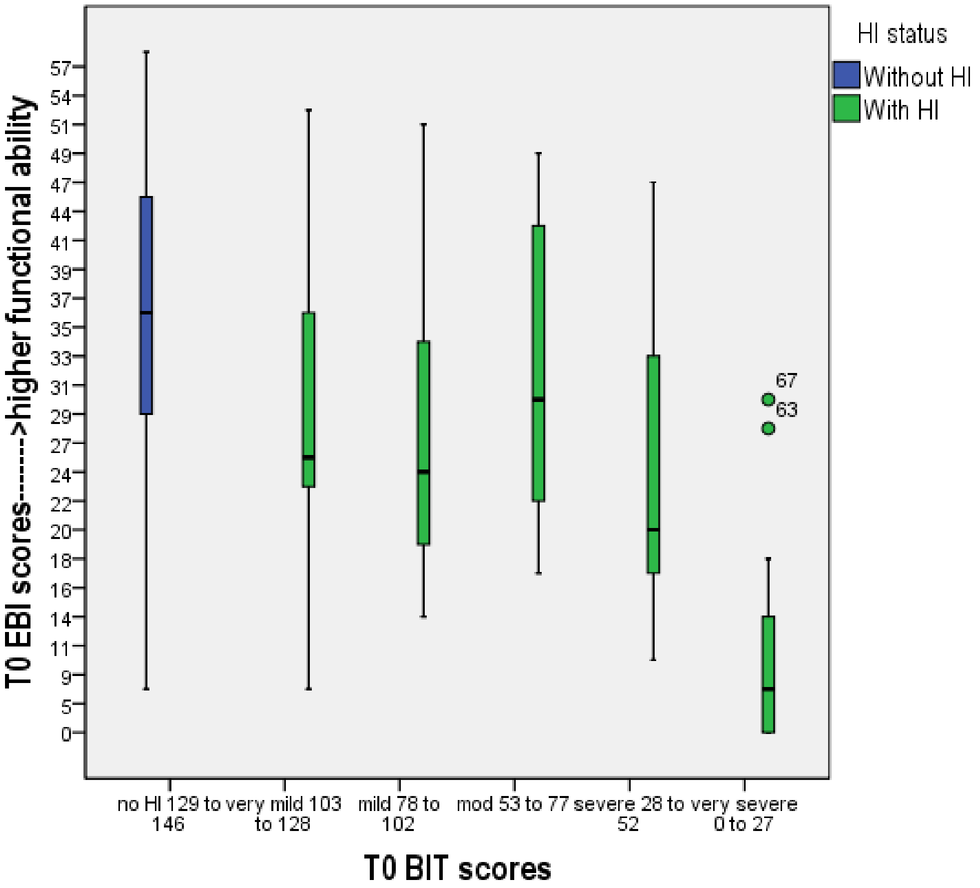
3.3 Section three – *Management of extreme and missing data*

All the collected data was transferred from Microsoft Excel (2010) into SPSS statistical software package (version 18.0) and prepared for statistical analysis. The data set was checked for obvious (input) errors by means of descriptive SPSS functions. After error correction, all data values were within the range of the relevant measurement scale or expected range in case of age and gender. A second SPSS report highlighted missing and extreme values on each variable. Their management is described in text.

3.3.1. Management of extreme values

Extreme values are defined as scores lying outside the range of data in question (Peacock and Peacock 2011). When present they can skew the data distribution, consequently they were investigated as recommended in the statistical literature (Tabachnik and Fiddel 2007).

Figure 3.1 - Boxplot showing two extreme values (67 & 63) on the BIT and EBI variables



Abbreviations; T0 = baseline, BIT = behaviour Inattention Test, EBI = Extended Barthel Index, mod = moderate, HI = hemi-inattention

Extreme values associated with different patients were identified on individual variables (EBI, PASS, MEAMS, TMT and GSE) and relevant bivariate combinations. An example of extreme values belonging to patients 63 and 67 (encircled) can be seen in the boxplot of EBI x BIT baseline scores, in Figure 3.1. In the boxplot, the rectangle represents the second and third quartiles, the inside horizontal line indicates the median value, the lower and upper quartiles are shown as horizontal lines either side of the rectangle.

In regards to Figure 3.1, a negative trend in the data at baseline can be observed suggesting that severe HI levels were associated with lower EBI scores (besides severe strokes). Both baseline EBI scores (for patients 63 & 67) are relatively high compared to counterpart patients in the very severe BIT score category. Despite their severe HI levels, patients 63 and 67 were relatively mobile and consequently more independent within tasks measured by the EBI. This scenario is not uncommon in HI+ patients and is documented in the HI literature (Parton et al 2004, Barrett et al 2006, Singh and Curry 2010). Therefore it is reasonable to leave these extreme values in the data set.

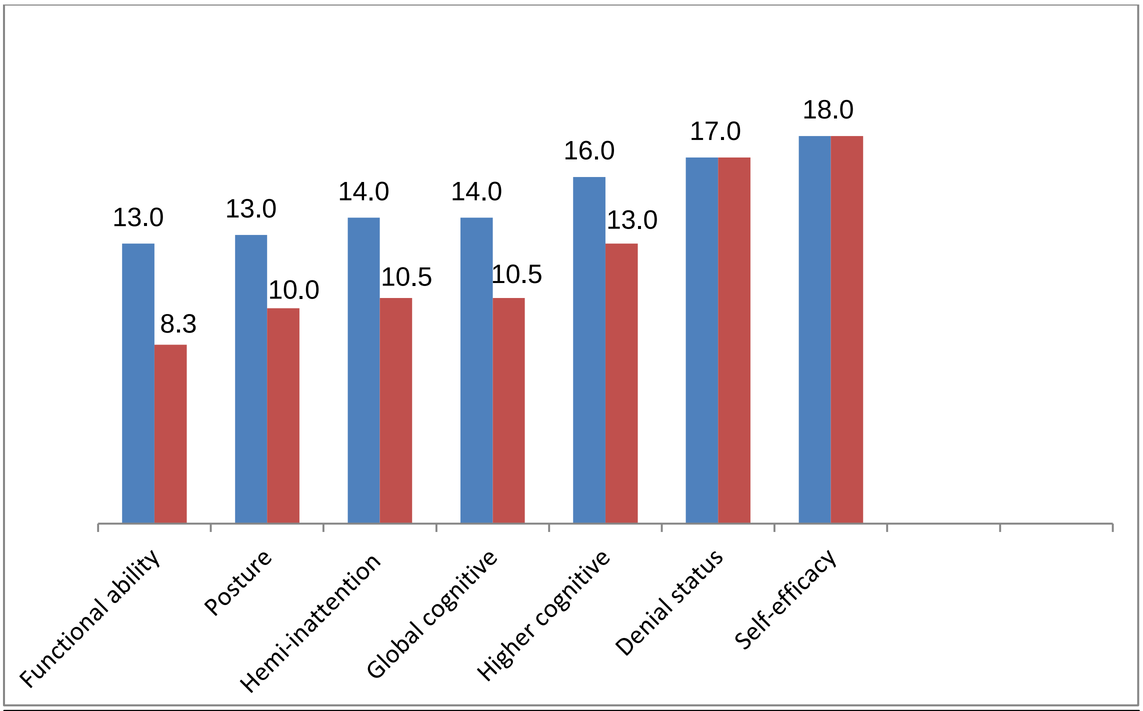
The highest number of extreme values (associated with 19 patients) was observed on the TMT – again this is possible due to the patient's variable cognitive motor processing speeds (20 to 300 seconds; median of 100) measured on a wide scale (300 seconds). Given the modest size of the data set, the known variation in HI presentation and recovery patterns and in RHS patient abilities (documented in Ch1 and Ch2) - extreme values were retained in the dataset because they were likely to represent characteristics of the RHS/HI± population.

3.3.2. Missing data

Missing data also referred to as 'missingness' (Allison 2012) was addressed in the study for reasons described in this section. Missingness amounted to ~ 15% of the total data expected; a breakdown by variable (%) is presented in Figure 3.2. At its lowest, is 13% (functional ability and posture/balance skills) and at its highest is 18% (self-efficacy). As expected, missingness was higher in the community (T2-T3) compared to the acute phase (compare T0-T3 figures in Table 4.3).

Figure 3.2

Percentage distribution of missing data on individual factors (before and after adjustment)



Colour code: blue columns (prior) and red (after) adjustment. An observation was classified missing when the patient was physically unavailable or was not willing to do certain assessments (e.g. self-efficacy and denial interview) versus inability to undertake specific assessment due to severe cognitive impairment levels or ill health

3.3.2.1. Literature guidelines and missingness

Statistical sources unanimously agree that ignoring missing data can seriously threaten validity of the results in at least three ways relevant to this study: by introducing bias in parameter estimation, by decreasing study power to detect differences between HI± groups and by increasing standard errors (used to calculate statistical significance of regression coefficients) (Burton and Altman 2004, Horton and Kleinman 2007, De Souza et al 2009, Peacock and Peacock 2011, Allison et al 2012, Tabachnik and Fidell 2007). These claims are substantiated by findings from computer simulation studies which showed that under certain data conditions (non-random missing data) missingness led to false conclusions and inaccurate inferences (Dong and Peng 2013, Dziura et al 2013). Therefore it was important to address missing data in this PhD study.

That being said, there is no consensus amongst experts on what constitutes unacceptable levels of missingness; more than 5%, 10% and 20% have all been cited in the literature (Cohen and Cohen 1983, Schultz and Grimes 2002, Kristman et al 2004, Almond and Walker 2010, Field 2009). Furthermore, it has been argued that the type, pattern and reasons for missingness need to be considered alongside the extent of missingness for optimal management solutions (Munro 2004, De Souza et al 2009, Tabachnik and Fidell 2007).

However, the problem still remains that there is no one advocated method of treating missing data (Raghunathan 2004, Shrive et al 2006, Horton and Kleinman 2007, Allison 2012). Robust, computationally, intensive methods are recommended e.g. Multiple Imputation (MI) and Likelihood-Based approaches (ML), however considerable professional expertise is essential to handle what is technically a very complex imputation process (Peacock and Peacock 2011). This is more so when numerous time-variant and related variables are involved (as in this PhD project) and when the data set is limited in size (Demirtas and Schafer 2003, Graham et al 2007).

In addition to the above, the pattern and type of missingness were difficult to establish in the case of patients who were deceased during the study (n=16) because the cause of death was not available to the researcher i.e. it was not possible to know whether this was a sudden death or a progressive gradual deterioration unless it happened in the acute phase (where MDT records were more indicative). However, from the sample description (in Table 4.1) it can be deduced that severely stroke affected patients were also more likely to have HI and a higher mortality risk in the first place. This suggested that a proportion of missing data was probably not missing at random. In principle, this implies that it could potentially influence systematic variance although the magnitude of the problem was unknown (difficult to establish).

On the other hand, data missing at random was less problematic in this study since it could be handled by Maximum Likelihood (ML) methods available in MLwin software (described in Ch3/section 3.4.9.). Theoretically, the use of ML would boost study power by maximising use of partial data sets (e.g. from deceased patients) which were left in the modelled dataset.

Given the uncertainty of the situation and the limited size of the data set, alternative ways were used to estimate a portion of missing data associated with (n=10) patients, who were alive for the duration of the study and whose cause of missing data was more certain than the deceased patients (n=16). This cause was due to three having moved out of area, five were unwell or failed to complete the assessment protocol and two discontinued participation (refer to data flow Diagram 4.1/Initial Results).

3.3.2.2. Management of missing data

Traditional methods such as group mean substitution or carrying last observation forward or using a missingness dummy variable were unsuitable because they tend not to preserve natural variation patterns in the data (Allison 2002, Tabachnik and Fidell 2007, Graham et al 2009).

Another method is professional judgement, which is generally less advocated but acceptable under conditions where data loss is present on a small scale and data on individual patients already exists from previous observations on the same variable/s (Munro 2001) supported by Schafer and Graham (2002), Engels and Diehr (2003) and Schlomer et al (2010). Although not without limitations, the professional judgement method was appropriate to use in this study for the following reasons:

- The researcher was an experienced practitioner, familiar with the measurement scales and expected scores of patients with mild, moderate and severe stroke at different stages of stroke recovery.
- Professional judgement would be guided by at least one and in some cases two already available data observations per patient per relevant variable, in addition to the research progress records for affected patients (e.g. the NIHSS score) which were extra indicators.
- The EBI, PASS and MEAMS had well defined scoring profiles which reduced ambiguity as to where patients fell on the scale. Further, the five affected patients at baseline already had a proportion of observable scale scores which informed other aspects of the assessment e.g. level of orientation to time, place, faces, simple problem solving, object

identification and use). Subsequently, it was not justified to assign a zero for patients with missing data at baseline across the board.

Together, the above mentioned factors increased the probability of an accurately judged estimate to that actually observed had objective assessment been possible. On the other hand, the risk of over or under estimating the true patient score cannot be negated and is arguably the main limitation of the professional judgement method. This could result in bias but possibly less bias than if left missing or assigned a zero (Dzuira et al 2013). Another issue is that other researchers under the same circumstances may have assigned a different score. Other limitations include difficulties judging patient abilities whilst lying in bed or not fully orientated or not sufficiently cognizant of the stroke event as in patients with denial. However, these limitations were up a point overcome by assessing patient's physical abilities such as bed mobility when they were being nursed in bed, increasing the amount of time spent observing and talking to the patients to determine their basic cognitive ability levels and waiting for sufficient cognitive recovery before attempting to score aspects of cognition such as problem solving abilities.

The author acknowledges the possibility that estimation bias may have incurred as a result of addressing missingness in the data. However, this was necessary to limit the impact of missing data on the results.

In regards to the PhD study and context, the professional judgement method was judiciously used to estimate missing data for 5 patients at baseline with incomplete records and for 10 at T2 and/or T3 - on selected variables (EBI, PASS, MEAMS, TMT and BIT). The same approach was used by Viken et al (2012). After adjustment, three-quarters of the patients had four data points

(T0, T1, T2, T3) on the dependent variable (EBI), posture & balance, HI levels, cognitive function and 70% on executive function, self-efficacy and denial status (refer to Figure 3.2 red columns).

Adjustment was less appropriate on categorical predictor variables (denial status and nutrition status) due to the high risk of false estimates – 50% probability of error (Field 2009) Neither was it appropriate to estimate missing data for the 10 patients on the GSE because the scores on this scale depended on the patient's perception which for some was flawed (unrealistic probably due to denial of illness).

Complete records for 93 patients were available for neurological stroke severity, initial (T0) HI status, age and initial carer status. Also for duration of stay and discharge destination outcome (n=87). Seventy percent had four records of continence status (T0, T1, T2 and T3).

Issues associated with data collection are further addressed under the critical evaluation section (discussion Ch6). Some examples are provided here for illustration; e.g. six patients had their initial assessment at 30 days since stroke due to severe cognitive impairment at admission. Cognitively impaired patients had limited response to the GSE and denial interview questions which contributed to missing data at T0.

3.3.3. Summary of the findings

Seventy-five percent of the patients had four data points at T0, T1, T2 & T3 on the dependent variable (EBI) and potential predictor variables (PASS, HI levels and MEAMS), 70% on the TMT, GSE and denial status (Figure 4.3 red columns). This represents an improvement of 3.5% average across five variables (EBI, PASS, MEAMS, TMT and BIT) after estimation of a proportion of the missing data for ten patients. The amount of data available is sufficient for the MLM analysis (Ch5) to proceed judiciously i.e. within constraints of the data available. Any unforeseen modelling issues will be addressed in the main discussion (Ch6). The same applies for potential threats to the results such as implications arising from missingness due to patient mortality during the study (n=16). Summary statistics are presented next followed by a comparison of scores between HI± groups.

3.4 Section four – *Data Analysis*

This section outlines the statistical data analysis methods undertaken to answer the research question and address the objectives set at the beginning of this chapter.

The first two objectives required a comparison of group (HI+/-) scores and characteristics in order to identify important differences in clinical, patient and care process factors identified earlier in Table 3.1. For the first part, all the data available for analysis was evaluated including that collected at interim observation points (IT1 and IT2). The data was grouped by baseline HI status for each variable and observation-point (T0, T1, T2 & T3 and interim TI1 & TI2). Descriptive and summary statistics (median and quartiles) were then calculated and tabulated by group (with and without HI). They are displayed in Ch4 along with a series of line graphs to visually enhance comparison between patient groups (HI±) over time (Singer and Willett 2003). The resultant progress patterns identified were then used to inform the multilevel modelling (MLM) analysis undertaken to meet objective three i.e. identify the relationship importance between HI and functional change over time with and without the influence of other important factors evaluated in the study.

The rest of this section is dedicated to MLM, its rationale and use in this study. Also included is a beginner's description of MLM methodological principles, modelling processes and techniques used to derive the MLM results in Ch5.

3.4.1. Rationale behind the use of MLM

MLM also known as mixed methods and random coefficient models is an advanced statistical regression based method appropriate for situations in which dependency in the data and/or substantial between patient or group heterogeneity exists (Singer and Willett 2003, Peacock and Peacock 2011). These situations include <u>hierarchical data</u> and <u>serial designs</u> which are relevant to the current project for reasons that follow;

Hierarchical data refers to a naturally occurring order (as in stroke conditions) in which patient characteristics such as age, gender and pre-stroke intelligence levels are likely to influence the extent of post stroke cognitive recovery and measureable performance on assessment tools e.g. PASS, MEAMS, GSE. Therefore patient characteristics (higher levels in the hierarchy) potentially influence the lower level factors (measurable scores).

Another form of dependency is inherently caused by the current serial design (in diagram 3.1) which involves testing the same patient with the same measures on multiple occasions. This process gives rise to 'auto-correlation' or artificially high correlations between two or more sets of scores, especially if observations are close in time (e.g. T0, T1, T2 and T3 in the design). If unaccounted for, this artificially high correlation increases the risk of type 1 error i.e. obtaining a statistically significant result when one does not exist) which may lead to inaccurate inferences from the results (Twisk 2006, Snijders and Boskers 2012).

Another reason is the interdependency between the factors (in Table 3.1) being evaluated e.g. stroke severity is associated with motor and cognitive recovery but the extent of motor recovery depends also on the extent of cognitive recovery, which is turn is related to HI severity levels (the subject of interest in this study). As already stated, if left unaccounted for, this inter-dependency between potential explanatory factors may impact on the results and make interpretation difficult (Peacock and Peacock 2011, Goedert et al 2013).

Of relevance to the research question is the concept of 'ecological fallacy' described in the MLM statistical literature (Diez Roux 2002, Snijders and Boskers 2012). Ecological fallacy can arise when inferences are drawn on results from aggregated data (single level regression) assuming that the same relationships between variables will be the same as when disaggregated (modelled at more than one level). For example, in relation to the current study it would be highly erroneous to assume (or worse conclude) that what holds true when time invariant factors (e.g. patient characteristics age, gender) are modelled with time variant factors (cognitive, motor recovery) also holds true for when they are modelled at different levels.

Given the extent of individual variation present in the critically reviewed studies (Ch2), it was important to know how much unexplained variation and at what level of the hierarchical model this was (Figure 3.1). This information not only helped to assess or judge how well a particular model fitted the data but also identified different sources of variance which assisted with interpretation of the results (Diez Roux 2002, Cheng et al 2009). In order to engage at this level of depth with the data, a multi-level model was structurally necessary, which is described later on.

Of relevance to the study is also Simpson's Paradox in regard to the clustering effect that arises when there is grouping of patients natural or otherwise. In this case, grouping by HI status is of primary interest but it would be unreasonable to assume that what applies at group level also applies to individual level. Consequently, it was important to obtain not only group tendencies but also variation from the mean across individuals in the models evaluated (Ch5). Obtaining information on both the average and the individual level increased the depth at which inferences could be made from the data in the main discussion (Ch6). In the same vein, Simpson's Paradox provides justification and rationale for including only RHS rather than LHS and RHS patients in the research sample (see selection criteria section 3.1.3.).

Traditional analytical methods used in past critically reviewed studies discussed in Ch2 (e.g. ANOVA and single multivariate regression in Paolucci et al 1996, Katz et al 1999) were not suitable because they do not account for the dependency in the data (described above) and make assumptions that potentially increase the risk of making inaccurate inferences from the results (see Ecological Fallacy and Simpson's Paradox). Besides, they do not possess the flexibility in modelling techniques required to explore in depth the relationship dynamic between HI status, potential explanatory factors and functional change over time. For example, ANOVA requires balanced datasets which are difficult to guarantee in stroke and HI serial studies because of the relatively high residual impairments (Goedert et al 2013). Dropping incomplete datasets would have meant large amounts of missing data which reduces sample representation and application of findings. In contrast, MLM does not require balanced data sets. Special MLM features (described in section 3.4.2.) enable the exploration of the research question both theoretically (in terms of modelling) and clinically without the assumptions made by traditional analytical methods. These assumptions are further commented on and highlighted in the next section. For the same reasons, past stroke research studies with similar designs and data requirements have used MLM methods e.g. Tilling et al (2001), Kollen et al (2005), Kwakkel et al (2006), Ekstam et al (2007), Nijboer et al (2013).

3.4.2. MLM principles

MLM is a relatively complex method to understand and operate. In principle MLM works by estimating the variance around specific parameters (regression lines) in a model rather than the actual parameters themselves as happens in standard regression (Twisk 2006, Field 2009). It uses both *fixed and random* coefficient effects. However prior to going any further it is important to define and explain MLM terminology so that the less familiar reader can follow subsequent text.

3.4.2.1. MLM terminology

Fixed and random terms

There are two parts to the MLM models used in this study – fixed and random.

The fixed part contains fixed regression coefficients which are the same as in ordinary regression and interpreted in the same way (Tabachnik and Fiddel

2007, Field 2009). Fixed parameters assume that change (difference) occurs by a fixed amount across patients.

The random part contains ‘random coefficients’ - which can take up different values (variable) from an existing distribution. This specific MLM feature is useful when there is substantial variation around the mean (be it intercept or slope) as was the case in the current data set (Figure 5.1). Random coefficients lead to a tighter model fit (i.e. regression line) because they can accommodate considerable variation in the data. This is in contrast to fixed coefficients (ordinary regression) which are less able to do so.

With respect to the MLM analysis (in Ch5) random coefficients estimated the amount of variation across time (differences between and within individuals) that existed around the mean. The mean estimated by the fixed part of the model represented average tendency across time.

Residual variance

Residual variance refers to unexplained variance in the random part of the model. Unexplained variance was represented by specific error terms in all the evaluated models (see Appendix D). Error terms were automatically estimated by the software package used to analyse the data (MLwin version 2.28). Unexplained variance estimates were used to assess the ‘goodness of fit’ i.e. how well a particular model fitted the data and identify optimal models.

3.4.3. Selection of the multi-level structural model

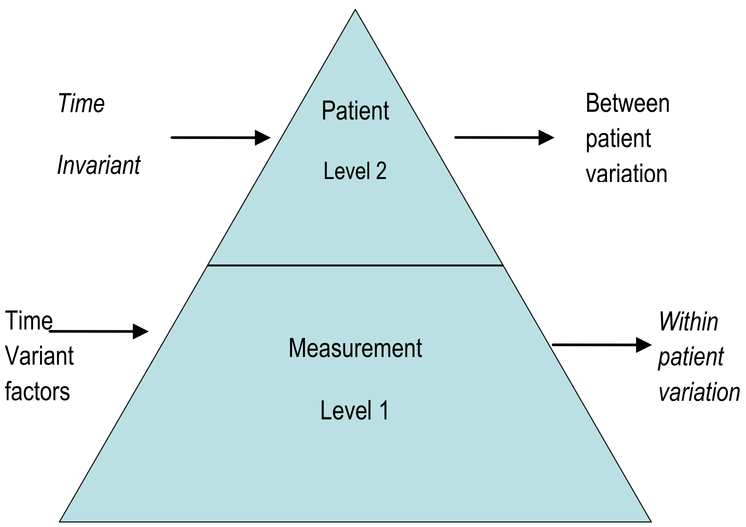
Due to the amount of variation present in the raw data (see Ch5/Figure 5.1) a conventional two-level structural model with a random intercept and slope was set-up (Singer and Willet 2003, Tabachnik and Fiddel 2007, Peacock and Peacock 2011). The same structural model was used to evaluate all the models presented in Ch5. It is illustrated in Figure 3.1 and referred to in text. Time since stroke was initially modelled as a categorical variable and later as an orthagonal polynomial as described in Ch5/section 5.3.

3.4.4. Factor definition and specification by level (L1 and L2)

The dependent variable (DV) was functional ability measured at T0, T1, T2, T3 by the Extended Barthel Index (EBI) described in section 3.2. EBI scores were modelled as continuous.

In the two-level model (Figure 3.3), time variant factors (variables PASS, MEAMS, TMT, BIT, GSE, continence status, denial status) were defined at level one (L1). Time variant refers to the measureable change in scores between observation points T0 to T3 (i.e. time since stroke).

Figure 3.3 Two-level structural Model



In contrast, patient related time invariant factors (age, gender, carer status, lesion type and site, stroke severity, nutrition status, LOS, amount of therapy, stroke unit identifier) were defined at level two (L2). 'Time invariant' meant only recorded once i.e. not expected to change in the context of this study. This distinction between L1 and L2 factors made sense since the performance on measures in L1 hierarchically depended upon patient characteristics and/or context defined at L2.

3.4.5. Units of measurements

Different levels have different units of measure; by convention the unit of measurement at L1 was the number of observations i.e. n=4 (T0, T1, T2, T3). The unit of measurement at L2 was the number of patients in the sample (n=93) (Singer and Willet 2003).

N.B. Data from the two interim observations (TI1 & TI2 between T0 and T1) were not sufficient for MLM, this data will be descriptively analysed in Ch4.

3.4.6. Interpretation of L1/L2 estimates (between and within patient variation)

In the two-level structural model illustrated in Figure 3.3, MLM estimates from L1 can be interpreted as changes within the patient over time and from L2 as differences between patients over time (Goldstein 1999, Singer and Willet 2003, Gibbons et al 2010).

3.4.7 Adjustment for confounding factors

Stroke severity, age and time (since stroke) were a priori identified as confounding factors in the literature review (end of section 2.7) and statistically adjusted for in all the models evaluated in Ch5. That being said, statistical sources such as Nezlek (2001) and Twisk (2006) distinguish between predictive and explanatory models, whereas the more clinically oriented stroke literature does not - both descriptive terms tend to be interchangeably used (Di Monaco et al 2011, Langhorne et al 2011, Kwakkel and Kollen 2013, Nijboer et al 2013).

From a statistical standpoint, Twisk (2006) and Shmueli (2010) argue that important confounding factors should be adjusted for in associative/explanatory models whereas adjustment is less important in purely predictive models – in which the main aim is to predict future outcome from the smallest possible variable combination.

In relation to the research question and the current project, the emphasis was more on associative/explanatory rather than predictive strategies, although it can be argued that clinically one would expect a strong explanatory factor (one which explains more than 10% change in the DV – Field 2009) to be also a good predictor of future functional ability. Hence the distinction is probably less important than argued in some of the statistical literature and not rigidly adhered to in later discussions (Ch5).

3.4.8. Significance levels (α) and confidence intervals (CI)

Significance level (α) was conventionally set as 0.05 with 95% confidence intervals (CI). This means that 95% of the scores in the wider RHS population are expected to fall within the estimated parameters (Field 2009).

3.4.9. Relevant technical detail

Data management and estimation method

Seventy five pecent of the patients had data available at all four key assessment time-points (T0, T1, T2 and T3). This data were modelled in subsequent MLM analysis (refer to table 4.3 for figures). However, less than 35% of patients had data available at interim observation points (TI1 and TI2), which although informative was not sufficient for modelling analysis; hence data from TI1 and TI2 was not modelled but descriptively analysed by HI± group status. The data to be modelled was entered in a longitudinal format as required by MLwin statistical software package (version 2.28), once it had been checked as described below.

3.4.9.1. Data checks

Linearity of relationships between functional ability (dependent variable) and individual predictor variables was visually checked by means of bivariate scatter plots (Tabachnik and Fiddel 2007, Field 2009). The relationships observed were reasonably linear and gave no cause for concern.

Multicollinearity refers to a correlation of more than 0.8-0.9 between predictor variables, when present it can adversely affect accuracy of the model estimates (Tabachnik and Fiddel 2007, Field 2009). Multicollinearity was checked by means of a correlation matrix of all modelled variables and the correlation coefficient Spearman's rho. The results identified three potentially problematic correlation values as follows:

- Number of in-patient contacts x length of in-patient stay (Spearman's rho 0.89)
- Bladder x bowel continence control (Spearman's rho 0.81)
- The two variables which comprise the Trail Making Test used for assessment of dysexecutive function - TMTA x TMTB (Spearman's rho 0.078)

As a result, one of the two variables in each correlation was included in the evaluated models.

Centred predictor variables - In order to further minimise threats from potential multicollinearity, MLM literature sources recommended centring predictors which also enhances interpretation of regression coefficient estimates (Kreft and De Leeuw 1998, Singer and Willett 2003, Hox 2010). In line with the recommendation, continuous and interval level variables were centred on a fixed point, as is the grand (overall) mean or median score on individual variables (refer to specific details in Ch5/Table 5.1). It should be noted that Grand mean centring does not affect the interpretation the slope but only the intercept i.e. the model fit is retained (Nezlek 2001, Tabachnik and Fidell 2007). In contrast, group mean centring (HI±) was not chosen because it would have complicated the interpretation of modelled results as it distorts the overall model fit (Kreft and De Leeuw 1998, Field 2009).

3.4.9.2. Estimation method

All regression coefficients and variances were estimated by Maximum Likelihood method (ML) and the implemented algorithm Iterative Generalised Least Squares (IGLS). This enabled the fit of similar successive models to be compared (Field 2009, Rabash et al 2009). ML is analogous to ordinary least squares (OLS) (used in ordinary regression). IGLS uses an iterative process in which results from the last estimation are used as starting point for the next estimation (new model).

During the estimation process, IGLS steps through possible values of the data until the likelihood of obtaining the specified model with the given data reaches maximum probability (hence maximum likelihood), at which point convergence is said to occur i.e. a mathematical solution is found by the equation derived from the model (Field 2009, Rasbash et al 2012).

3.4.9.3 Assessment of model fit - Chi-square Likelihood Ratio Test

The 'goodness of model fit' i.e. how well a particular model fitted the data, was assessed by the *Chi-square Likelihood Ratio Test (LR)* available in

MLwin software. LR compares the (-2log likelihood) of the new model with that of the previous one (of similar specifications e.g. plus or minus one parameter). The difference between the two models is known as the IGLS deviance and follows a Chi-square (x^2) distribution. The number of degrees of freedom (df) for this x^2 distribution is equal to the difference in the number of parameters to be estimated in the model (1df for fixed and 2 df for random parameters because both coefficients for intercept and slope have to be estimated). In MLwin, new parameters are highlighted in blue in the equation window so they were easily identifiable.

3.4.10. Modelling strategy

A stepping up approach advocated by Singer and Willet (2003), Twisk (2006) and Field (2009) was used. Following the estimation of a basic model consisting of functional ability – EBI scores as (DV) and predictor variables HI status, stroke severity, age, time since stroke, a series of variant models was separately estimated (refer to Ch5/Tables 5.3-5.4). During the process, the most important predictor variables available were identified and taken forward to the last phase of the analysis in which the final model was identified (Twisk 2006, Royston et al 2009). This was the model that best fitted the data based on sound theoretical and clinical justification for the inclusion of the variables in it (details in Ch5/Table 5.7/Figure 5.4).

3.4.11. Sensitivity analysis and model assumptions

A sensitivity analysis was undertaken to assess the robustness of the findings and conclusions based on MLM results from the primary MLM analysis (Graham 2009, Thabane et al 2013). This included checking of four MLM assumptions cited in the statistical literature (Snijders and Berkhof 2007, Field 2009) as follows:

1. Regression residuals were normally distributed and uncorrelated.
2. No perfect multicollinearity.
3. The relationship between outcome and predictor variables was linear.
4. Homoscedasticity (constant variance of the residuals).

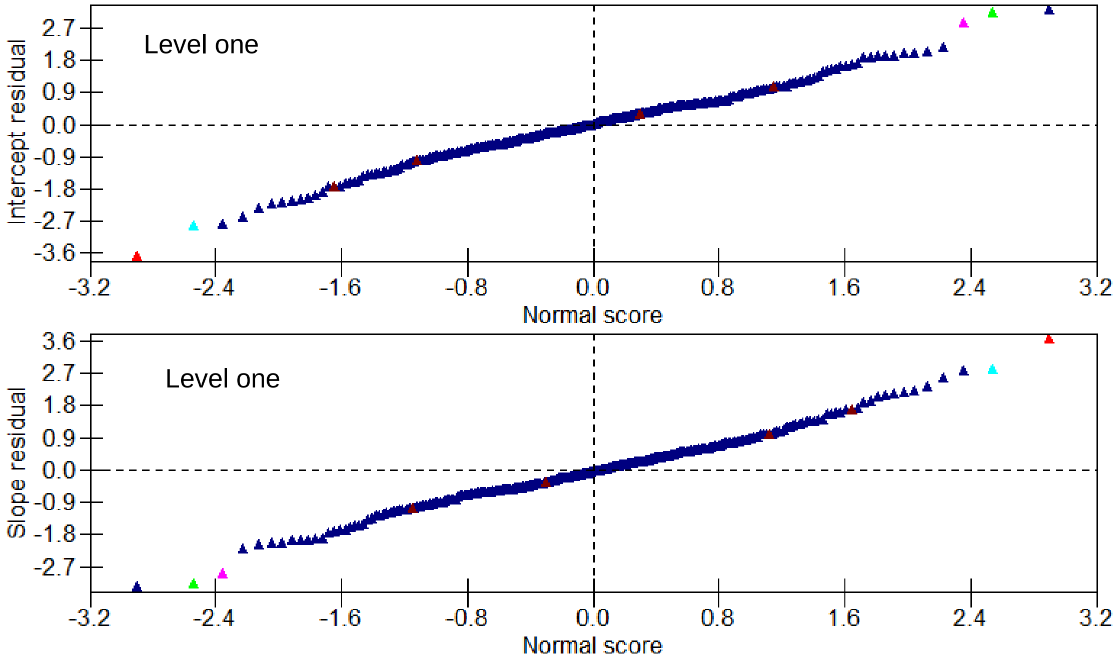
Following is a summary of the results from the sensitivity analysis which did not highlight specific or important concerns.

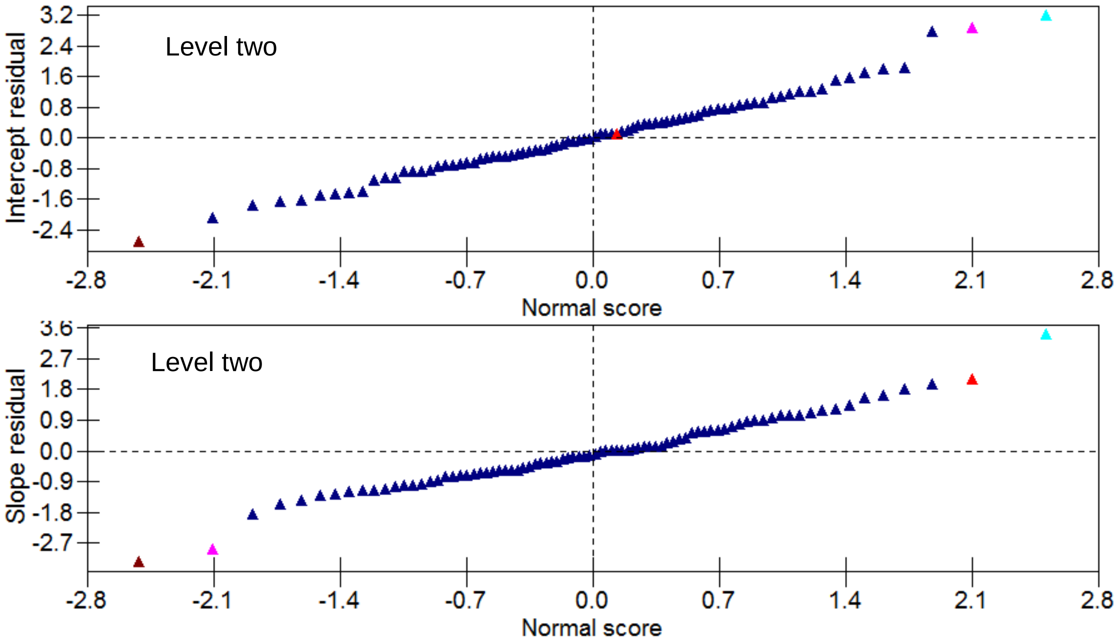
3.4.11.1. Diagnostic checks

Assumption - *Regression residuals should be normally distributed.*

Figure 3.4

Standardised regression residuals x normal scores for Intercepts and Slopes at levels (L1 & L2) in the final model.





The distribution of the regression residuals was checked by plotting normal scores against standardised residuals in the final model (Mf) (refer to Ch 5/MLM/section 5.3).

As illustrated in Figure 3.4, all the residuals lie along a reasonably straight line. This means that the assumption of normality was tenable at both levels (L1/L2) in Mf. Extreme values are highlighted but these fall within the 5% of patients whose scores are expected to deviate from the overall mean at 95% CI.

Checks and results on *multicollinearity* were described earlier in section 3.4.9.2

Assumption - *Homoscedasticity*

Homoscedasticity is the assumption that the variance of the regression residuals is constant across all individuals. This was checked by plotting standardised residuals (by level) against the fixed part of the model. The graphs indicated that variances were relatively constant except for points associated with extreme values, which tended to increase with lower predicted scores. In other words, the result indicated that the assumption of homoscedasticity was tenable.

Assumption – *Independence of observations*

This was checked by comparing the standard error (SE) estimates in multi and single level (final) models. As expected, the standards error estimates were larger in the multi than in the single level model (see results in section 5.4.2.1). This suggests that the multi-level model accommodated for dependency present in the data generated by auto-correlation of same patient responses (Singer and Willett 2003, Steele 2008).

Additional checks - Influential points on the model (Mf)

MLM guidelines recommend checking leverage and influence factor, which respectively refer to the likelihood and actual impact of specific data point/s on the model's regression line (Langford and Lewis 1998, Rasbash et al 2012).

Leverage and influence values were calculated and plotted as histograms at each level (L1 & L2) so that extreme points could be evaluated. Approximate cut-off values for high leverage were based on 2p/n where p and n are the number of random variables (2) and number of units at each level (L1=4, L2=93) (Langford and Lewis 1998, Rasbash et al 2012). The histograms highlighted point 51 as having the highest leverage and influential value on the intercept and slope at L2, point 91 as influential on the slope. This finding is not surprising because both values were already highlighted as extreme in Figure 5.6-7 (highlighted points in pink and light blue). However, no firm conclusion can be made from the results because statistical sources disagree on the appropriate equation for calculation of leverage which is in turn used to calculate the influence factor e.g. Field (2009) cites Hoaglin and Welsch (1978) and Stevens (2002) as 2(k+1)/n and 3(k+1)/n where k is the number of predictors in the model respectively. This yields different cut-off scores to those obtained earlier using formula (2p/n) (Langford and Lewis 1998, Rasbash et al 2012) and leads to different results. To this end, earlier observations from plots in Figure 5.6 indicated that point 91 may be highly influential, however not to the extent that it influenced fixed coefficient values. This is reassuring in terms of the accuracy and interpretation of the results.

3.4.11.2. Multi-level versus single-level regression analysis

This analysis was carried out to compare the precision of standard error (SE) estimates in a single versus multi-level (Mf) analysis. SE is used to compute confidence intervals (CI) and significance levels (p-value); therefore precise estimates enhance also the accuracy of inferences made from the results (Peacock and Peacock 2010). The results are in Appendix K.

With reference to the results, as expected the SE tends to be underestimated in the single compared to the multi-level method. This has the effect of potentially inflating CI and p-values. Although the main conclusion from the results remains the same, the regression coefficient for (non-linear) time varies i.e. in the single level regression it is hardly significant (p=0.05) but is clearly significant in multilevel regression (p=0.0049), indicating a stronger relationship between time since stroke and functional change in the acute phase.

Random parameters tended to be underestimated at single compared to multilevel regression. Consequently covariance between individual intercepts and slopes was clearly significant at multi-level (p=4.074e-005) but not significant at single level (p=0.94). Again, this leads to different conclusions; in the multilevel model the amount and rate of progress across individuals varies significantly from the fixed mean and is associated with functional change whereas the opposite conclusion is implied by the single level estimates.

Overall the findings support the use of MLM method of analysis because the standard error estimates tend to be larger (i.e. not underestimated) than those for single level (refer to Appendix K) (Tabachnik and Fidell 2007, Steele 2008).

3.4.11.3. Comparison of MLM results with and without missing data.

A comparison of MLM results with and without the (estimated) missing data (estimated portion) was undertaken to assess the extent of agreement between the results (refer to Management of Missing Data/Ch4/section 4.2.2.2). The final model (Mf) was re-estimated using the unadjusted dataset. Relevant results are included in Appendix L.

Based on MLwin output, there were 267 and 269 cases of data used to compute Mf, in the original and adjusted data set respectively. Subsequently both sets of results are very similar i.e. they do not change the conclusions drawn from the results based on the adjusted dataset. The finding makes sense considering that only a relatively small proportion of missing data was adjusted in order to maintain study power. Finally, the results also lend support to the assumption that the adjusted data was likely to be missing at random with minimal influence on the results (Allison et al 2012, Dong and Peng 2013, Dziura et al 2013). The potential impact of missing data on the results is further addressed in the main discussion (Ch6).

3.4.11.4. Comparison of MLM results from MLwin and SPSS statistical software

This comparison was done to check the extent of agreement between different software packages (SPSS version 20.0 and MLwin 2.28) and hence the validity of the results. The closest model in SPSS to that already set up in MLwin included a covariance structure known as 1st order autoregressive (ARH1) in which variances are assumed to be heterogeneous. That is, the correlation between any two elements (covariates) is equal to ρ (rho) for adjacent elements, ρ^2 for two elements separated by a third, and so on; ρ is constrained to lie between –1 and 1. As can be seen from both outputs (placed in Appendix M), there are no appreciable differences at any level. This is reassuring in regards to the validity and precision of the estimates from MLwin.

3.4.11.5. Sub-analysis of BIT scores (individual versus HI± group)

The purpose of this sub-analysis was to determine whether different levels of measurement for the same variable HI status yielded similar MLM results. This was important to check because individual BIT scores were initially grouped into the categorical variable (with or without HI) to answer the research question. However, the BIT scores may have been more sensitive to the variation within the HI status (identified in the preliminary results - Figure 4.1 & 4.2) than the grouped variable. Results from the analysis are summarized in Appendix N.

The results show that the difference in IGLS deviance (goodness of model fit) between the model with HI status as categorical and that as continuous variable is only 3 IGLS deviance units (1747 to 1744), which is not statistically significant ($p=0.083$) in Chi^2 distribution at a 1df. This indicates that BIT scores do not appreciably improve the model and is further supported by a non-statistically significant BIT-score coefficient ($p=0.06$) at 95% CI. All other fixed and random coefficient estimates remain relatively unchanged which is reassuring. Again, the result is supported by a predicted mean difference of 4 EBI units for a patient with very severe HI (BIT score 0) and no HI (BIT score = 146) when BIT scores were separately modelled as a categorical and continuous variable in the final model.

To conclude this important section, the post-hoc sensitivity analysis indicated that MLM statistical assumptions were met in regards to the distribution of regression residuals which was normal; independent observations; and homoscedasticity (constant variances across individuals). Leverage and influence factors highlighted extreme points 51 and 91 as being most influential, however for reasons explained in section 5.3.3/extreme values in the data, these points were unlikely to have exerted a detrimental effect on the overall regression line.

3.5 Section five *– Ethical issues*

Project approval

The study was approved by the South East Research Ethics Committee (REC), Brunel University, and the East Kent Hospitals Acute Primary Care Trust (EKHT) Research Committee who issued the researcher with an honorary contract for a maximum period of two years. A copy of the REC approval letter has been placed in Appendix E.

The main ethical issues related to (i) potential patient and researcher fatigue (ii) clarification of ethical aspects in the research protocol (iii) sharing of assessment information with MDT (iv) participation and assessment of patients with severe stroke conditions (v) content of patient information sheet (PIS). These were addressed as follows;

Participation of patients with *severe stroke conditions* was clarified. Eligible patients who were deemed unable to give informed consent at admission were given the opportunity to participate up to 30 days after stroke onset if they sufficiently recovered cognitive ability to provide written consent. These patients (n=8) joined the study at the 1st interim time-point, 30 days since stroke (TI1). Such flexibility in assessment was needed in order to include patients with a full range of severity. This enhanced sample representation, the value and application of the findings.   Less severe patients tended to provide informed written consent on the same or next day of admission to the stroke unit. A copy of the PIS and consent form is placed in Appendix F and G. All participants kept a copy of the consent form, a copy was put in their MDT documents and the original was retained by the researcher. All patients consented for the researcher to access MDT documents and communicate with family and professional staff regarding their progress.

Concern by the ethical committee for *stress and fatigue* in the patients and the researcher was minimised by staggering assessments throughout the week over a seven day period. In addition, frequency of assessment was kept to a bare minimum. Participants could stop the assessment when they wished or could opt to undertake it on the weekend when they were less in demand by the rehabilitation staff. A summary of patient assessments undertaken by the researcher was made available to the MDT team as requested by EKHT. This minimised duplication of assessments and potential stress on patients. On the PIS, patients were referred to independent advice at *INVOLVE* website and the following sentence was added “This study is being undertaken as part of a PhD. It has been reviewed and approved by the School of Health Sciences and Social Care Research Ethics Committee at Brunel University”.

Other relevant issues

Patients with reduced vision were provided with visual aids to enhance their vision e.g. magnifying lenses, bright light and large print. Mild communication difficulties e.g. dysarthria were overcome by means of pen and paper methods (sketching), use of a calendar for appointments and help from the family.

First hand psychological and emotional support was provided by the researcher who has professional counselling qualifications in addition to relevant competencies gained as an Occupational therapist. Additional support was available on stroke units via the stroke support worker, hospital based counselor and chaplain or general practitioner in the community. As far as the researcher was aware no participants needed referral to these sources in connection with the research.

The data were collected by the author of the thesis who is an experienced clinician in stroke rehabilitation. This factor may introduce bias since the researcher was aware of the patient’s HI status. Measures were in place to check a proportion of the data collected by another researcher. Confidentiality was maintained through not identifying the stroke units.

Chapter 4 – Initial Results

Chapter Four

Initial Results

4.0. Introduction

This chapter contains a detailed description of the participant sample followed by a detailed account of the recruitment process and flow of participants through the dtudy data. A summary of the data collected is presented next including reports of linearity and data distribution on individual variables prior to the preliminary analysis.

The preliminary analysis commences with descriptive summary statistics followed by comparison of both patient group scores based on HI status (i.e. with and without HI). This addresses the first two objectives identified earlier in the methods chapter (Ch3), which are repeated here for clarity:

1. To measure and compare the overall functional outcomes of patients with and without HI in the first six months after stroke.
2. To measure and compare the outcomes of patients with and without HI on clinical, patient and care process factors (e.g. cognitive function, self-efficacy and continence status) associated with HI and functional ability in the first six months after stroke. These factors were previously specified (in Table 3.1) under three categories, however the grouping is for ease of writing and description purposes rather than strict definition.

A summary of the preliminary findings including emerging trends concludes chapter four (Ch4) prior to the multilevel modelling analyses in chapter five (CH5).

4.1. Description of the sample

The sample consisted of 93 right hemisphere stroke patients (RHS); 58 with hemi-inattention (HI+) and 35 without hemi-inattention (HI-); 11 of whom (7 HI+, 4 HI-) had experienced a previous stroke. As evident from the demographic data summarised in Table 4.1, there was similar variation (SD=10.0) around the <u>mean age</u> which was 77 years HI+ and 74 years HI-; range 46 to 93.

<u>Gender</u> distribution differed significantly across both (HI±) groups (Chi-square test; p=0.003); the HI+ was 65% female and HI- group 66% male. Approximately (~) 80% of patients in the HI+ and HI- groups had an identified informal carer at the time of admission and discharge from the stroke unit.

Table 4.1 Sample demographics and group (HI±) characteristics

		HI^+ (n=58)	**HI^- (n=35)**	p-value	Statistical test
Age	Mean (SD) Range	77.4 (10.5) 46 – 93	73.5 (8.9) 58 - 89	0.073	t-test
Gender	Female	65%	34%	0.003	Chi-square
Carer status	Carer present	86%	80%	0.562	Chi-square
Stroke type	Infarct (94%) Haemorrhage (6%)	57% 5%	37% 1%	0.404	Chi-square
Lesion site	Cortical Sub-cortical Cortical + sub-Cortical Unspecified	27 (46.6%) 6 (10.3%) 16 (27.6%) 9 (15.5%)	8 (22.9%) 8 (22.9%) 5 (14.3%) 14 (40%)	0.005	Chi-square
Stroke severity	Mild Moderate Severe Very severe	0 (0%) 15 (25.9%) 34 (58.6%) 9 (15.1%)	3 (8.6%) 25 (71.4%) 7 (20.0%) 0 (0%)	<0.0001	t-test
Comorbidity; 1 condition from ⟶	Small vessel disease, cardiac, diabetes, 2nd stroke, obesity	20(34%)	13(37%)	n/a	n/a
Conditions associated with RHS/HI	*Hemianopia *Sensory dysfunction **Signs of Motor HI	7 (12.1%) 50 (90.9%) 36 (63.2%)	1 (2.9%) 10 (28.6%) 0%	0.251	Fisher's Exact n/a n/a
	* Data extracted from NIHSS, ** data source = patient presentation				
Abbreviations: HI^+ & HI^- patients with and without HI respectively. n/a = not applicable					

In 94% of the sample, stroke was caused by an infarct (versus haemorrhage) which was equally distributed in both HI+/- groups. Statistically significant group differences (Chi square test; p=0.005) were found with respect to lesion site; 27/58 (46%) HI+ patients had predominantly cortical lesions, followed by 16/58 (28%) with more complex pathology involving cortical and sub-cortical lesions. In comparison, 14/35 (40%) HI- patients had diffused non-focal lesions. The figures tend to support the hypothesis that HI+ patients have larger and more defined stroke lesions (Jehkonen et al 2006, Appelros et al 2007). The potential impact of lesion site and HI status on functional ability was estimated in the MLM analysis (Ch5/Table 5.4).

Further support for larger stroke lesions involving both cortical and sub-cortical structures in HI+ group comes from stroke severity levels as measured by The National Institute of Health Stroke Scale (NIHSS). Accordingly, 74% of the HI+ patients had severe or very severe stroke (NIHSS >15 & 25 respectively) compared to 7% of HI- patients who had severe stroke. The majority of HI- patients (71%) had moderately severe (NIHSS = 6 to 14) compared to 26% in the HI+ group. The only three patients diagnosed with mild stroke severity levels (NIHSS = 1 to 5) were in the HI- group. As expected, differences in stroke severity levels between HI± groups were statistically significant (t-test; p<0.0001).

In addition it was noted from the individual NIHSS patient profiles that 8/93 patients had hemianopia (7 HI+, 1 HI-) and 12/93 (5 HI+, 7 HI-) received thrombolysis procedure. Also, a high rate of sensory (tactile) dysfunction was noted from NIHSS profiles in 50 HI+ (91%) compared to 10 HI- (28.6%) patients. Furthermore, signs of motor HI could be visually observed by the researcher in 36 (63%) patients with HI. These included rotation of the head, neck and/or trunk and/or disturbances in visual gaze which is consistent with reports in the literature and indicative of heterogeneous sub-types of HI (Husain and Rorden 2003, Buxbaum et al 2004, Punt et al 2006, Kerkhoff and Schenk 2012, Dimitrios et al 2013). HI sub-types are highlighted in Ch1/diagram 1.

The impact of hemianopia, sensory dysfunction and motor HI is reflected in the NIHSS overall score which is modelled in Ch5. The potential confounding effect of thrombolysis was taken into account when interpreting the results.

The frequency of comorbid conditions was similar in both (HI±) groups; overall 33 (35%) had a history of small vessel disease or cardiac or diabetes, three patients were morbidly obese. The author acknowledges that co-morbidity is a potential confounding factor, which was taken into consideration when interpreting the results in the discussion chapter (Ch6).

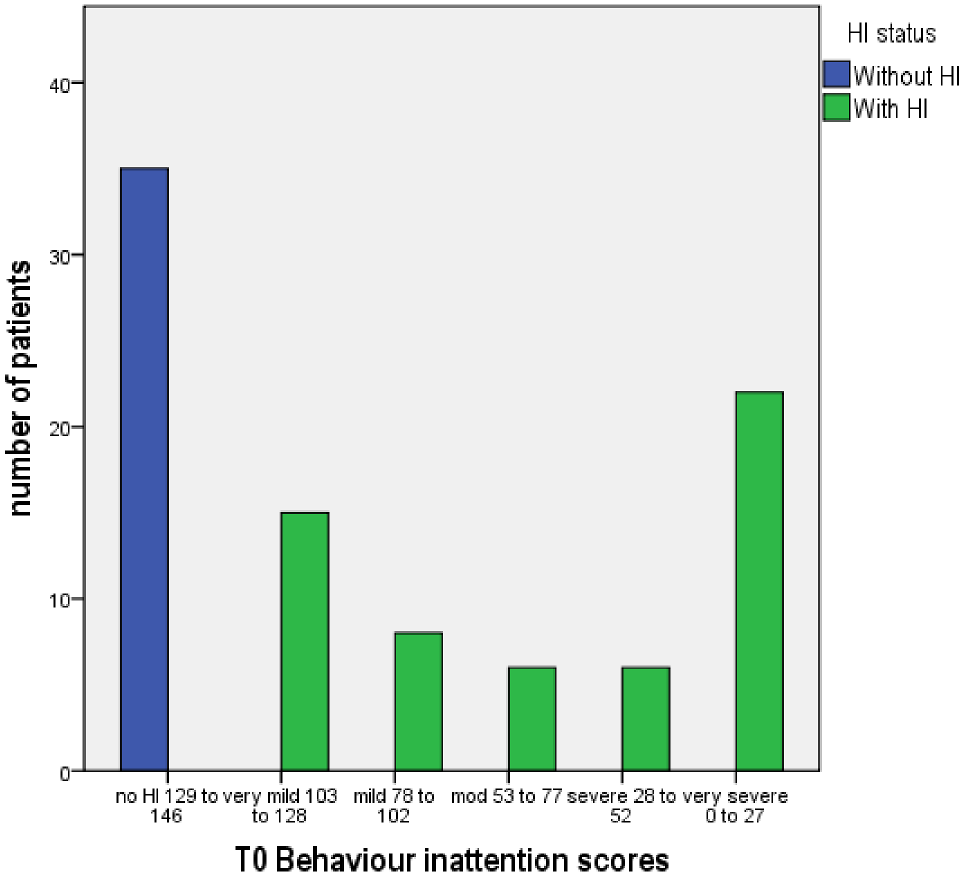
HI severity levels were measured by the Behaviour Inattention Test (BIT). Figure 4.1 shows the distribution of HI severity levels in the sample. All HI- patients scored in the highest category indicating least hemi-inattention. All of the HI+ patients showed some degree of hemi-inattention varying from a gradient of very severe (BIT= 0 to 27) to very mild (BIT=103 to 128).

Overall the data in Figure 4.1 shows considerable variation in HI severity levels, particularly in the HI+ group which may impact differently on functional ability and outcome. This was taken into consideration when interpreting MLM results and further elaborated on in the main discussion chapter (Ch6).

To summarise, age, carer status and type of stroke were similarly represented in both HI± groups. However despite an RHS homogenous sample, considerable heterogeneity was observed with respect to stroke severity, lesion site, HI severity levels and sensory dysfunction. Gender was unequally distributed in the HI± groups. These differences are likely to reflect not only the variation in the natural RHS stroke population but also within the HI condition.

Figure 4.1

Bar chart showing the distribution of HI severity levels by category in the sample



4.2 Recruitment and flow of participant through the study.

This section contains a detailed descriptive summary of the recruitment and follow-up undertaken by the researcher on the stroke units and in the community. For convenience, they are summarised in flow diagram 4.1.

4.2.1. Recruitment setting and process

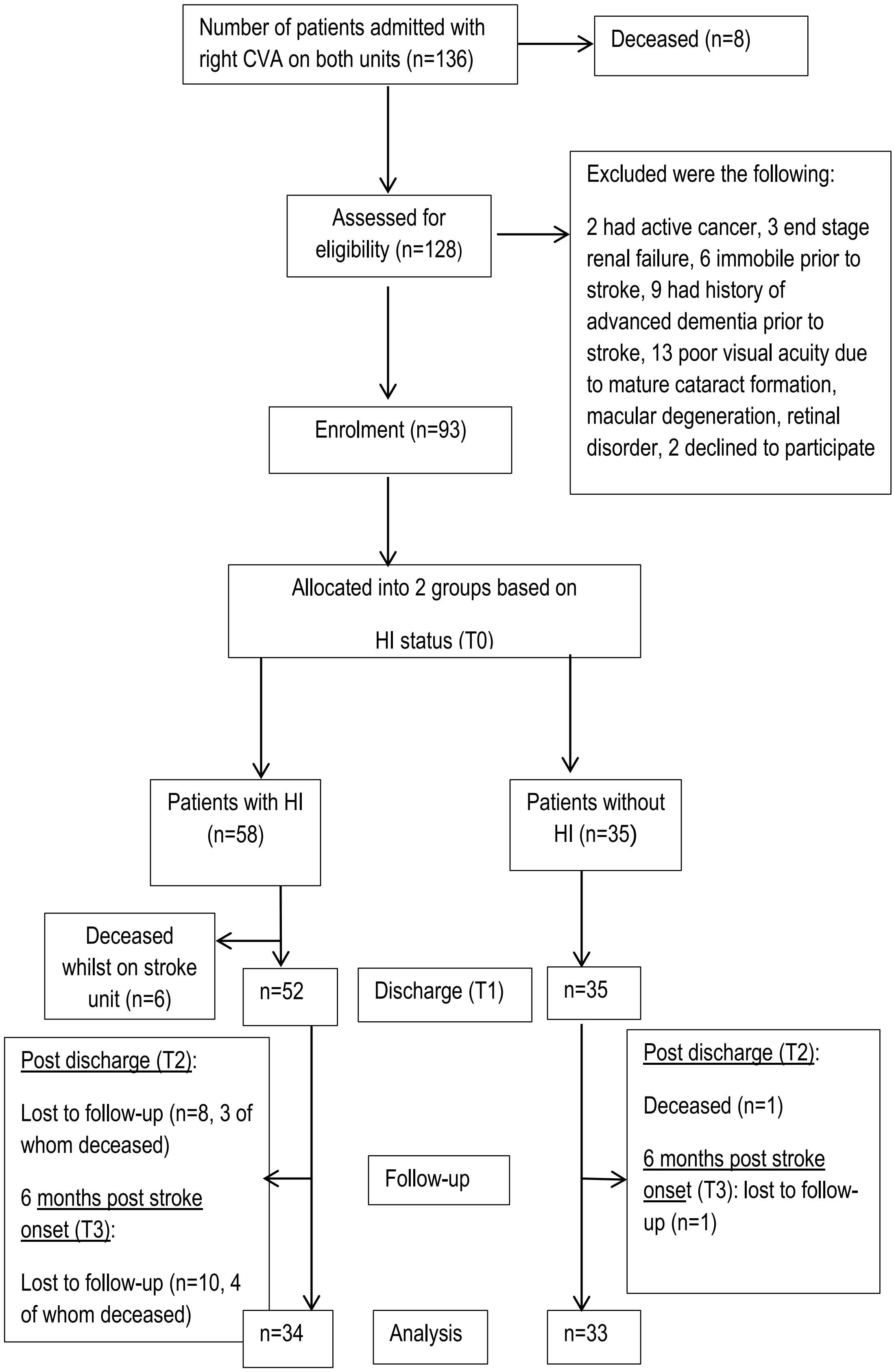
Formal approval to carry out the research was initially obtained from the East Kent Hospitals Trust for a one year period with access to three acute care stroke units situated on different sites (A, B & C) with a total capacity of 70 beds. Due to local organisational difficulties beyond the researcher's control, recruitment was largely restricted to two units (A & B), each with a capacity of six acute and 19 rehabilitation beds with 95% stroke occupancy (taken from stroke unit records). Practical challenges associated with data collection and their management form part of the main Discussion Chapter (6).

As part of the new stroke care pathway which operated on unit A and B, all 93 patients had their stroke confirmed by CT and/or MRI scan. They were assessed for thrombolysis treatment by a consultant neurologist or thrombolysis nurse who used the NIHSS for this purpose. Thrombolysis treatment was subsequently performed on 4 HI+ and 7 HI- patients from the recruited sample. Recruitment occurred on the stroke units after patients were transferred from accident and emergency, either on the same or next day of the stroke event.

Between May 2008 to September 2009 (17 months), 136 RHS patients were admitted to A & E, of whom 128 were eligible to participate in the study (please refer to flow diagram 4.1). They were provided with patient information sheets (PIS) and a brief verbal description of the project whilst on the stroke unit. Formal written consent to participate was obtained from 93 patients (58 HI+ & 35 HI-) who were enrolled in the study; 65 from unit A and 28 from unit B. They were assessed as per the research protocol summarised in Table 4.2 and described in text. N.B. attrition and missing data have already been discussed in the Methods Chapter; section 3.3.

Diagram 4.1

Detailed breakdown of recruitment and follow-up patient numbers



4.2.2 Baseline (T0) Observations:

The researcher recorded demographic and baseline data for all enrolled patients and undertook the assessment battery detailed in Table 4.2/T0 over the course of seven days (since stroke), although mildly affected patients (n=53) were assessed within the first 3 days since stroke.

Table 4.2 Research protocol details

Observation point/N	Formally assessed by researcher	Data extracted by researcher from multi-disciplinary documents
T0= Within 7 days since stroke N=93	BIT first followed by PASS, MEAMS, TMT, GSE, Denial Interview, EBI in no specific order	Stroke unit identification, patient hospital number, name, gender, date of stroke and admission, telephone number, address, summary of CT/MRI report detailing type of lesion and stroke, NIHSS profile scores, nutrition status, continence status, relevant past medical history, social situation including carer status, pre-stroke level of independence
TI1=interim N=35	BIT, PASS, MEAMS, TMT, GSE, Denial Interview, EBI	Not applicable
TI2=interim N=14	As for TI1	Not applicable
*T1= Discharge N=87	BIT, PASS, MEAMS, TMT, GSE, denial interview, EBI in no specific order	LOS, destination outcome, recommended support services, Number of pre-recorded therapy contacts (physio, occupational, speech and language)
T2= 6 weeks post-discharge N=77	BIT, PASS, MEAMS, TMT, GSE, denial interview, EBI in no specific order	Place of residence (home or transfer to institution), support services, hospital re-admissions were applicable
T3= 6 months post stroke onset N=67	BIT, PASS, MEAMS, TMT, GSE, denial interview, EBI in no specific order	Place of residence (home or transfer to institution), support services, hospital re-admissions were applicable

Abbreviations: BIT=Behavioural Inattention Test, PASS=Postural Assessment or Stroke scale, MEAMS=Middlesex Elderly Assessment of Mental State, TMT=Trail making Test, GSE=General Self-Efficacy Scale, EBI=Extended Barthel Index, NIHSS=National Institute of Health Stroke scale, LOS=duration of in-patient (stroke unit) stay, CT= Cat and MRI=Magnetic resonance imaging. *T1= modified protocol to EBI & PASS for 42 patients (details in text).

4.2.3 Follow-up Observations

- *Interim observation time-points (TI1 &TI2)*

Thirty-five patients (27 HI+, 8 HI-), who were more severely affected by stroke were assessed at TI1 (30 days since stroke); of whom 14 (11 HI+, 3 HI-) were re-assessed at TI2 (60 days since stroke) with the protocol in Table 4.2/TI1.

- *Discharge (T1)*

Forty-two patients were discharged within a few days of admission or in the interim e.g. two weeks after the last assessment. For these (42) patients, the whole protocol was not repeated but modified to: assessment with EBI and PASS because scores on these measures were expected to change considerably within two weeks. Scores on the TMT, MEAMS, BIT, GSE and Denial Interview questions were not expected to change appreciably in two weeks – these scores were carried over (from ~ two weeks earlier) to discharge. This method also minimised possible practice (confounding) effects on the results which would otherwise have been incurred if the TMT, MEAMS, BIT, GSE and Denial Interview questions had to be repeated more frequently than once every four weeks (Duff et al 2008, Bartels et al 2010). It would have also unnecessarily burdened the patient and researcher with extra assessments which was not ethically justifiable (see ethics section 3.5). The adjustment to the discharge protocol were further supported by findings from critically reviewed studies (e.g. Katz et al 1999, Gillen et al 2005, Stein et al 2009) which indicated that progress rate was considerably faster in physical-motor skills than psychological-cognitive skills, predominantly required for the TMT, GSE, BIT, MEAMS and denial interview questions. For the other 45 patients unaffected by the problem of early or (mid-month) discharge, data was collected every four weeks of their in-patient stay as per the original design. In addition, six patients were deceased during (T0 – T1) (refer to missing data in chapter three).

- *Community follow-up at six weeks post-discharge (T2)*

Community follow-up was undertaken for 77 patients (44 HI+ & 33 HI-) who were assessed with research protocol Table 4.2/T2 within six weeks post-discharge at the patients' home (44), intermediate care facilities (7) and long term institution (26). As shown in diagram 4.1, four patients deceased between T1 and T2, and five were lost to follow-up; of whom (3) moved out of area, one moved abroad and another was unwell at the time of assessment.

In reality, data collection in the community was practically and logistically complex to organise due to the amount of factors (variables) not within the control of the researcher. Consequently, a pragmatic approach to assessment was adopted as follows:

When direct observation was not possible, professional judgement and skilled observation techniques were used to indirectly rate patient abilities on specific ADL tasks - toileting, continence status, personal care and grooming in ~ 17 patients living at home and 20 in institutions. In relation to continence more than 50% of patients living at home and/or carers forwarded the information without solicitation from the researcher. In 23 (30%) of the patients assessed at T2, the presence of a catheter bag was suggestive of bladder dysfunction and rated as such. The patients affected were severely impaired e.g. had marked postural instability, perceptual deficits and a general lack of balance and motor co-ordination which clearly limited independence and fell within well-defined scoring criteria on the EBI and PASS scale i.e. there was no ambiguity about the score. It is acknowledged that professional judgement is inherently biased, however when faced by obvious impairment this method was very similar to that used on the stroke unit, wherein the environment was more supportive to formal assessment. Missing data is discussed in Chapter three and six, but contributory factors were restricted access to MDT community records and timely access to the patient.

- *Community follow-up at six months since stroke (T3)*

Follow-up was undertaken for 67 patients (34 HI+ & 33 HI-) who were assessed with research protocol Table 4.2/T3 at six months since stroke, at the patients' home (47) or residential/nursing institution (20). Six patients deceased between T2 and T3, and five were lost to follow-up; of whom three could not be contacted and two were unwell at the time of assessment (see Diagram 4.1). The same pragmatic approach to assessment and data collection (described for T2) were used at T3, in almost all patients living in long-term institutions and 15 living at home. Formal assessment was possible for all other patients with minimal improvisation within the home to simulate assessment requirements.

To summarise, the implementation of the design was possible for approximately two-thirds of patients in the sample. For the remaining third, data collection was inevitably hampered by practical difficulties and inherent challenges encountered in the research environments (stroke unit and community). These challenges were reasonably overcome where possible by adopting less rigid, flexible ways of working (described above). Although these methods may have increased the risk of bias, this was off set by the potential minimisation of incurring a large amount of missing data which would adversely affect the project findings. In support of this statement, professional judgement was also used by Cameron (2000) and Viken et al (2012) in their studies.

Similar challenges to data collection in stroke are documented by other researchers in the field (e.g. Jeffries et al 2009, Barrett et al 2010, Jones et al 2011 and Wilkinson et al 2011).

4.2.4. Amount of collected data and distribution checks

An overview of the amount and type of data collected per factor and assessment/observation point is summarised in Table 4.3. The 1st row identifies individual variables, the 2nd row shows the amount of missing data and the 3rd row shows the amount of data available for the analyses.

Data distribution checks were necessary to examine assumptions of normality prior to the use of statistical tests (parametric versus non-parametric) to preliminarily analyse the data. Visual inspection of data distribution plots indicated a good spread of scores and a mixed tendency towards a non-normal distribution in scores for BIT (HI levels), MEAMS (cognitive function) and (TMT) executive function and GSE (self-efficacy) scores at T0, T1, T2 and T3. A tendency towards a normal distribution was observed at T0 & T1 in EBI (functional ability) and PASS (motor) scores but less normal at T2 and T3. Considering the overall tendency for a non-normal distribution, the most appropriate way to summarise the data is the median statistic, which is less affected by extreme values at either end of the distribution than the mean (Tabachnik and Fidell 2007). Therefore it will increase accuracy of inferences made from the results.

Table 4.3 Summarised raw data by factor, observation point and patient groups (with and without HI).

Enrolled (n=93; 58HI+, 35HI-)	Main assessment time-points								Interim observation points			
	T0		**T1**		**T2**		**T3**		**TI1**		**TI2**	
Evaluated factors	**HI+**	**HI-**	**HI+**	**HI-**	**HI+**	**HI-**	**HI+**	**HI-**	**HI+**	**HI-**	**HI+**	**HI-**
Functional ability (EBI)	58	35	52	35	44	33	34	33	27	8	11	3
Missing	0	0	6	0	14	2	24	2	0	0	0	0
Available after estimation	58	35	52	35	49	33	42	34	27	8	11	3
Balance/posture (PASS)	58	35	50	35	44	33	34	33	27	8	11	3
Missing	0	0	8	0	14	2	24	2	0	0	0	0
Available after estimation	58	35	50	35	49	33	42	34	27	8	11	3
Hemi-inattention (BIT)	58	35	50	35	41	34	33	33	27	8	11	3
Missing	0	0	8	0	17	1	25	2	0	0	0	0
Available after estimation	58	35	50	35	46	34	41	34	27	8	11	3
Cognitive function (MEAMS)	58	35	51	35	40	34	33	33	27	8	11	3
Missing	0	0	7	0	18	1	25	2	0	0	0	0
Available after estimation	58	35	51	35	45	34	41	34	27	8	11	3
Higher cognitive (TMTA)	58	35	50	35	40	32	31	30	27	8	11	3
Missing	0	0	8	0	18	3	27	5	0	0	0	0
Available after estimation	58	35	50	35	45	32	39	31	27	8	11	3
Higher cognitive (TMTB)	58	35	50	35	40	32	31	30	26	8	11	3
Missing	0	0	8	0	18	3	27	5	1	0	0	0
Available after estimation	58	35	50	35	45	32	39	30	26	8	11	3
Self-efficacy (GSE)	58	35	47	34	37	31	30	33	12	4	6	2
Left missing	0	0	11	1	21	4	28	2	15	4	5	1
Denial status (interview)	51	35	48	33	44	32	35	31	26	7	11	3
Left missing	7	0	10	2	14	3	23	4	1	1	0	0

Abbreviations: with (HI+) and without (HI-) hemi-inattention T0 = baseline, T1 = discharge, T2 = 6 weeks post-discharge & T3 = 6 months since stroke. TI1 & TI2 = interim observation points at 30 & 60 days since stroke (only for patients with severe stroke as per design/methods). EBI (Extended Barthel Index), PASS (Postural Assessment Scale For Stroke), BIT (Behavioural Inattention Test), MEAMS (Middlesex Elderly Assessment Scale for Stroke), TMT (Trail Making Test), GSE (General Self-Efficacy Scale)

4.3 Descriptive and summary statistics

For this analysis, baseline ability levels were established first, then follow-up abilities. These are presented in Table 4.4 (page 181). In view of the tendency for non-normal distribution of scores, the median, upper and lower quartiles or percentage (%) proportion for each group (with and without HI) at T0, T1, T2 & T3 are provided. This will facilitate comparison of group scores required to address the first two research objectives restated in section 4.0. Descriptive statistics for patients with severe stroke at interim observation points (TI1 and TI2) can be found in Appendix H.

4.3.1. General progress trends

The figures in Table 4.4 show a general positive progress trend in that all patients tended to improve (irrespective of baseline HI status and HI severity levels) in functional ability, balance and functional posture and global cognitive dysfunction albeit patients with HI (HI+) underscored those without HI (HI-). In comparison, self-efficacy levels and executive function (cognitive-motor processing speed/seconds) tended to be relatively stable with little change in both groups scores over time since stroke. In general, the largest improvements tended to occur between baseline and discharge. However there are clearly differences between groups both in the amount and rate of progress on different factors - they are elaborated on in section 4.4. For example, the lower 25% of patients in the HI+ group tended to deteriorate on most factors as measured by the EBI, PASS, MEAMS, TMT, GSE and BIT between 6 weeks post-discharge and 6 months since stroke.

The frequency of patients in denial tended to reduce with time i.e. more patients became aware of their stroke (data in Figure 4.10). Further, bowel and bladder function tended to improve with time since stroke (data in Figure 4.11). Nevertheless, the disparity in scores between the upper and lower quartiles on the EBI, PASS, MEAMS, TMT and LOS suggests substantial overall variation in abilities between and within groups. This is further supported by a wide range of stroke severity scores and HI severity levels (BIT). Taken together, the figures in Table 4.34 tend to suggest that those patients who start with low scores (low functioning) especially on the EBI, PASS, BIT and TMT tend to finish with low scores and vice versa.

4.4. Comparison of baseline group scores

Baseline (T0) data in Table 4.4 shows substantial differences in baseline median scores between groups (HI±). Statistical analysis of the (T0) NIHSS, EBI and PASS scores confirmed that respective differences were highly significant (t-test for normal data distribution in NIHSS, EBI, PASS; $p<0.0001$).

Similar results were obtained for the MEAMS, TMT and BIT scores (Mann Whitney U-test for non-normal distribution in MEAMS, TMT, BIT; $p<0.0001$) but differences in GSE (self-efficacy) scores were not significant (Mann Whitney U-test, $p=0.43$).

The frequency of patients at risk of malnutrition, bladder and bowel dysfunction was higher in the HI+ group; the differences were statistically significant (Fisher's exact test; $p<0.0001$, $p=0.005$, $p<0.0001$) respectively but not for denial of illness (Fisher's exact test; $p=0.15$) which occurred at similar rates in both (HI±) groups.

Table 4.4 - Summary of RHS patient scores by group (with and without hemi-inattention) at baseline and follow-up

	With hemi-inattention				**Without hemi-inattention**			
Baseline (T0)	n	Median	Upper quartile	Lower quartile	n	Median	Upper quartile	Lower quartile
NIHSS	58	18.5	13.8	23.0	35	10.0	7.0	13.0
EBI	58	18.5	30.3	9.5	35	36.0	45.0	28.0
PASS	58	10.0	21.3	2.0	35	22.0	27.0	22.0
MEAMS	58	6.0	9.0	0.25	35	11.0	12.0	9.0
TMTA	58	300.0	237.3	300.0	35	63.0	50.0	99.0
TMTB	58	300.0	300.0	300.0	35	180.0	120.0	300.0
GSE	58	30.0	35.0	30.0	35	32.0	36.0	32.0
BIT	58	63.0	104.0	0.0	35	139.0	143.0	136.0
Discharge (T1)								
EBI	52	30.3	44.0	21.3	35	48.0	54.0	37.0
PASS	50	19.0	27.3	6.0	35	27.0	30.0	22.0
MEAMS	51	8.0	10.0	6.0	35	11.0	12.0	10.0
TMTA	50	300.0	147.5	300.0	35	63.0	50.0	99.0
TMTB	50	300.0	300.0	300.0	35	148.0	133.0	240.0
GSE	47	30.0	34.8	22.3	34	31.0	35.0	31.0
BIT	50	98.0	120.5	44.8	35	139.0	144.0	136.0
LOS	58	37.0	58.0	20.0	35	18.0	39.0	9.0
Therapy	54	32.0	36.8	10.8	35	15.0	19.0	7.0

Continued……next page

Continued…………Table 4.4 - Summary of RHS patient scores by group (HI±) at baseline and follow-up

6 weeks post-discharge (T2)	With Hemi-inattention				Without Hemi-inattention			
	n	Median	Upper quartile	Lower quartile	n	Median	Upper quartile	Lower quartile
EBI	49	33.5	46.5	22.5	33	55.0	62.5	48.0
PASS	49	18.0	28.0	9.3	33	32.0	34.0	27.0
MEAMS	45	9.0	10.0	6.0	34	12.0	12.0	11.0
TMTA	45	295.0.0	76.0	300.0	32	55.0	85.8	85.8
TMTB	45	300.0	300.0	300.0	32	151.5	97.8	300.0
GSE	37	27.5	33.3	18.0	31	32.0	37.0	29.0
BIT	46	106.0	132.5	40.5	34	141.0	144.0	135.5
6 months since stroke (T3)								
EBI	42	37.0	37.0	17.0	34	62.0	64.0	53.0
PASS	42	25.0	28.0	7.0	34	32.0	35.0	17.5
MEAMS	41	9.0	11.0	3.8	34	12.0	12.0	11.0
TMTA	39	300.0	92.3	300.0	31	51.5	36.8	62.0
TMTB	39	300.0	300.0	300.0	30	110.0	83.0	209.0
GSE	30	28.0	33.0	16.5	33	32.0	36.0	28.0
BIT	41	89.0	135.0	1.00	34	143.0	145.0	138.0

Abbreviations: n = number of observations.

NIHSS = National Institute of Health Stroke Scale, EBI – Extended Barthel Index, PASS = Postural Scale for Stroke, MEAMS = Middlesex Elderly Assessment of Mental State, TMT = Trail Making Test, GSE = General Self-efficacy Scale, BIT = Behavioural Inattention Tests

Number of deceased patients (n=16); T0-T2 (6HI+, 0HI-), T2-T3 (3HI+, 1HI-), T2-T3 (6HI+, 0HI-)

Overall, baseline measures indicate important clinical differences in functional ability, motor, cognitive and executive function, HI severity levels and continence function between patient groups (HI±). The findings are consistent with higher stroke severity levels reported earlier in HI+ patients in the RHS sample (summarised in Table 4.1). In contrast, there were no important differences in the self-efficacy levels or the distribution of denial of illness between groups. Differences in group trends are elaborated on in section 4.5.

4.5. Comparison of group trends

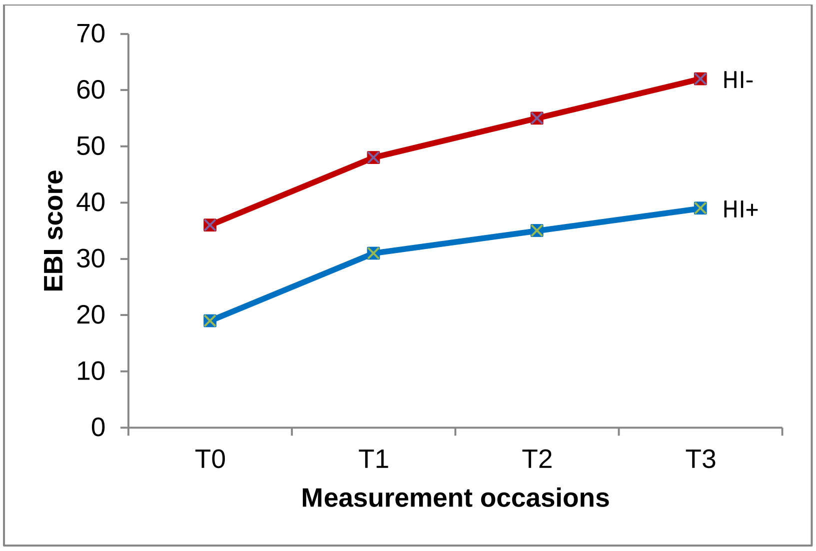
This section offers an in-depth comparison of group median scores on individual factors evaluated in the design. It addresses the first two research objectives stated at the beginning of this chapter. To aid visual comparison, relevant data in Table 4.4 are supplemented by line graphs showing group (HI±) trends. The illustration method is recommended by Singer and Willett (2003) for serial longitudinal data.

4.5.1. Overall functional ability

With reference to Table 4.4/Figure 4.2, the median overall functional ability score was consistently lower in HI+ versus HI- patient group, addressing research objective one. The most gain occurred between baseline and discharge followed by slower, more modest gains up to six months after stroke. However, the large difference in the upper (U) and lower (L) 25% of patients in either group suggests substantial between and within-group variation, especially in the HI+ group. Patients with HI appear to lag behind by approximately (~) 50% of the EBI score at all levels (median and U and L quartiles).

Figure 4.2

Comparison of median EBI scores between (HI±) patient groups in the first 6 months after stroke



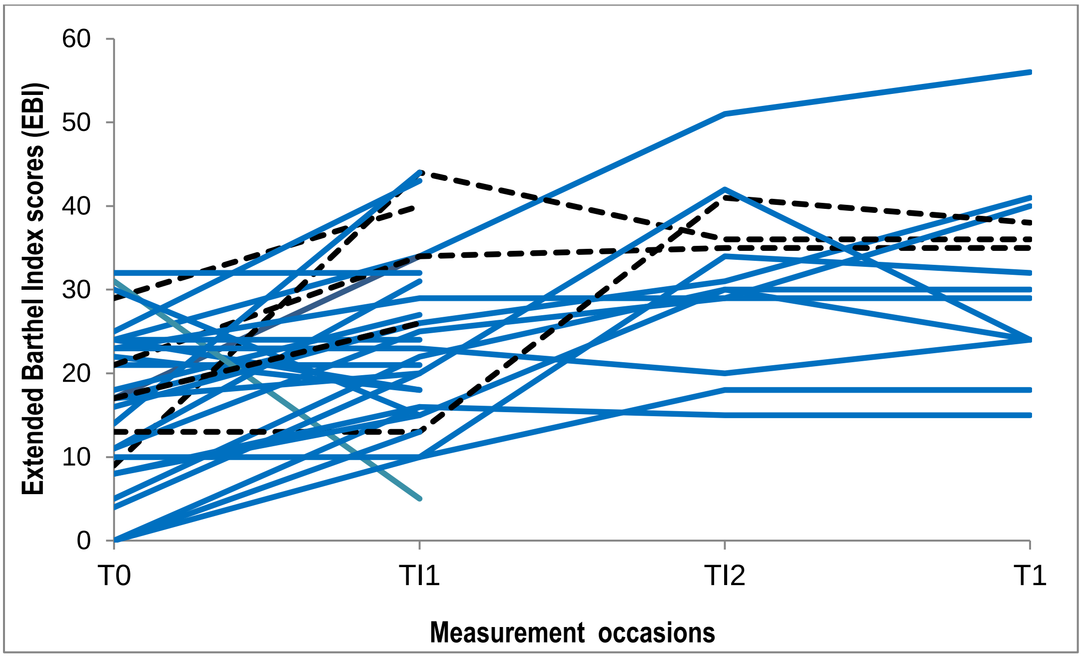
Abbreviations: HI+ & HI- (patients with and without hemi-inattention respectively), BIT = Behaviour Inattention Test, T0, T1, T2, T3 (baseline, discharge, 6 weeks post-discharge and 6 months since stroke). Lower and upper refer to quartiles.

Together the EBI scores strongly suggest that, as a group HI+ patients were consistently functioning at lower levels compared to HI- patients. This suggests higher levels of residual functional impairments in the HI+ group supported by severe baseline stroke severity scores (compared to moderate) (median NIHSS score 18.5 HI+ versus 10 HI-).

Further evidence for low EBI scores particularly in HI+ patients comes from analysis of interim data for 33 patients with severe stroke at TI1 (30 days since stroke) 15 of whom, were also assessed at TI2 (60 days since stroke) because they were still receiving stroke unit care (as per design in Diagram 3.1). Individual progress trajectories (for the 33 patients) between T0 and T1 were plotted in Figure 4.3 to visually enhance comparison and increase insight into the data.

Figure 4.3

Overall functional progress patterns of patients with severe stroke impairment at baseline.



Colour code: HI+ patients are shown in blue, HI- patients in dotted black line. T0 = baseline, Interim observation point (TI1 & TI2) which correspond to 30 and 60 days since stroke. T1 = discharge form in-patient stroke care.

Close inspection of the trajectories shows considerable variation in the amount and rate of progress of HI+ (solid blue lines) and HI- patients (dotted black lines) marked by a tendency for low EBI scores (EBI < 30). That being said, there are exceptions - some patients starting with very low EBI scores (below 15) have almost doubled this by TI1 (30 days since stroke).

The progress of patients who were still in the stroke unit at 60 days after stroke (TI2) is also marked by variable progress between 30 and 60 days; during which some clearly deteriorate, others stabilize whilst others improve. Interestingly, there is very little change between TI2 and T1 (discharge; range/days 5 to 182 for HI+ and 3-119 for HI-). Three patients (tracked in blue) continued to progress from TI2 up to discharge; in fact one of these progressed exceptionally well with a score clearly in the upper half of the EBI scale by TI2 and improving up to T1. However, the three patients are the exception rather than the rule. The patient who progressed exceptionally well was a 65 year old male diagnosed with moderate stroke (NIHSS score = 9) and mild HI (BIT score=127) who was in good health and worked as a postman prior to the stroke. He was 88 days on the stroke unit. The other two patients were (i) 56 year old male diagnosed with very severe stroke and HI, he was 182 days on the stroke unit and specialized (brain injury) rehabilitation ward and (ii) a morbidly obese, 67 year old female diagnosed with severe stroke and severe HI. All three patients were assessed by the dietician as being 'not at risk' of malnutrition at baseline.

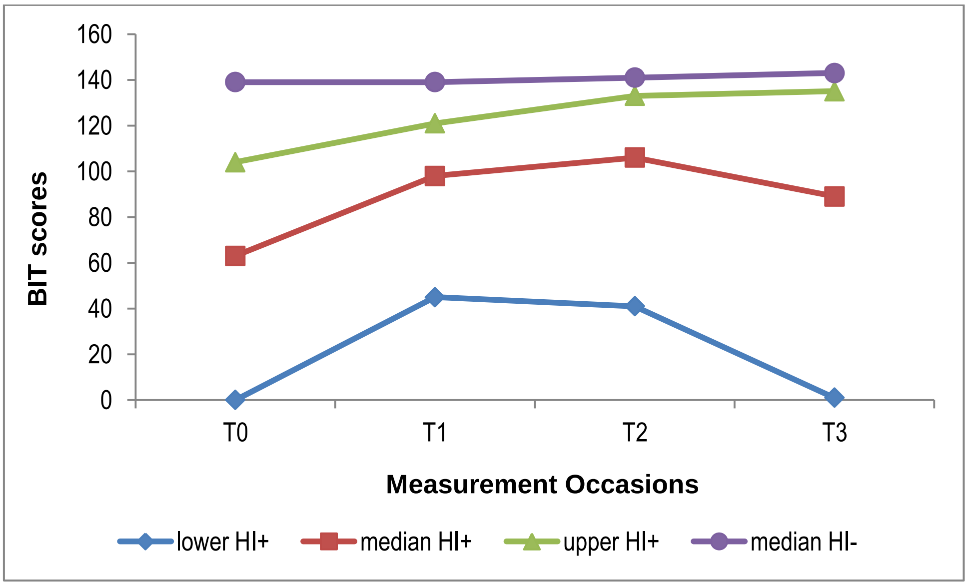
The reasons for an apparent early halt in progress of both HI+ and HI- patients with severe stroke can be varied and would need to be studied on an individual basis from clinical and research records. However, it is noted that at TI1 (30 days since stroke), 12 patients were transferred to long term institutions, 3 opted for home discharge rather than transfer to other generic rehabilitation facilities, wherein another two patients were transferred to Intermediate care and 15 remained on the stroke unit. The basis on which the multi-disciplinary team decisions were made primarily focused on potential for future rehabilitation as perceived by the MDT which was not always supported by validated standardized measures (usually BI scale 0-20). The functional progress of patients with severe stroke is further commented on in the main discussion (Ch6); however it is not the main focus of this study. For the interested reader, additional data on the outcomes of patients with severe stroke has been placed in Appendix H.

4.5.2. HI severity levels

The median group (HI±) scores and the upper/lower quartile scores for HI+ patients over time are plotted in Figure 4.4. In terms of change, as expected, the median BIT scores for patients without HI (purple line) remained stable over time (see also upper/lower quartile scores in Table 4.4). In comparison, the recovery of HI levels in HI+ patients was less predictable over time (blue line) - with those starting in the lower quadrant showing limited HI recovery from very severe to severe impairment levels by discharge (T1). However, they show signs of deterioration after T1 which rapidly accelerates to (initial) very severe levels between 6 weeks post-discharge (T2) and 6 months after stroke (T3).

Figure 4.4

Comparison of median BIT scores (HI severity levels) by patient group (HI±) over time



Abbreviations: HI+ & HI- (patients with and without hemi-inattention respectively), BIT = Behaviour Inattention Test, T0, T1, T2, T3 (baseline, discharge, 6 weeks post-discharge and 6 months since stroke). Lower and upper refer to quartiles.

Research records indicated that these patients tended to be discharged to institutions where post-stroke rehabilitation was not available (especially for cognitive dysfunction). Patients who started with moderate HI levels (median scores/red line) appear to have progressed steadily to borderline mild/moderate HI levels up to T2 but then tend to deteriorate between T2 and T3. Patients who start with mild HI impairment appear to progress steadily to normal HI levels on the BIT scale.

Overall, the above picture suggests that HI+ patients with initial moderate to severe HI level of impairment (i.e. the blue line) gradually deteriorate between discharge and six months after stroke; the more severe the HI, the faster the deterioration. The relationship of T0/HI levels with functional change is modelled in Ch5 and is discussed in depth in Ch6.

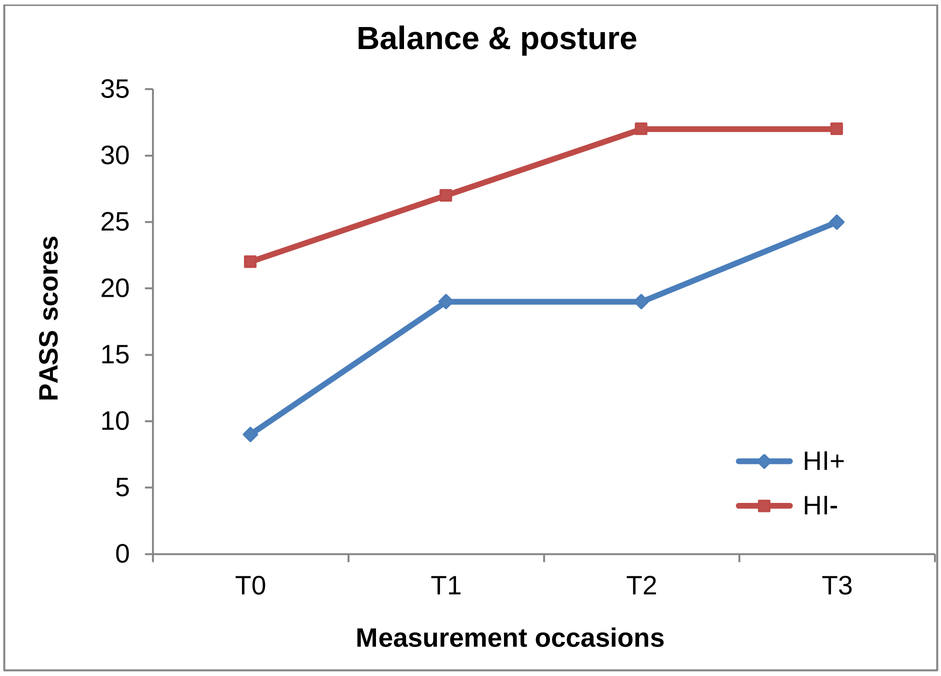
4.5.3. Motor function

Balance and posture control were measured by the PASS, the group (HI±) median scores are plotted in Figure 4.5. The graph shows that both HI± patient groups made considerable progress in motor function, with the HI+ group almost tripling their T0/PASS score during the six month period. However, in comparison to the HI- group, there is a marked tendency for poorer balance and posture control up to T3 (six months since stroke), at which point where the overall between group (HI+/-) disparity shows signs of diminishing.

In terms of progress rate, the HI- patient group made steady gains in motor function over time, ending up well within the high functioning range on the PASS scale (maximum 36) prior to stability of their scores at T2 (six week post-discharge). In comparison, the rate of change was more variable among HI+ patients and appears to be associated with assessment time since stroke. Given the likely association between motor recovery and physical aspects of ADL function, these results support earlier observations of generally low functional levels in the HI+ patient group. The relationship between T0/HI status and motor function will be revisited in the MLM analysis.

Figure 4.5

Comparison of median PASS scores between patient groups (HI±) in the first 6 months after stroke



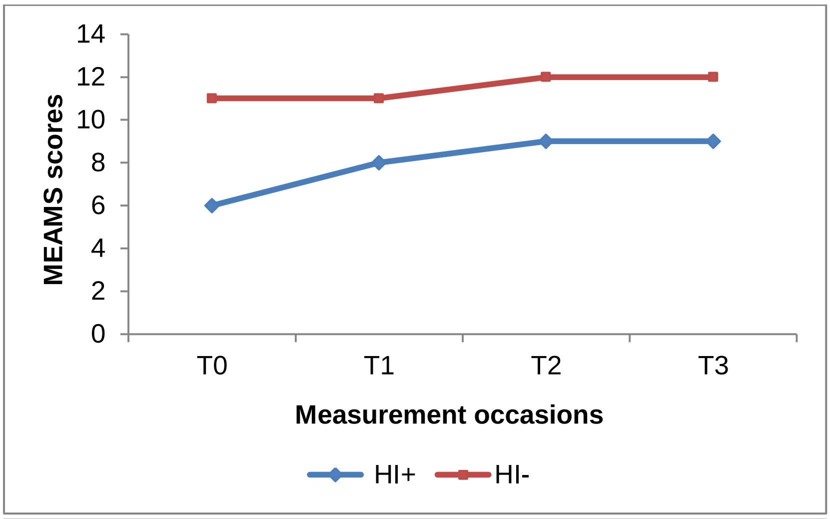
Abbreviations: HI+ & HI- (patients with and without hemi-inattention respectively), PASS = Postural Assessment Scale for Stroke, T0, T1, T2, T3 (baseline, discharge, 6 weeks post-discharge and 6 months since stroke respectively).

4.5.4. Global cognitive function

Global cognitive function was measured by the MEAMS, the median scores group scores are plotted in Figure 4.6. This clearly shows that the majority of patients without HI were hardly cognitively impaired in the first six months (MEAMS score = 11 to 12). In contrast, patients with HI were considerably cognitively impaired at baseline (scoring below the cut-off point of 7) but by T2 the majority had progressed steadily from (median) MEAMS score 6 to 9, which indicates borderline cognitive function on the MEAMS scale. However the majority of HI+ patients remained relatively lower functioning in terms of global cognitive ability at T3 (six months after stroke).

Figure 4.6

Comparison of median MEAMS scores between patient groups (HI±) in the first 6 months after stroke



Abbreviations: HI+ & HI- (patients with and without hemi-inattention respectively), MEAMS – Middlesex Elderly Assessment of Mental state, T0, T1, T2, T3 (baseline, discharge, 6 weeks post-discharge and 6 months since stroke respectively).

Overall the MEAMS scores suggest that group (HI±) differences in the community (between six weeks post discharge and six months after stroke) may not be of substantial importance but this does not necessarily hold true from a clinical perspective. The relationship between T0/HI status and global cognitive function with change in functional ability will become clearer during the MLM analysis in Ch5.

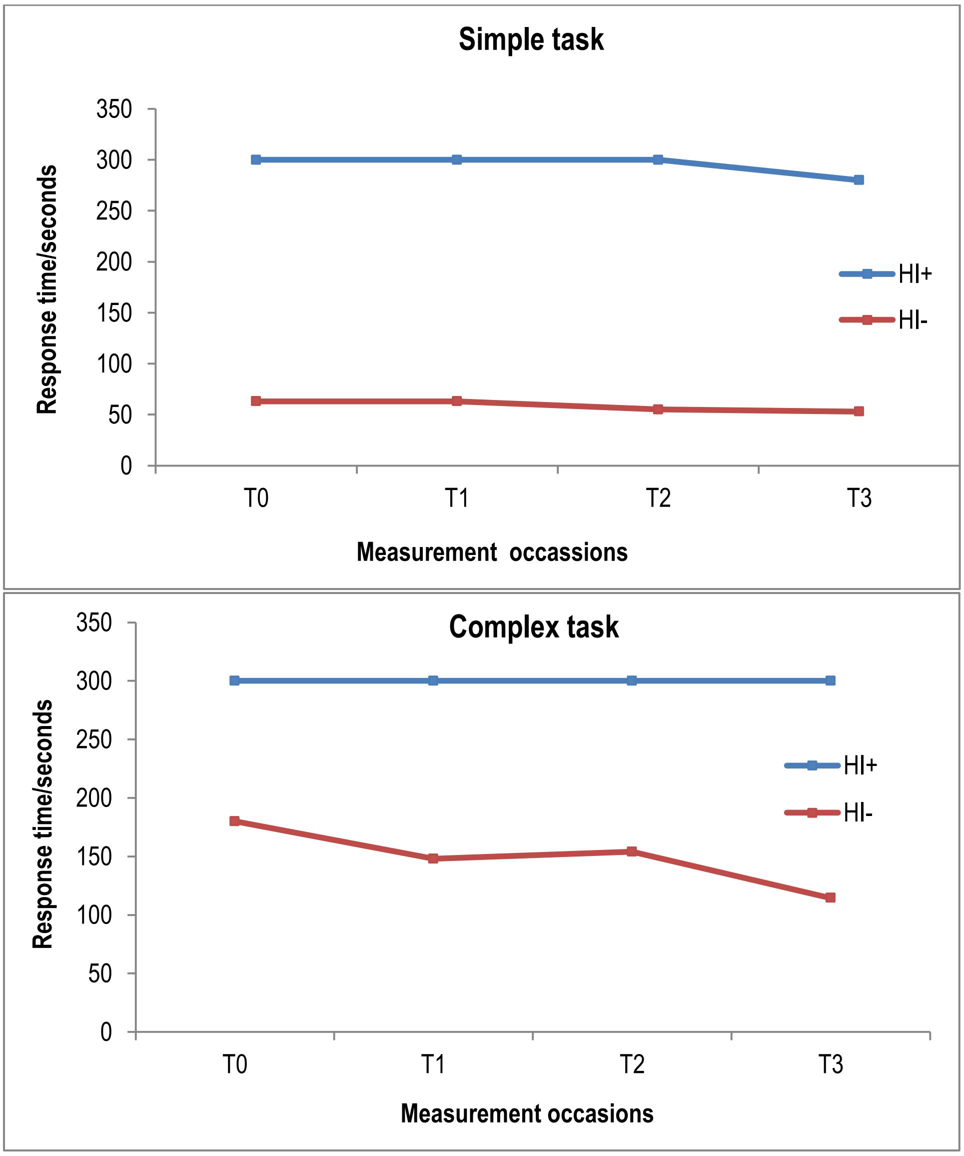
4.5.5. Executive function

Demands on cognitive motor processing speed imposed by simple and complex tasks were measured by two TMT timed tasks (refer to methods/TMT detailed description). Maximum time allowed to complete each task was 300 seconds.

To enhance HI± group contrast, median TMT scores in Table 4.4 were visually illustrated in Figure 4.7.

Figure 4.7

Cognitive-motor processing speeds – comparison of (median) response times in (HI±) patient groups in the first six months after stroke



Abbreviations: HI+ & HI- (patients with and without hemi-inattention respectively), TMT - Trail Making Test, T0, T1, T2, T3 (baseline, discharge, 6 weeks post-discharge and 6 months since stroke respectively).

The data in Figure 4.7 shows that as a group, the majority of HI- patients (red line) were markedly more efficient at completing both simple and complex TMT tasks when compared to HI+ patients (blue line) - at least, five times faster for simple and twice as fast for complex processing. This means that as a group, HI+ patients were inefficient despite indications that their simple task processing speeds were beginning to pick up by T3 (TMT median score = 280 seconds). More efficient HI+ patients (in the upper quartile) reduced their response time for the simple task, from T0 (237) to T3 (92 seconds) (in Table 4.4) but they were still markedly slower than the most inefficient patients (lower quartile) in the HI- group at T3 (62 seconds) for the same (simple) task. By T3, the most efficient HI+ patients were not able to finish the complex task on time (requiring more than 300 seconds) compared to the slowest HI- patients with a median response time of 209 seconds. This is important as impaired executive function is likely to have negative implications in terms of safety (e.g. increases risk of falls and injury due to low stamina and fatigue levels incurred with increased time to complete a task such as washing and dressing).

As a result the relative cognitive inefficiency in HI+ patients may indirectly limit their independence and functional ability levels. A more precise measure of the within-group variation and across patients (HI±) is estimated in the MLM analysis (Ch5).

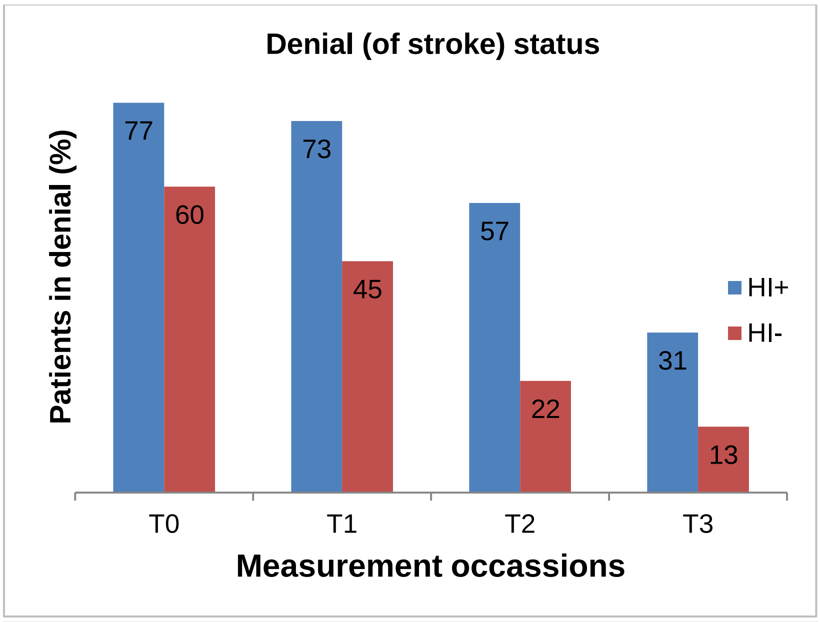
4.5.6. Self-efficacy levels (and denial status)

With reference to the self-efficacy (GSE) group median scores in Table 4.4, the majority of HI+ patients had similarly high self-efficacy levels as the HI- group (differed only by 2 GSE units) during the six months after stroke. However, HI+ patients falling into the lowest quadrant had considerably lower GSE scores at T2 (18.0) and T3 (16.5) compared to their counterpart T2 (29.0) and T3 (28.0).

The overall results are somewhat surprising in the sense that one might expect a larger median group difference in the GSE score based on HI± disparities in the results so far e.g. EBI & PASS scores. One interpretation could be that HI+ patients had high rates of denial and reduced self-awareness which would probably result in unrealistic perceptions of coping abilities, thereby yielding similar GSE scores. When put to the test, this turned out to be the case as illustrated later in Figure 4.10. The data clearly show a high frequency of denial of illness in HI+ patients which peaks to more than twice the frequency rate in HI- when assessed in the community (T2-T3). Both HI± groups showed high T0/denial rates which is not surprising because T0 was within 7 days of the stroke.

Figure 4.8

Bar chart: frequency (%) of patients in denial of stroke impairments by HI± group in the first six months after stroke



HI+ (n)	39/51		25/48		35/44		11/35	
HI- (n)	21/35		15/33		7/32		4/31	

Abbreviation: HI+ & HI- with and without hemi-inattention respectively, baseline (T0), discharge (T1), 6 weeks post discharge (T2) and 6 months (T3) after stroke onset

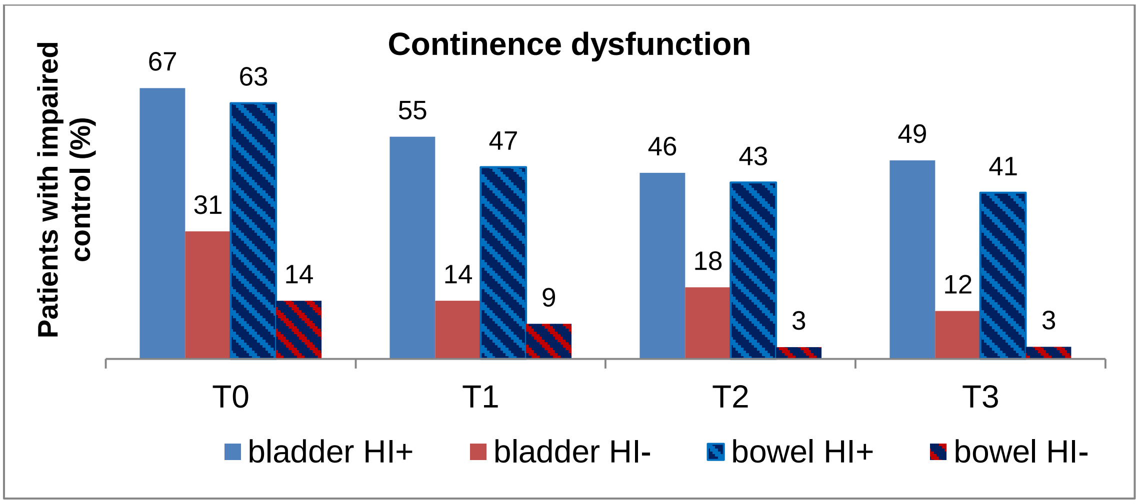
The data in Figure 4.8 also suggests more patients may have become aware of living with the consequences of stroke once in the community. This is plausible since they would have had to face the adversity of a more complex social and physical environment. In fact the largest drop in denial rates occurred at T2 after discharge in both HI+/- groups. Nevertheless, the frequency rate of denial is still relatively high at T2 and T3 in HI+ patients which may have clinical, safety and risk implications (elaborated on in the main discussion/Ch6).

4.5.7. Bladder and bowel continence levels

The frequency of bladder and bowel dysfunction in each group (HI±) is graphically illustrated in Figure 4.9. This shows that HI+ patients had higher rates of bowel and bladder dysfunction in the first six months after stroke.

Figure 4.9

Comparison of bladder and bowel (percentage) dysfunction rates in HI± patient groups in the first six months after stroke



Abbreviations: HI+ and HI- (with and without hemi-inattention respectively)

% = percentage, n=total number of cases analysed in each HI± group

Bladder, HI+ group, n = T0 (53), T1 (52), T2 (45), T3 (39), HI- group n = T0 (35), T1 (35), T2 (34), T3 (34),

Bowel, HI+ group, n = T0 (53), T1 (52), T2 (45), T3 (38), HI- group n = T0 (35), T1 (35), T2 (33), T3 (33)

Approximately 70% (36/52) of HI+ patients lacked both bladder and bowel control by discharge with little recovery occuring in the community - up to six months after stroke (T3). In comparison fewer HI- patients lacked T0/bladder control (31%) and/or bowel control (14%) which fell considerably by discharge and reduced again by T3 to 12% (bladder) and 3% (bowel). These figures strongly suggest that the recovery of bladder and bowel control was faster in HI- patients especially when the shorter duration of stay on the stroke unit (LOS) is taken into account (median 18 versus 37 days). The data in Table 4.4 and Figure 4.9 does not reflect different grades of continence dysfunction (e.g. partial versus complete dysfunction), these are reflected in the overall EBI score (please refer to Methods/section *3.2.2.12)*. Nevetheless, the observed discrepancy is likely to have clincial implications for rehabilitation and dependency levels especially when bladder and bowel dysfunction occur togther. The data in Figure 4.9 suggests a relationship between the two and lends support to earlier observations that as a group, HI+ patients had more severe strokes than the HI- patient group (refer to sample description). The relationship between functional ability (change over time), stroke severity, continence status and HI status was further studied during the MLM analysis and is reported on in Ch5.

4.5.8. Nutrition status

Nutrition status was assessed by the Malnutrition Universal Screening Tool (MUST) at admission to the stroke unit by dietiticians. Based on dietetic data extracted from MDT records, 26% (15/58) of HI+ patients were deemed at high risk compared to only 3% (1/35) of HI- patients at low risk of malnutrion (no HI- patients were assessed as at high risk). These figures suggest important differences between HI± patient groups in nutrition status which may have longer term medical and rehabilitative implications (e.g. low tolerance of fatigue and endurance among HI+ which may indirectly influence progress rate by limiting the amount and type of therapeutic input possible). The relationship between initial nutriton status and functional change in the first six months after stroke was further studied during MLM analysis, as reported in Ch5.

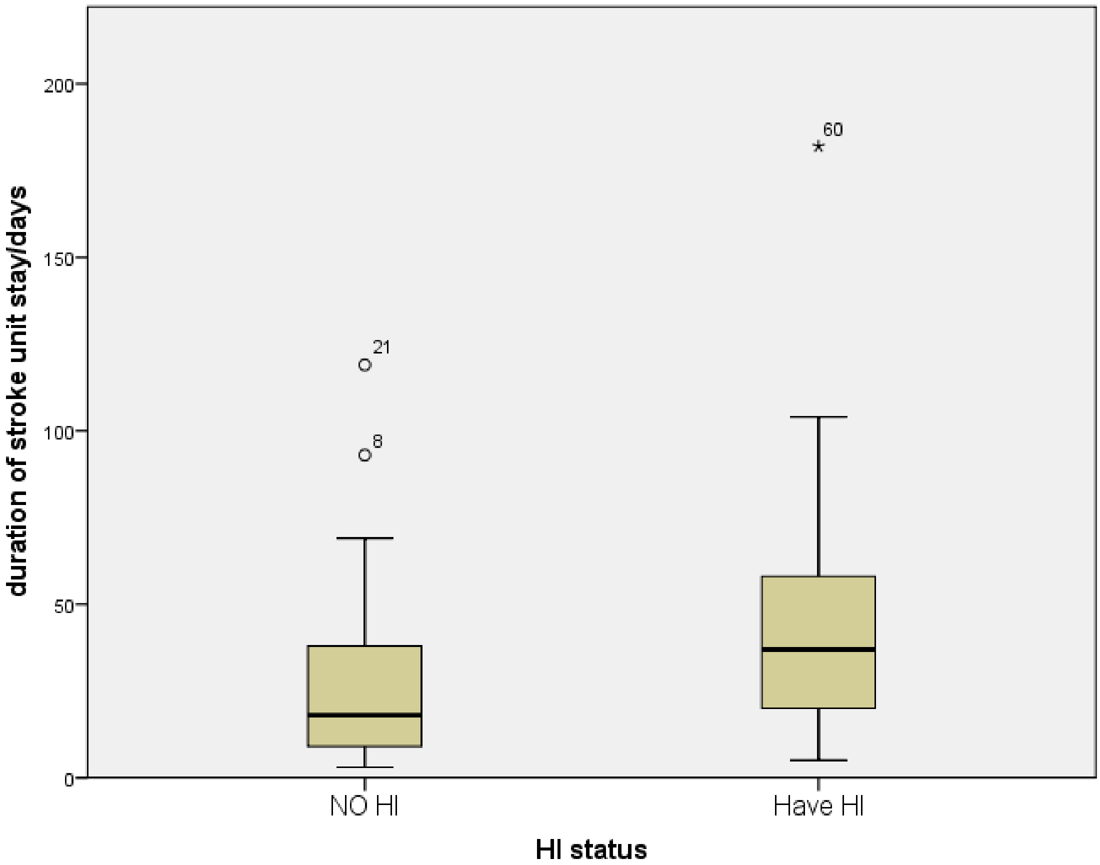
4.5.9. Duration of stroke unit in-patient stay (LOS)

The number of days spent on the stroke unit (LOS) is illustrated by HI± group in Figure 4.10 (box-plot). This shows that the majority of HI+ patients stayed a median of 37 compared to 18 days in the HI- group. Aside from the median difference, there is also considerable variation within and between both groups (e.g. in the 75 percentile (58 days for HI+, 38 days for HI-) and in terms of maximum stay (110 days for HI+, 75 days for HI- for non-outliers). In addition, there are extreme values (outliers - patient 8, 21, 60) on the LOS variable. Research records show that patient 60 had the longest duration of in-patient stay in the sample (180 days) consisent with a severe stroke (NIHSS score = 22) and severe HI. She was eventually discharged home supported by her husband (as the main carer) and community generic rehabilitation support.

Patient 8 lived on his own prior to his stroke of moderate severity (NIHSS score = 11) and stayed 93 days until he was recovered sufficently to manage at home supported by community services. Patient 21 had a relatively mild stroke (NIHSS score = 6) but developed associated medical complications. She was discharged home after 118 days supported by her husband and generic community rehabilitation. All three extreme values are plausible and as explained earlier in Methods Chapter (section 3.3) left in the data set.

Figure 4.10

Duration of stroke unit stay; comparison by patient group (with and without hemi-inattention (HI)



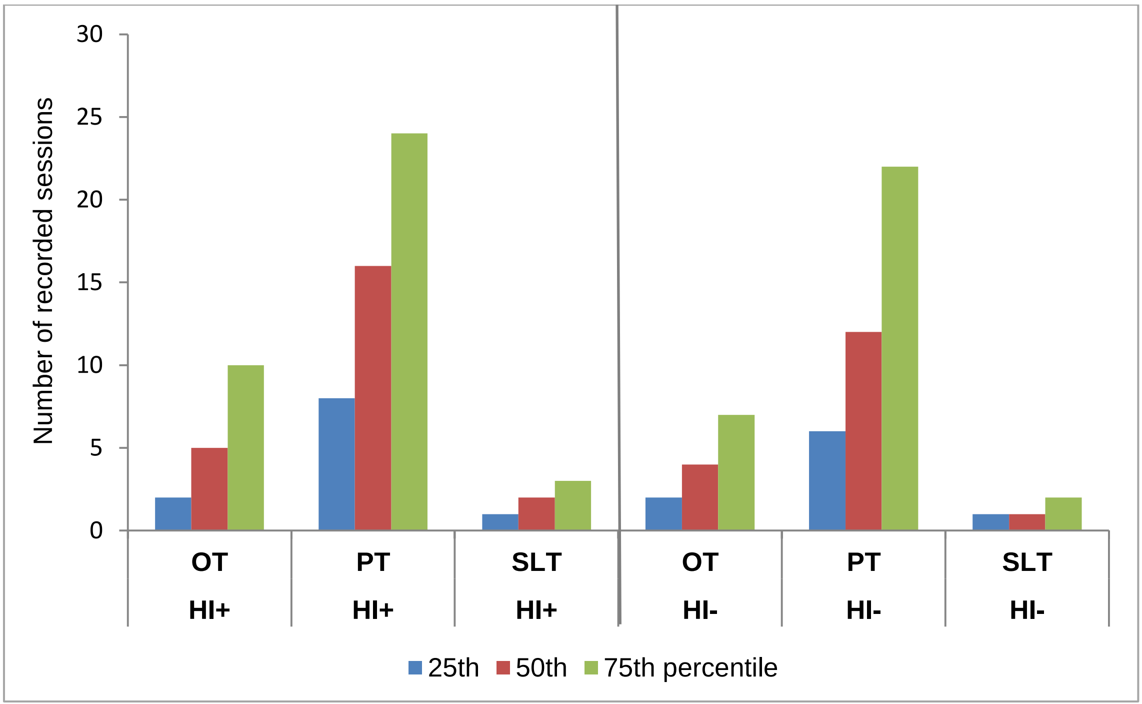
Overall the data indicates that HI+ patients had substantially longer exposure to stroke unit care which further suggests that their rehabilitative needs were considerably different to the HI- patients. Although the influence of time since stroke was separately estimated during MLM analysis, differing lengths of exposure to rehabilitation may have implications for functional outcome (results), which are further commented on in the main discussion chapter.

4.5.10. Recorded stroke unit therapy input

Relevant data for the indicative amount of therapy received by patients on the stroke units is presented in Figure 4.11, broken down by Occupational (OT), physiotherapy (PT) and speech and language (SLT) therapy.

Figure 4.11

Comparision of therapy records by HI status and discipline during stroke unit care



Abbreviations: OT = Occupational, PT = Physio, SLT = Speech and Language therapy, HI+ and HI- (patients with and without hemi-inattention respectively).

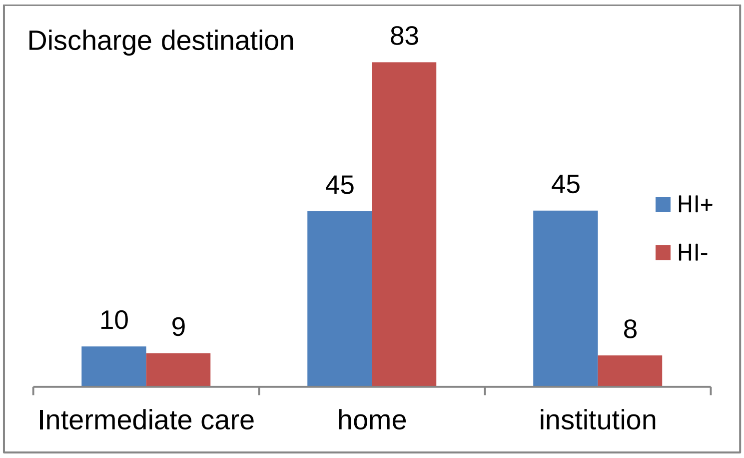
Despite their differing lengths of stay, on average, the two (HI±) groups seem to receive similar numbers of therapy sessions, according to case records. Physiotherapy input predominates followed by OT and small amounts of SLT. The findings are difficult to interpret. On the one hand, one would expect greater average discrepancy (in favour of HI+) in the data, given the longer LOS and higher dysfunction with ADL tasks observed in the HI+ group. Alternatively, the records reflect limitations imposed by other factors e.g. medical, nursing complications and behavioural (e.g. high rate of denial and cognitive impairment in HI+ group) which may limit therapeutic engagement. These and other reasons are further explored in the main discussion (Ch6).

4.5.11. Discharge destination outcome

Relevant data on discharge destination outcome is presented in Figure 4.12. This shows that the majority (n= 29/35) of HI- patients were discharged home compared to (n=27/58) of HI+ patients discharged to caring institutions (residential or nursing) and (n=26/58) home. In addition, 5 HI+ and 3 HI- patients were discharged to intermediate care for an extra 6 weeks of intensive rehabilitation prior to discharge home.

Figure 4.12

Discharge destination outcome grouped by HI status (percentage figures).



Overall the findings support earlier results that HI+ patients tended to have poor functional outcomes at discharge even when the presence of an informal carer (spouse, family) is taken into account (n=50 HI+, 28 HI- had carers). The relationship between T0/HI status, discharge destination outcome and functional ability levels was also explored by means of MLM analysis and is described in subsequent chapters.

4.5.12. Summary of the results and conclusion

As a group, HI+ patients tended towards low baseline scores in levels of functional ability, motor function (balance and postural abilities), cognition including executive function, and self-efficacy. Furthermore, 26% (15/58) were at high risk of malnutrition. High rates of bladder and bowel dysfunction were also noted in this group. With the exception of denial status and self-efficacy status, baseline group differences were statistically significant (please refer to supplementary data in Appendix I). Overall, the findings indicate that at admission, HI+ patients were substantially more impaired than HI- patients which is further supported by predominantly severe stroke levels found in the HI+ patient group (refer to demographics in Table 4.1).

On average, all patients improved at follow-up irrespective of their initial HI status. However, change in progress varied considerably by factor and by group (HI±) in the 1st six months since stroke. In general, progress rates peaked at discharge followed by a marked dip by six weeks post-discharge and a tendency for gradual stabilization of scores towards the six months mark since stroke. This pattern suggests that time since stroke would be optimally modelled as a quadratic trend which would also preserve the order of change in scores over time. This is further explored in the following chapter.

Substantial variation within groups was observed, supported by a wide distribution of scores on several factors and especially in the HI+ group (compare median, upper and lower quartile scores for variables summarized in Table 4.4). Of specific importance is the variation observed on the HI factor (BIT scores) within HI+ patient group (Figure 4.4). This deserves attention not only because of its primary interest to the study but because it is likely to limit the inferences that can be made from group tendencies in the next phase of the analysis. To this end, MLM will be employed to estimate the amount of variation from average modelled (group) trends.

In relation to patient discharge, patients without HI were twice as likely to be discharged home following shorter periods of stroke unit rehabilitation compared to patients with HI. Preliminary evidence from discharge destination figures suggests that the availability of a carer (e.g. partner, spouse, relative) does not necessarily increase the chances of a patient with HI returning home as it does for a patient without HI under the same conditions. Relevant to this point was the observation that those patients who started with low T0/scores tended to be also discharged with low scores, irrespective of HI status (supported by data in Figure 4.3). The reverse is also true.

In conclusion, substantial differences in the abilities of HI± patients within and between groups were highlighted, on multiple time-variable factors e.g. HI levels and motor function, addressing research objective two. The statistical importance of these differences will be identified in the next chapter (Ch5) which is the multi-level modelling analyses.

Chapter 5 – Multilevel Modelling Results

Chapter Five

Multilevel Modelling Results

5.0. Introduction

This is an in-depth report of the multi-level modelling (MLM) undertaken to address the final research objective identified in the Methods Chapter (3). This is an in-depth study of the dynamic relationship between early HI status and functional progress (change over time), when other factors (descriptively analysed in Ch4) are also taken into account.

The research question is restated:

> *"What is the relationship between early*** *HI status (HI±) and functional change in the 1st six months after right hemisphere stroke?"*
>
> ***(within 7 days since stroke)*

The layout of the chapter is as follows:

Section one contains descriptive data for the modelled variables (in longitudinal format as required by MLwin software version 2.28) followed by exploratory analysis of individual patient scores over time. This leads to step by step estimation of the basic model (M1) on which subsequent more complex models were constructed. M1 consisted of functional ability (DV), the predictor variable of interest (baseline hemi-inattention group status) denoted as HI status (HI±) and the confounding factors; time, stroke severity and age which were identified (a priori) in the methods chapter (ch3). Refer to section 5.1 for more detail.

Section two is focused on the identification of important relationships between predictor factors (preliminarily analysed in ch4 through graphical representation), HI status and functional progress (change) in the 1st six months since stroke. For this analysis, a series of variant models was set up on the basic model (M1) and estimated. Relevant results and findings are included in section 5.2; they informed the selection of appropriate predictors in the final model.

Section three is concerned with derivation of the final model (Mf) from potential predictor factors identified in section two, supported by current research in stroke and clinical knowledge in the field. Mf consisted of time, stroke severity, age, motor function, cognitive function, self-efficacy and bladder control. Group HI status was not a statistically significant explanatory factor when modelled together with the other influential factors in Mf.

An overall summary concludes chapter five.

Important consideration was given to the modelling of time which refers to 'time since stroke'. Together with initial HI status, time is of principal interest and relevance to the research question. In addition, both fixed (average population trends) and random effects (residual variance in the models) were considered during the modelling process and interpretation of the results.

Integrated into the report is a narrative aimed at guiding the less familiar reader through the MLM decision making process and the rationale behind key models used to study associations in the data. The purpose is also to assist with understanding and following the MLM results. In addition, the reader is referred to the Methods Ch3 in section 4.3, where important information on MLM is located as follows;

Section 3.4.1 contains the justification behind the use of MLM instead of traditional (single level) multivariate regression and analysis of variance methods (ANOVA) employed by past studies reviewed in the literature (Ch2).

Section 3.4.2 describes MLM operational principles and specific terminology used in the current MLM analysis.

Section 3.4.3 and 3.4.4 contains the rationale for the two level structural model used to evaluate all the models and relevant factor definition by level.

Other information on measurement units and comparison of 'fit' between models is found in the Methods chapter (Ch3) but will be repeated as appropriate in the narrative here in Ch5.

5.1. Section one

5.1.1. Summary statistics

Following on from data checks for linearity and multicollinearity in the Methods/section 3.4.9.1., the summary statistics of potential explanatory variables (from Ch4) in longitudinal format are presented in Table 5.1 according to the shape of the distribution (mean/SD for normal and median/range for skewed distributions).

In line with MLM guidelines (Methods/section 3.4.11.1) appropriate variables were standardised by centring on a fixed value (Singer and Willett 2003, Field 2009). This is either the grand mean or median, which appears next to the variable (in Table 5.1/ column 1). For ease of interpretation, the expected ability of a patient at the fixed value on a specific measure is commented on in column 5. The information will assist with the interpretation of MLM regression intercepts (i.e. the mean functional ability level (DV) when all variables in a given model are at their fixed value).

Table 5.1 Summary statistics and fixed point centring of variables

Normal distribution Centred variables*	N	Mean	SD	Comments** Represents a patient who/with/is….
Age-75	372	75.96	10.089	75 years old
NIHSS-16	372	15.76	6.27	Severe stroke (NIHSS =15 - 24)
EBI	338	37.64	17.70	DV (conventionally not centred)
PASS-20	336	20.42	11.18	Able to stand supported, scale
GSE-29	275	28.52	10.02	Has relatively high self-efficacy (upper half of GSE scale 0 to 40)
Non-normal distribution		Median	Range	
BIT-128	333	128.00	146.00	Borderline clinically significant HI (cut-(BIT cut-off=129)
MEAMS-10	333	10.00	12.00	mild cognitive impairment
TMTA-130	325	130.00	280.00	Represents a patient who takes 130 sec. to complete simple task
TMTB-300	324	300.00	300.00	A patient who finishes complex TMT task in 300 sec. (max. time allowed)
LOS-30	372	29.00	179.00	A patient who received 30 days of stroke unit rehabilitation
I/P-20	356	21.00	179.00	A patient who had 20 therapy sessions (pre-recorded in MDT notes)

Abbreviations: N = number of cases in the longitudinal format. SD = standard deviation. NIHSS – National Institute of Health Stroke Scale, EBI – Extended Barthel Index, PASS – Postural assessment scale for stroke, GSE – general self-efficacy levels, BIT - Behaviour Inattention Test, MEAMS – Middlesex elderly assessment of mental state, TMT – Trail Making Test, LOS – Length of in-patient stay, I/P – amount of in-patient therapy sessions (recorded in the MDT records).

** centred variables will appear as shown in column 1 in the result Tables*

*** Descriptions in column 5 represent the ability level of a patient at the centred value for a specific variable (shown in column 1). This information is needed for the interpretation of the regression intercept (= mean of EBI when all other variables are centred at the value indicated in column 1).*

To recap from the Methods Chapter (section 3.4.9.1), the process of centring minimises the adverse effects of multicollinearity (i.e. a correlation of more than 0.8 between predictor variables) and enhances interpretation of the regression intercept estimates (Nezlek 2001, Twisk 2006, Field 2009) as illustrated by this example:

In Table 5.1, age is fixed at 75 (age-75), stroke severity at 16 (NIHSS-16) and LOS at 30 (LOS-30). Consequently, the estimated the regression intercept for a model containing the three variables will refer to an ‘average’ 75-year old patient with severe stroke who received 30 days of in-patient stroke care. If age, stroke severity and LOS were not fixed at meaningful values, the estimated intercept would refer to a healthy patient (NIHSS=0) of aged 0 years who did not receive in-patient rehabilitation (LOS=0), which is not meaningful in this case.

5.1.2. Definition of factors in the (two level) structural-model

The rationale for the chosen structural model and factor definition by level can be found in Methods/section 3.4.4, they are briefly summarised in this section.

Table 5.2

Summary of modelled factors and respective variables as defined at set-up by structural level

Dependent variable (DV)	Overall functional ability [EBI]
Potential predictors (IV’s)	Level 1 (time variant factors)
	Motor function (PASS), cognitive function (MEAMS), executive function (TMT), self-efficacy (GSE), HI severity level (BIT), denial status (does or does not acknowledge stroke), continence status (impaired/not impaired)
	Level 2 (time invariant factors)
	T0/HI status (HI+/- group) stroke severity (NIHSS), type and site of lesion, age, nutrition (health/unhealthy), duration of in-patient stay (LOS), carer (available/not available), amount of recorded in-patient therapy sessions (ITS), stroke unit (A/B)
Apriori confounding factors	Time post-stroke, stroke severity, age
N.B. In modelling, potential explanatory variables are also referred to as predictor or independent variables (IV’s) but they are not under the control of the researcher as they would be in an experiment.	

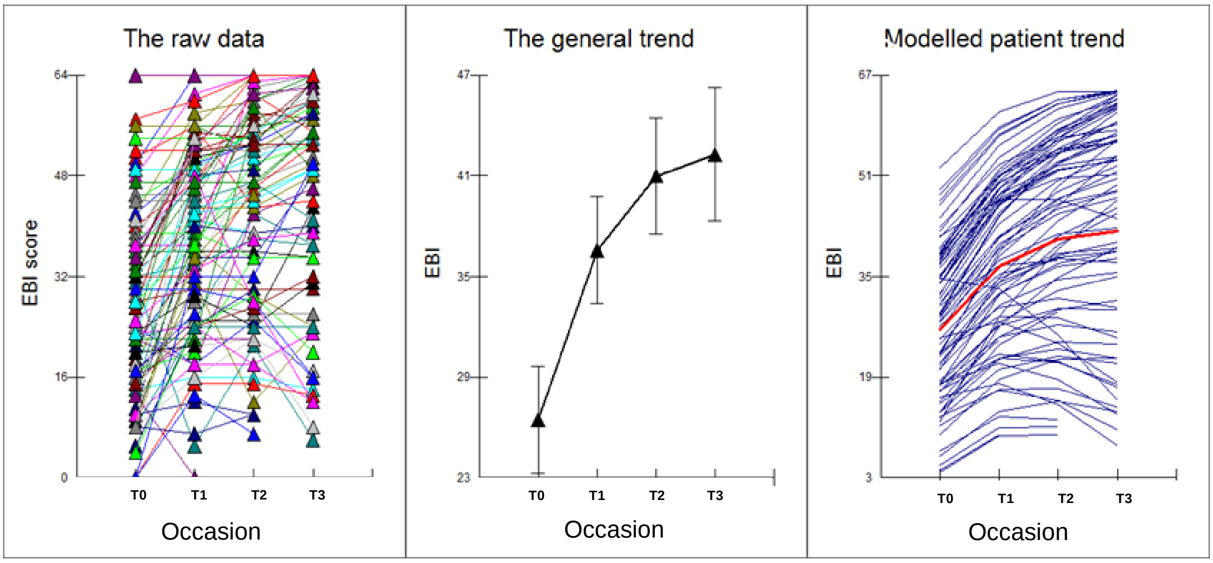
The basic structure used for all the models evaluated in the study is a two level (random intercept and slope) model consisting of time-variant factors (measures at T0, T1, T2, T3) at level one (L1) and patient related (time in-variant factors in this study) at level two (L2) as (illustrated in Diagram 3.1). A complete list of time variant/invariant modelled factors defined by level is shown in Table 5.2.

5.1.3. Basic model exploration

The preliminary results (ch4) highlighted substantial differences in HI± group scores and general progress patterns however the source and nature of individual variation in functional ability (DV) is relatively unknown. This information is important because it provides insight into change over time both within and between patients and therefore how best to model 'time since stroke'. For this purpose a method advocated by Singer and Willet (2003) was used as a starting guide to the identification of an appropriate model.

Figure 5.1

Patient progress trends - change in functional ability over time (n=93)



Abbreviations: EBI = Extended Barthel Index, Occasion refers toT0, T1, T2 & T3 = baseline, discharge, 6 weeks post-discharge and six months since stroke

According to the method, patient trends were initially studied from raw EBI scores illustrated in Figure 5.1/left graph. This shows considerable individual variation in the rate and amount of progress in functional ability over time characterized by a chaos in which trajectories are going everywhere. However, when studied closely amid all the background noise (chaos), a general pattern of progress emerges in the majority of patients. When plotted (in the middle graph) this pattern is clearly non-linear; it shows that on average change in overall function is fastest prior to discharge into the community, after which it slows down and gradually begins to taper off around the six month mark post stroke onset. This supports group functional progress trends identified in the previous chapter (in Figure 4.2) which indicated a linear, faster rate of change between T0 and T1 (discharge; median 29 days, range 3 to 179 days) followed by a gradual tapering off post-discharge and up to six month since stroke (T3) in the majority of patients. When modelled, that growth or progress trend is shown in the right graph/ Figure 5.1. Importantly, it suggests that those patients who started with low EBI scores i.e. below the red mark also tended to finish with low scores (EBI<30) (below the red mark) and vice versa. There are clearly some exceptions to the rule but these are fewer and far in between compared to the average trend. In fact, the overall pattern would suggest that T0 (EBI scores) may predict functional outcome in the 1st six months after stroke. On the other hand, exceptional differences suggest that the picture is complex (at the level of the individual) which is supported by earlier observations from severely stroke impaired patients (illustrated in Figure 4.3/interim observations).

5.1.3.1. Variance components (unconditional) model

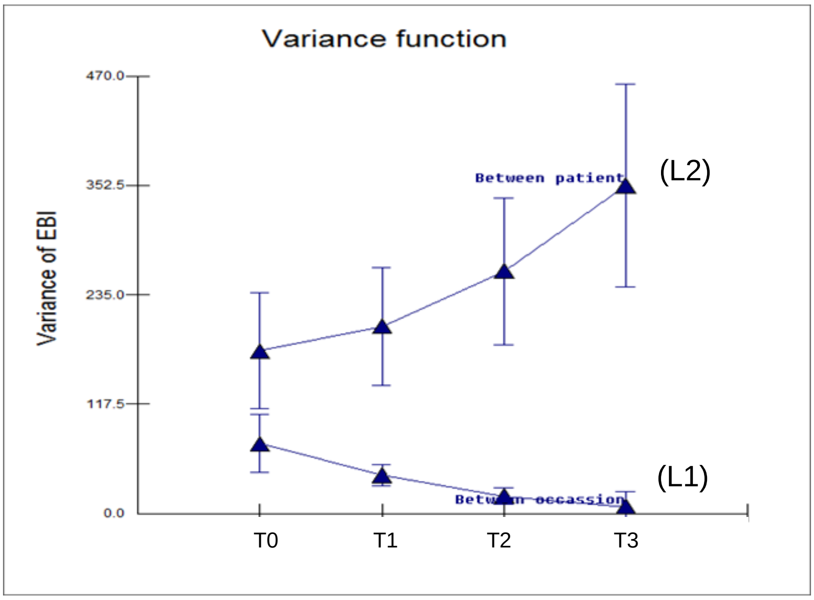
In support of the Methods section 3.4.10, a stepping up approach to building the basic model was used as advocated by Singer and Willet (2003) and Twisk (2006). This starts of with a variance components also known as empty model.

P*urpose* – its purpose is to partition existing variance around the EBI (DV) and estimate estimate it at separate level of the model i.e. at the measurement level (L1) and patient level (L2). As explained in the Methods/MLM section 3.4.6/ in the structural model used, regression coefficient estimates from L1 can be interpreted as differences arising from within the individual and those from L2 as differences resulting from changes between individuals across the sample with time since stroke (Singer and Willet 2003, Tabachnik and Fiddel 2007, Steele 2008).

Results - MLM estimates yielded 335 (EBI) variance units spread between L1 (113 units) and L2 (221 units). Calculation by means of the intra-class correlation coefficient (ICC) indicates that <u>66% [221/335] of the total variance in functional ability can be attributed to differences between individual patients</u> across the sample e.g. due to age, but can also be due to unmeasured characteristics. In contrast, <u>34% [114/335] of the variance can be attributed to changes within individuals</u> e.g. change in cognitive function or motivation.

Figure 5.2

Distribution of variance at level one (L1) and level two (L2) with time since stroke



This result is illustrated in Figure 5.2. The upper graph clearly shows that the differences between patients tend to widen or increase over time - thus dominating the 'variance picture'; whereas differences originating from changes within the patients become smaller over time as they tend to progress on measurement scales. Further, the high ICC of 0.66 is indicative of significant high dependency in the data (significant correlation exists) which supports the need for MLM in order that the correlations can be accounted for by the MLM modelling procedures (Nezlek 2001, Twisk 2006).

5.1.4. Modelling of time since stroke

The general progress trend (in Figure 5.1) was accommodated in two ways documented in MLM statistical literature (Singer and Willett 2003, Twisk 2006, Hedeker and Gibbons 2006, Steele 2008) - by a linear and a quadratic growth curve (otherwise referred to as 1st and 2nd order orthogonal polynomial) in later models or categorical variable for time in earlier models. The choice of method depended on the purpose of the model and ease of interpretation of regression coefficients. This will become clearer later on. Both methods were used by other researchers in the field (e.g. Kollen et al 2005, Kwakkel et al 2006 and advocated by Cheng et al 2010).

5.1.5. The basic model (M1)

Purpose – The basic model estimated the independent effect of baseline HI status (which will be referred to simply as HI status) on functional ability (DV) before and after accounting for the effect of *a priori* confounding variables - time, stroke severity and age (identified in the Methods/section 3.4.7). M1 was subsequently used as basis for the next set of models described in section 5.2.

5.1.5.1. Model parameters

M1 was gradually built from models1a-d and estimated 4 times in the order shown. The DV was always functional ability measured by the EBI scale.

(1^{st}) Functional ability (DV) = HI status,

(2^{nd}) DV = HI status & time,

(3^{rd}) DV = HI status, time and stroke severity

(4^{th}) DV = HI status, time, stroke severity and age.

Time was introduced as a categorical variable in the fixed part of the models with the referent category being baseline (T0) and three dummy variables (T1, T2, T3) contrasted to T0. A complex variance function involving continuous time was also introduced in the random part to make for a parsimonious (simple) model with only three random terms (intercept, slope and covariance). This method is described in Twisk (2006) and Cheng et al (2010).

5.1.5.2. Results – Basic Model estimates

Regression Coefficient (RC) estimates from models (1a-d) are presented in Table 5.3 along with their standard error (SE) (in the row below). Refer to comments accompanying Table 5.3 which supplement the explanation in text. For clarity and focus of Tabel 5.3, corresponding confidence interval (CI) and significance levels (p values) have been placed in Appendix O.

When functional ability (EBI scores) was regressed on HI status only (model 1a), the group difference between patients was approximately (~) 19 EBI units with HI+ scoring lower than HI- group, and is statistically significant (RC is more than twice its SE).

Table 5.3 – Estimates from the development of the basic model (1a to 1d)

N=338/372		C1	C2	C3	C4	C5	C6	C7
Model	Variables	HI status	T1	T2	T3	NIHSS	age	IGLS
1a	HI status	-18.81 (2.76)						2712
1b	Time-T0	-16.63 (2.60)	10.13 (1.21)	14.64 (1.35)	16.12 (1.64)			2476
1c	NIHSS-16	-3.64 (2.36)	10.25 (1.21)	14.79 (1.35)	16.29 (1.63)	-1.68 (0.19)		2421
1d	Age-75	-2.95 (2.25)	10.21 (1.20)	14.74 (1.35)	16.27 (1.63)	-1.66 (0.18)	-0.29 (0.088)	2411

Abbreviations; C = column, NIHSS-16 = stroke severity, IGLS = IGLS deviance = model fit statistic = the smaller the deviance the better the fit.

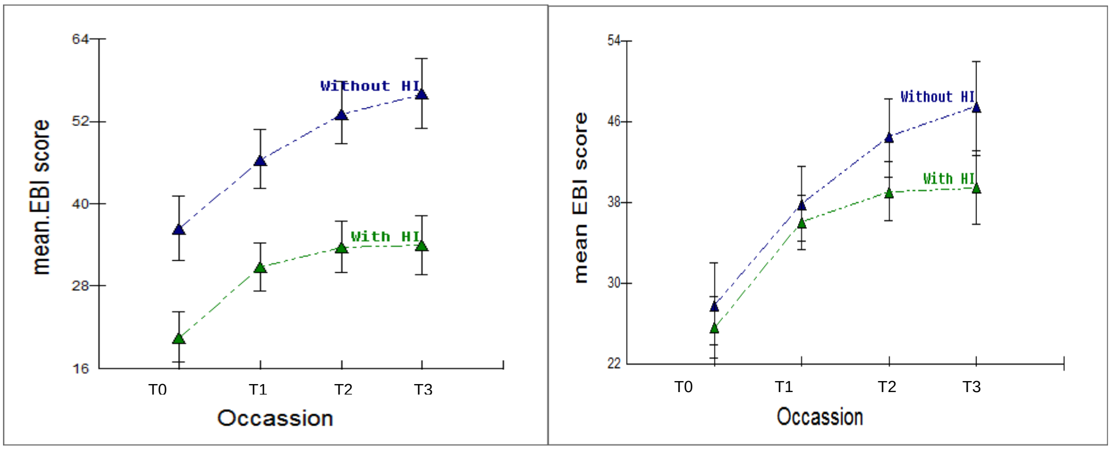
Confidence intervals and p-values were calculated but for clarity of table 5.3 in text, they were put in appendix O. However regression coefficients (RCs) which are at least twice their SE are statistically significant ($p \le 0.05$); the larger the coefficient compared to its SE the higher the significance level. Non-statistically significant regression coefficients are highlighted in yellow. HI status – estimates represent difference between HI+ and HI- groups (estimates provided are with respect to the HI+ group). 'Time' – estimates provided are in comparison to baseline (T0) which was the reference category

When time was added to model 1b (column C 1-4), the contribution of HI status to functional ability was slightly lower (from 18.81 to 16 .63) but the difference between HI± groups was still highly significant (16.3 EBI units less for HI+ group). Compared to T0, time contributed an increase of approximately 10, 15 and 16 EBI units at T1, T2 and T3 respectively. This result supports earlier findings in Ch4 that most of the improvement occurred between T0 and T1 (discharge).

When stroke severity was added to model 1c (C1-5), the difference between HI± groups dropped remarkably from 19 to 3.64 EBI units, which is not statistically significant; p=0.061. This result strongly suggests that stroke severity explains a considerable portion of the earlier differences observed in HI status and is graphically illustrated in Figure 5.3. In the left graph, group differences are significant and no overlap can be seen between error bars (CI's). In the right hand graph, stroke severeity has been taken into account – s a result the same group differences now tend towards statistical insignificance with CI's error bars overlapping zero except for T3 which appears to be borderline statistical significance.

Figure 5.3

Modelled relationship between functional ability and HI status prior to (left) and after statistical adjustment (right) of stroke severity in model 1c/Table 5.3.



Abbreviations: EBI=Extended Barthel Index, Occasion refers to measurement at T0 – T3 = baseline, discharge, 6 weeks post discharge and 6 months post stroke onset.

From data in Table 5.3 (model 1c/C5) it can be deduced that for every unit increase in the NIHSS stroke severity scale, the EBI score significantly drops by 1.68 units (p=4.70e-019). This is equivalent to a drop of 33.6 EBI units in a severely stroke impaired patient (NIHSS score = 20) and 6.72 EBI units in a mild impaired patient (NIHSS score = 4). This result supports the predictive importance of stroke severity in regard to functional ability at 6 months after stroke.

When age was added to model 1d (Table 5.3/C1-6), the HI status-coefficient remained insignificant. However, for every year increase in age the EBI score drops by 0.29 units which is statistically significant (p=0.00058). This result supports the predictive importance of age in this particular model. All other coefficient estimates in model 1d remain relatively unchanged from previous estimates. Overall, data in Table 5.3 suggests that time since stroke and stroke severity may be independent predictors of functional ability in the first 6 months i.e. they are relatively unaffected by the addition of other variables e.g. age. This may become clearer as the analysis proceeds.

With respect to the *random* (variance) parameters in the basic model, the covariance between individuals' patient intercept and slope was -25.52 with SE of 9.07, which is statistically significant (p=0.0025). This result is interpreted as: patients starting with extremely low T0/EBI scores (below the mean) progress at faster rates than those starting with higher scores who progress at lower rates, however differences tend to stabilise with time.

IGLS deviance estimates are used to compare the fit of similar models; the smaller the value the better the fit (refer to Methods/section 3.4.9). Deviance estimates in Table 5.3/C7 drop significantly between successive models (1a-d) indicating that the inclusion of time, stroke severity and age statistically, significantly improves model fit.

5.1.5.3. Summary of results so far

MLM results so far do not support an important relationship between early (T0) HI status and functional ability in the 1st six months after stroke, once the effect of time since stroke, stroke severity and age are accounted for. Under the same model conditions, any remaining differences between HI± groups are likely to be of negligible importance (statistically insignificant). Random coefficient estimates support a positive relationship between T0 functional ability and later outcome in the 1st six months after stroke. Further, relevant data suggests that stroke severity and time since stroke may be independent predictors (explaining more than 10% of the DV) of functional ability in the first six months after stroke (Twisk 2006). Age also showed significant predictive importance when modelled with HI status, time, and stroke severity.

5.2. Section two – *(Transient model series)*

Purpose – The next set of transient models aimed to identify the effect of HI status on functional ability when potential predictors (in Table 5.2/Ch4) were separately added to the basic model so that the effect of stroke severity, time and age were accounted for. As discussed earlier in the Literature Review and Methods Chapters, theoretically and clinically it is possible that the causal effect of HI status changes when other influential factors are taken into account (as they would be in clinical presentations of stroke).

5.2.1. Model parameters

There were 17 model variants in the series (M2a-q) – one for each potential predictor factor evaluated. Hence for each separate model the equation is:

Functional ability (DV) = HI status + time + stroke severity + age + x

where x was one of the following factors – *lesion type, lesion location, carer status, gender, motor function (balance/posture), cognitive function, executive function (two variables TMT/A & TMT/B), self-efficacy, denial status, continence status (two variables – bowel and bladder control), nutrition status, LOS, amount of recorded in-patient therapy sessions, discharge destination and stroke unit identifier (A or B).*

Time since stroke was modelled as a categorical variable exactly as described for the basic model (M1). In total, there were 17 estimations followed by extraction of the following data from each MLwin output. For each model:

- Fixed effect of HI status on functional ability.
- Fixed effect of predictor variable (covariate-x) on functional ability
- From the random part of the models - Residual (unexplained) variance at L1 (within) and L2 (between) patients and intercept-slope covariance.
- Overall regression-intercept.

5.2.2 Presentation of the results

The MLM estimates for model series (M2a-q) are presented in Tables 5.4 – 5.6 and with accompanying comments in text and below the tables. The coefficients for stroke severity, age and time in each model (M2a-q) were checked to see if they remained statistically significant during the process. For clarity, these estimates are presented in Appendix P (not in Table 5.4).

Table 5.4 is labelled in columns (C1-9) and rows (a - q). One must read from left to right along individual rows. Each row contains MLM results for a specific model variant defined by covariate (x) e.g. row (a) contains estimates from model (M2a) when type of stroke is in the model. Columns (C2-4) contain fixed coefficient estimates, confidence intervals (CI) and significance levels (p-value) for covariate x respectively. Columns (C5-7) contain fixed coefficient estimates, CI's and p-value for HI status in a specific model from (M2a-q). The last two columns (C8-9) contain the number of cases used to compute the analysis and IGLS deviance statistic for a specific model from (M2a-q) respectively. Deviance statistics are used to compare the goodness of fit between similar models.

Table 5.5 (p. 207) contains the overall regression intercept (RI) for each model variant for patients with and without HI. Table 5.6 (p. 222) contains random coefficient estimates for models (M2a-q)

5.2.2.1. Restults - Fixed effect estimates

With reference to data in C5-7/Table 5.4, HI status does not contribute significantly to functional ability in any of the models evaluated (M2a-q) when the effect of time since stroke, stroke severity and age are accounted for. In all the models (M2a-q), the difference between patients with and without HI (data in C5) is ~ 3 EBI units in favor of the HI- group. This result is supported by CI estimates which consistently overlap "0" (data in C6). This implies that at any point in the estimation the slope can be "0" which would mean no change in the EBI score–even though the HI status coefficient is statistically significant as in M2e (Nakagawa and Cuthill 2007).

With reference to data in C2-4/Table 5.4, the regression coefficient for the variables (carer status, motor function, cognitive function and executive function, self-efficacy, bladder and bowel control, nutrition status, duration of stay and stroke unit identification) is significant at 95% CI, ($p \leq 0.05$). These results support the presence of significant relationships between the afore-mentioned factors and change in functional ability, even when the confounding effects of time, stroke severity and age are taken into account.

Table 5.4 – Fixed estimates for model series (M2a-q)

Regression coefficients, confidence intervals, p-values and deviance statistics (when stroke severity, time and age are adjusted for)

Model		Predictor variable (x)			HI status			Deviance	
series	C1	C2	C3	C4	C5	C6	C7	C8	C9
M2	Predictor variable (x)	RC	95% CI	P-value	RC	95% CI	P-value	N	IGLS*
a	Stroke (infarct vs haemmorhage)	-1.08	5.87, -8.02	0.38	-2.98	1.44, -7.40	0.093	338	2412
b	Lesion (cortical vs all other)	1.30	4.30, -2.33	0.24	-3.30	1.19, -7.79	0.075	338	2411
c	Carer (present vs absent)	-4.44	0.12, 9.00	0.028	-2.80	1.52, -7.12	0.10	338	2408
d	Gender (female vs male)	2.146	5.84, -1.55	0.13	-3.44	1.03, -7.91	0.066	338	2410
e	Motor function (PASS-20)	0.85	0.97, 0.73	2.35e-47	-3.05	0.18, -6.28	0.032	334	2231
f	Cognitive function (MEAMS-10)	1.34	1.73, 0.95	1.04e-11	1.30	5.30, -2.70	0.26	331	2314
g	Executive function (TMT- A-130)	-0.025	-0.0093, -0.041	0.00089	-0.43	4.25, -5.11	0.43	323	n/a
h	Executive function (TMT- B-300)	-0.020	-0.0024, -0.038	0.013	-1.25	3.31, -5.81	0.30	322	n/a
i	Self-efficacy (GSE-29)	0.64	0.84, 0.44	1.17e-10	-2.09	2.25, -6.43	0.17	275	1941
j	Denial (aware vs not aware)	-0.65	1.71, -3.00	0.30	-2.28	1.97, -6.53	0.15	307	2187
k	Bladder (continent vs incontinent)	-7.85	-5.41, -10.29	1.39e-10	-3.19	0.75, -7.13	0.056	333	2338
l	Bowel (continent vs incontinent)	-11.32	-8.63, -14.00	7.48e-17	-1.72	2.09, -5.57	0.19	333	2314
m	Nutrition (at risk vs not at risk)	-7.68	-2.21, -13.15	0.0030	-3.40	0.86, -7.66	0.059	331	2356
n	Duration of stay (LOS-30)	-0.073	-0.010, -0.14	0.011	-3.124	1.15, -7.40	0.076	338	2407
o	Therapy contacts (ITS-20)	-0.04	0.036, -0.12	0.15	-2.01	2.39, -6.41	0.19	334	2376
p	Discharge (institution vs home)	-4.48	0.30, -9.26	0.033	-2.24	2.11, -6.59	0.16	332	2360
q	Stroke unit (A vs B)	-5.89	-1.99, -9.79	0.0015	-2.53	1.72, -6.78	0.12	338	2404

Abbreviations: RC=regression coefficient, N = number of cases used in the estimation, n/a= not available, e^{-x} denotes a base of 10^{-x}

To aid interpretation, estimates in column C3-4 and C6-7 are highlighted yellow if not significant at 95% CI, p-value > 0.05 (see additional comments in text); all other estimates are statistically significant. For clarity,estiamtes for stroke severity, time since stroke and age are presented in Appendix P.

* IGLS deviance statistics are provided so that the accuracy of 'model fit' of individual models can be compared with that of the basic model **(M1, n=338, IGLS=2411).** Deviance estimates highlighted in grey do not differ significantly from M1 deviance estimates. In which case, the addition of covariate-x (e.g. LOS in M2n and stroke unit identification in M2q has not improved the model but addition of motor function in M2e has significantly improved on the basic model fit (M1) (a large drop in IGLS deviance). See additional comments in text).

As can be seen from results in Appendix P, all corresponding regression coefficient estimates for time since stroke, stroke severity and age in models (M2a-q) remained statistically significant at α=0.05, 95% CI. This result supports not only the confounding importance, of these three factors (time, stroke severity and age) but also their explanatory effects in relation to change in DV i.e EBI scores. In regards to model M2e, there is evidence that the influence of time, stroke severity and age is relatively weakened by the introduction of motor components (balance/posture) in the same model when compared to other predictor variables in C1/Table 5.4. This is supported by narrow CI's and low IGLS estimates in M2e which suggest substantial improvement in model fit (relative to the improvement brought about by addition of other factors from C1). The results from M2e suggest a unique relationship between motor function and functional change which will be evaluated further in the final model. The addition of self-efficacy in (M2i) is followed by a large drop in IGLS deviance, however this estimate is probably somewhat biased due to the smaller number of cases available for the computation of the model (Rasbash et al 2012).

Mean functional ability

The predicted mean EBI score is given by the overall regression intercept (RI) estimate which is shown in Table 5.5 - RI is the amount of change in EBI when predictor variables in specific models M2a-q are at their fixed point (given in Table 5.1/section 5.1.1). Example, in model M2-e/Table 5.5 the predicted mean (29.6) is for a 75 year old patient diagnosed with severe stroke (NIHSS-16) and hemi-inattention (HI+) who is able to stand supported at T0 (PASS-20).

Table 5.5

Predicted regression intercepts (mean estimates) for model series (M2a-q) by group (H+/-) (after statistical adjustment of time, stroke severity and age).

model		RI/group		model		RI/group	
(M2a-q)		HI+	HI-	(M2j-q)		HI+	HI-
a	Stroke	26.1	29.0	j	Denial	26.5	28.8
b	Lesion	24.5	27.7	k	Bladder	29.7	32.9
c	Carer	28.8	31.6	l	Bowel	31.2	32.9
d	Gender	23.8	27.2	m	Nutrition	26.3	30.2
e	PASS-20	29.6	32.7	n	LOS-30	25.6	28.8
f	MEAMS-10	30.9	29.6	o	ITS-20	26.3	28.4
g	TMT-A-130	27.6	28.0	p	Discharge	27.6	29.8
h	TMT-B-300	24.8	26.0	q	Stroke unit	29.7	32.2
i	GSE-29	26.0	28.1				

Abbreviation: RI = overall regression intercept

For clarity, standard errors have been omitted, however all estimates are highly significant ($p<0.0001$) at 95% CI

RI is the mean of the DV (functional ability) when all predictor variables in the model are at their fixed point - which by default is conveniently set at the group average or median as appropriate (see Table 5.1 and example later on).

Regression intercept group (HI±) estimates in Table 5.5 indicate that the predicted difference in the amount of change between groups is relatively small (~ 1 to 4 EBI units) when the confounding effects of time, stroke severity and age are taken into account. Nevertheless, the results support initial group findings (Ch4) that HI+ patients tended towards lower baseline scores. That being said, all predicted scores (at baseline) fall close to the 30 point mark (mid EBI score range) irrespective of HI status.

5.2.2.2. Random effects

Individual departure from the average (fixed effects) is given in the random part of the models M2a-q by three specific ‘random’ coefficients – one for each estimate of unexplained variance around the (i) individual intercept (mean), (ii) slope and (iii) respective covariance (correlation). The results are presented in Table 5.6. For clarity, corresponding p-values and CI’s for covariances are presented separately in Appendix Q.

Table 5.6

Random coefficient estimates for models (M2a-q)

model	Factor	Between individual / L2			Within individual / L1		
(M2)		I	S	I x S	I	S	I x S
a	Stroke type	87.6 (26.0)	16.8 (3.9)	-25.3 (9.1)	104.4 (37.5)	3.0 (5.7)	-18.5 (15.1)
b	Lesion type	89.0 (26.2)	16.8 (3.9)	-25.8 (9.1)	105.0 (37.5)	3.1 (5.7)	-18.8 (15.1)
c	Carer status	88.3 (26.3)	16.7 (3.9)	-26.2 (9.2)	110.7 (37.7)	3.9 (5.7	-21.1 (15.1)
d	gender	87.2 (25.8)	17.0 (3.9)	-25.6 (9.0)	100.2 (37.1)	2.4 (5.7)	-16.9 (15.0)
e	Motor function	44.8 (15.9)	8.9 (2.3)	-13.4 (5.5)	58.3 (24.2)	0.71 (3.8)	-8.1 (10.0)
f	Cognitive function	64.3 (21.9)	14.3 (3.5)	-20.9 (7.8)	91.3 (33.5)	2.0 (5.2)	-15.0 (13.6)
g	Executive function-TMTA	89.6 (26.4)	15.5 (3.8)	-24.7 (9.0)	91.6 (39.2)	0.52 (6.0)	-12.6 (16.0)
h	Executive function-TMTB	87.4 (26.2)	17.2 (4.0)	-26.4 (9.2)	97.8 (36.4)	1.2 (5.6)	-14.7 (14.7)
i	Self-efficacy	84.9 (28.8)	11.9 (3.7)	-21.5 (9.5)	111.9 (40.5)	4.5 (6.0)	-22.5 (16.0)
j	Denial status	111.4 (29.7)	20.3 (4.6)	-36.1 (10.7)	67.9 (35.7)	0.34 (5.8)	-7.1 (14.9)
k	Bladder control	65.3 (23.0)	13.6 (3.5)	-20.2 (8.1)	110.0 (36.3)	3.8 (5.4)	-20.8 (14.4)
l	Bowel control	74.6 (23.2))	13.5 (3.4)	-22.8 (8.1)	194.0 (33.0)	5.2 (4.9)	-22.3 (13.0)
m	Nutrition status	91.4 (27.3)	16.8 (4.0)	-27.8 (9.5)	116.0 (38.5)	4.5 (5.8)	-22.9 (15.3)
n	Duration of stay	83.7 (25.2)	17.3 (4.0)	-26.0 (9.0)	97.2 (36.6)	1.8 (5.6)	-15.3 (14.8)
o	Therapy contacts	79.2 (24.4)	17.3 (3.9)	-24.1 (8.7)	91.9 (36.5)	1.2 (5.7)	-13.6 (14.9)
p	Discharge destination	87.5 (26.0)	16.7 (4.0)	-26.1 (9.1)	103.0 (37.3)	2.9 (5.7)	-18.2 (15.0)
q	Stroke unit (A or B)	29.0 (25.9)	17.4 (3.9)	-28.4 (9.1)	86.8 (35.9)	0.4 (5.6)	-11.4 (14.6)
M1	Basic model estimates for comparison purposes	88.2 (26.0)	16.9 (3.9)	-25.5 (9.1)	102.8 (37.3)	2.8 (5.7)	-17.9 (15.1)

Abbreviations: I=intercept. S=slope, I x S = intercept, slope covariance (standard error shown in brackets)
Confidence intervals and p-values were calculated interceptxslope covariances but for clarity of table 5.6 in text, they were put in appendix Q.
However, Level 1 (L1) regression coefficients (highlighted yellow) are not statistically significant at 95% CI; all other coefficients are significant ($p \leq 0.05$)

With reference to data in Table 5.6 all random coefficient estimates at L2 are statistically significant and the covariance is negative. This would suggest important characteristic differences (presumably of an unknown origin) as the cause of the variation seen across 93 patients in the sample. The negative covariance pattern is interpreted as: those patients who started with very low scores had the fastest (growth) progress rate and vice versa; further, that both the amount and rate of change are associated with one another and impact on outcome (functional ability). Overall this picture suggests that there are substantial differences from the mean (average trend) important enough to be taken into account when interpreting the results from models (M2a-q).

In contrast, L1 random covariance estimates in Table 5.6 are not negative but not statistically significant in any of the models (M2a-q). This covariance pattern suggests that the amount and rate of progress arising from within the patient (probably due to intrinsic unmeasured pathological changes) are not associated and unlikely to be related to functional change. This picture implies that one cannot know how individual patients will progress on measurement scales just by looking at their baseline score.

Overall, these results from models estimates (M2a-q) support data from the variance components model (Figure 5.2) which showed L1 (within) variance to be steadily decreasing and L2 (between) variance to gradually increase over time.

5.2.2.3. Goodness of model fit

The appropriateness of individual models (accuracy of model fit) is indicated by IGLS deviance estimates; the lower the IGLS the better the fit between two similar models (refer to Methods/section 3.4.9.2).

With reference to Table 5.4/C9, deviance estimates are unchanged in models M2 a-d, n & q. This result implies that the addition of factors (type of lesion and stroke, carer status, gender, LOS and stroke unit identification) did not significantly improve the model compared to the basic model. In contrast, large (statistically significant) reductions in deviance were obtained when motor function, cognitive ability, self-efficacy, continence status and nutrition were separately added to the basic model (M1). Example, in model M2f the inclusion of cognitive function yielded a drop of 97 IGLS units (M1 - M2f = 2411 – 2314) which is highly significant p<0.0001 at 1degree of freedom and 95%CI. These results support the presence of important relationships with functional change, even when the effect of ‘time’, stroke severity and age are taken into account. The relative contribution of influential factors identified in this analysis is further evaluated in the final model.

N.B IGLS deviance failed to compute when executive function (TMT scores) were added to the basic model (M2g&h) in Table 5.4/C9. The reasons for this are not clear but TMT-coefficient estimates supported an important contribution to functional change; hence these were taken over to the next phase of analysis.

5.2.3. Section summary

On average, MLM results do not support a relationship of statistical importance between early (T0) HI status and functional change; nor do the results indicate important differences between HI± patient groups in the evaluated models and when the confounding effect of time, stroke severity and age are accounted for.

Statistically significant relationships were found between functional ability levels and modelled factors: motor function, cognitive function, executive function, self-efficacy, bladder and bowel control and nutrition status, supported by corresponding improvements in model fit and a reduction in unexplained variance estimates. In comparison, carer status, duration of stay and stroke-unit identification showed significant effects but did not result in model improvement which indicates a weaker relationship with functional change when time, stroke severity, age and HI status are accounted for.

MLM random coefficient estimates indicate considerable differences across individuals (L2) in the rate and amount of change in overall functional ability over time. At L2, statistically significant, negative, covariances between intercepts and slopes (Table 5.6) suggest that patients who start with high functional ability at baseline progress at lower rates with time since stroke and vice versa. In contrast there is no relationship between the amount and rate of change as recorded by measurement scales (at L1); this tends to be unrelated to overall functional change (Table 5.6 L1 estimates). In a nutshell, these results support earlier inferences that the principle source of variance is coming from characteristic and contextual differences between patients rather than from changes within individual patients measured in the 1st six months after stroke.

In turn, the above findings are not surprising given the hierarchical nature of the data and the multitude of factors (e.g. personality traits, socio-economic and cultural) that are thought to affect stroke recovery (but impossible to measure as part of this study). This point is further elaborated on in the main discussion (Ch6). It is also possible that unidentified interactions between predictor variables in the data could have affected the results.

To conclude section 5.2, the factors taken over to the next phase of the analysis are: motor, cognitive and executive functions, self-efficacy, bladder and bowel control and nutrition status together with time since stroke, stroke severity, age and HI status (the predictor variable of interest).

5.3. Section three – *(the final model)*

The aim of this analysis was to derive an appropriate model (M3) that optimally fitted the data from factors brought over from section 5.2 and helped to answer the research question i.e. a model that was statistically and clinically sound.

For the above purpose, the basic model (M1) was further simplified (more parsimonious) so that it could accommodate additional parameters without it becoming overly complex. This was achieved by modelling time as a quadratic trend instead of a categorical variable. In technical terms, an orthogonal polynomial was used for this purpose – this is a method of rotation employed in factor analysis that keeps the underlying factors independent i.e. uncorrelated (Field 2009). Consequently the effect of time is given by a linear and a quadratic (curve) term instead of four points (T0, T1, T2 & T3); the linear was allowed to vary randomly at both levels (L1 and L2). All other parameters (stroke severity, age and HI status) remained unchanged. With exception of time and HI status, MLM results from the simplified model (M3) are unchanged from those in M1; they were placed in Appendix J. A slight improvement in model fit (compared to M1) was noted, supported by IGLS deviance reduction of 4 units. In addition, there is evidence of a significant interaction ($p=0.0094$) between time and HI status, its influence on functional change decreases with time after stroke, as illustrated earlier in Figure 5.3 (right plot).

5.3.1. Derivation of the final model (Mf)

The procedure leading to the identification of the final model (Mf) is described in this section. The final model was derived from predictor variables: motor, cognitive and executive functions, self-efficacy, bladder and bowel control and nutrition status together with time since stroke, stroke severity, age and HI status (brought over from section 5.2).

In the first estimation, functional ability (DV) was regressed on M3 (time since stroke, stroke severity, age, HI status, time x HI status) + motor function which showed a relatively large effect in the previous analysis (M2e/section 5.2). Following estimation 1, the interaction between HI status and time became statistically insignificant (p=0.75) and was removed from the model. HI status was weakly significant (p=0.016, CI -0.694, -0.283) and for now retained. The difference between HI± groups was 3 EBI units.

In subsequent estimations, functional ability was regressed on predictor variables: time, stroke severity and age, HI status, motor skills and covariates (cognitive & executive function, bladder & bowel control, self-efficacy and nutrition status) which were introduced one at a time in the order stated. However, no order effect was detected in that coefficient estimates remained stable even if the order of entry was changed. This is not surprising because quantitative variables were centred – <u>a process which greatly minimises the effect of correlation between intercepts and slopes</u> of related variables (refer to Methods/centring and Table 5.1). During the estimation process these factors (HI status, executive function, bowel control and nutrition status) became clearly statistically insignificant at 95% CI and were dropped from the model but HI status was retained for now.

Next, the model consisting of time since stroke, stroke severity, age, HI status, motor function, cognitive function, self-efficacy and bladder control was evaluated for possible interactions. A highly significant negative interaction was identified between stroke severity and motor function (NIHSS x PASS; p=8.84e-

005) but no interactions were found with HI status. At this stage, HI status was removed from the model because it was statistically insignificant (p=0.26) and the model was re-estimated one last time with the remaining variables (time, NIHSS-16, age-75, PASS-20, MEAMS-10, GSE-29, bladder control, NIHSS x PASS).

The MLM results from the final model are presented in Table 5.7 and illustrated in Figure 5.4 (graphs 1-8), so that respective size effects can be visually compared irrespective of their level of measurement (categorical or interval). Their individual contribution is commented on in text.

5.3.2. Results - Fixed effects (Mf)

As can be seen from Figure 5.4, motor function has by far the largest effect on functional ability which is reflected by its steep slope compared to other slopes e.g. the one for age. That being said, the effect of motor function is moderated by stroke severity levels in a cross-level interaction shown in Figure 5.4 (bottom row, 2nd graph and later in Figure 5.5). The effect of this interaction is negative i.e. its effect decreases as functional ability increases which suggests that its effect is highest in the acute phase - characterised by lower functional ability levels (refer to Ch4/figure 4.2 and 4.3). In Figure 5.4, age shows the weakest effect as reflected by a corresponding shallow slope and lack of statistical significance (p=0.062). In the same figure, cognitive ability and self-efficacy have similar positive size effect as judged from the direction and steepness of corresponding slopes. Stroke severity has a negative steep slope indicating that the higher the NIHSS score (the degree of severity) the lower the rate of functional change (EBI score). In relation to bladder control (Figure 5.4, lower 3rd graph), it is clear that the predicted EBI score for patients with normal bladder control is relatively higher than that of their counterpart. The difference between those with and without bladder control is 5.27 EBI units and is statistically significant (p<0.0001). In relation to time since stroke, the graph in Figure 5.4 shows that its effect is positively non-linear and largest between admission and discharge from stroke unit care – this judging by the steepness of the slopes between observations in the graph.

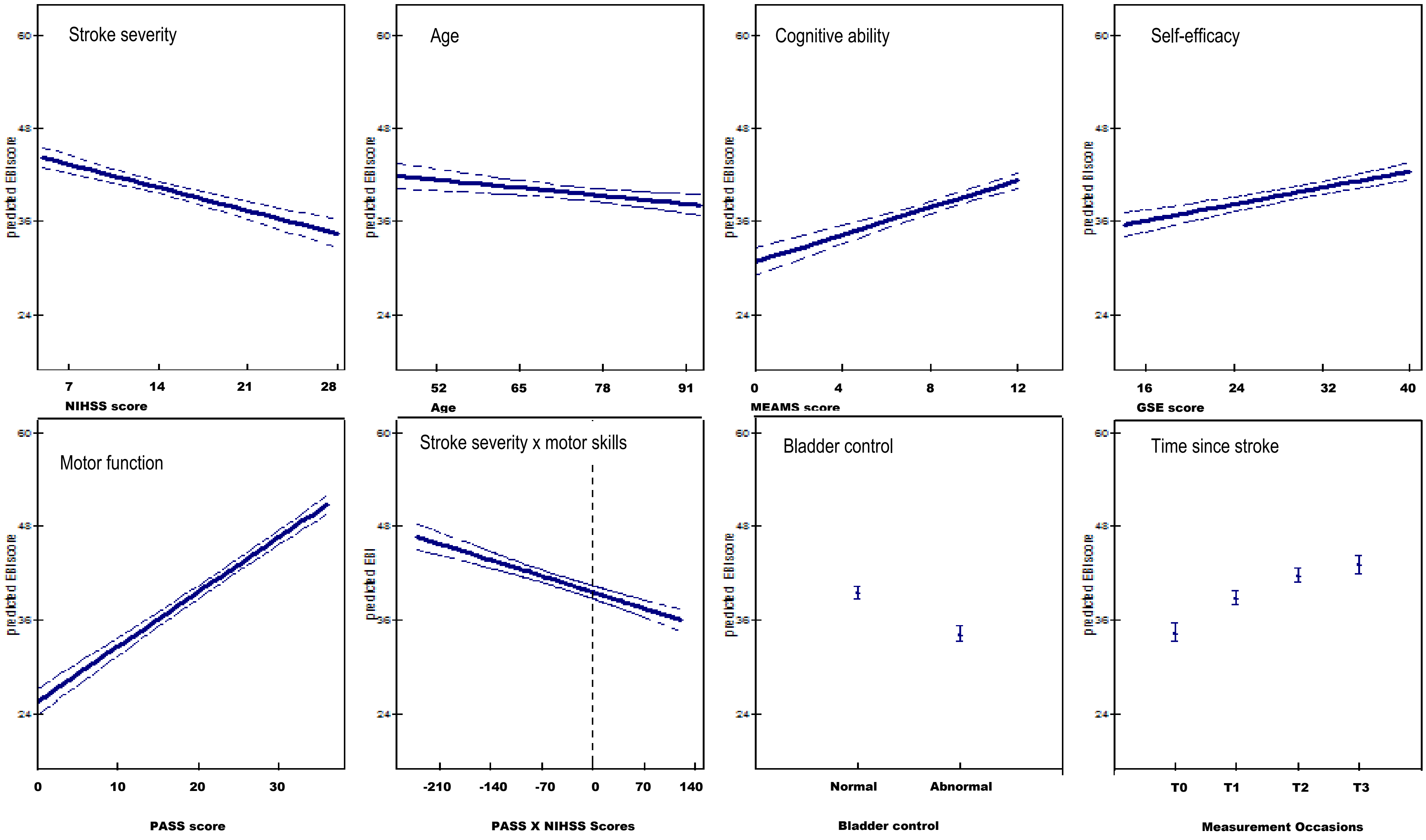
Table 5.7

Estimation of the final model (after removal of HI status)

C1 Variable	**C2 Non-standardised**		**C3 Standardised**	**C4**	
(n= 270 cases)	RC	SE	RC (SD)*	p-value	95% CI
Time (linear)	6.54	1.08	-	7.24e-010	4.42, 8.66
Time (non-linear)	-1.52	0.59	-	0.0049	-2.68, -0.36
Stroke severity (NIHSS-16)	-0.43	0.12	0.152	0.00017	-0.67, -0.20
Age-75	-0.077	0.052	0.044	0.062	-0.18, 0.025
Posture (PASS-20)	0.71	0.065	0.448	4.63e-028	0.58, 0.84
Cognitive (MEAMS-10)	0.88	0.18	-	5.042e-007	0.53, 1.23
Self-efficacy (GSE-29)	0.27	0.079	0.153	0.00031	0.12, 0.43
Bladder control	-5.27	1.18	-	3.91e-006	-7.58, -2.96
NIHSS x PASS	-0.03	0.007	-	8.93e-006	-0.044, -0.016
Regression intercept	39.54	0.84	-	-	37.89, 41.19
Random effects			*Intercept (SE)*	*Slope (SE)*	***Cov (SE)*
(L2) Between patient			15.17 (3.71)	35.83 (12.27)	13.11 (4.73)
(L1) Within patient			18.68 (3.79)	18.91 (18.67)	-14.58 (3.703)
IGLS deviance = 1747					

Abbreviation: RC = regression coefficient , SD = standard deviation, SE = standard error, e^{-x} denotes a base of 10^{-x}
***some variables could not be standardised; for standardised variables 1 SD increase in predictor variable = 1SD change in DV (SD=17.7) ** covariance between individual intercepts & slopes**

Figure 5.4 - A thumbnail comparative illustration of the predicted mean change in functional ability (EBI score) for predictor variables in the final model (95% CI). All the graphs are to the same EBI scale i.e. the four nicks on the y-axis correspond to EBI score 24, 36, 42 and 60.



5.3.2.1 Time since stroke

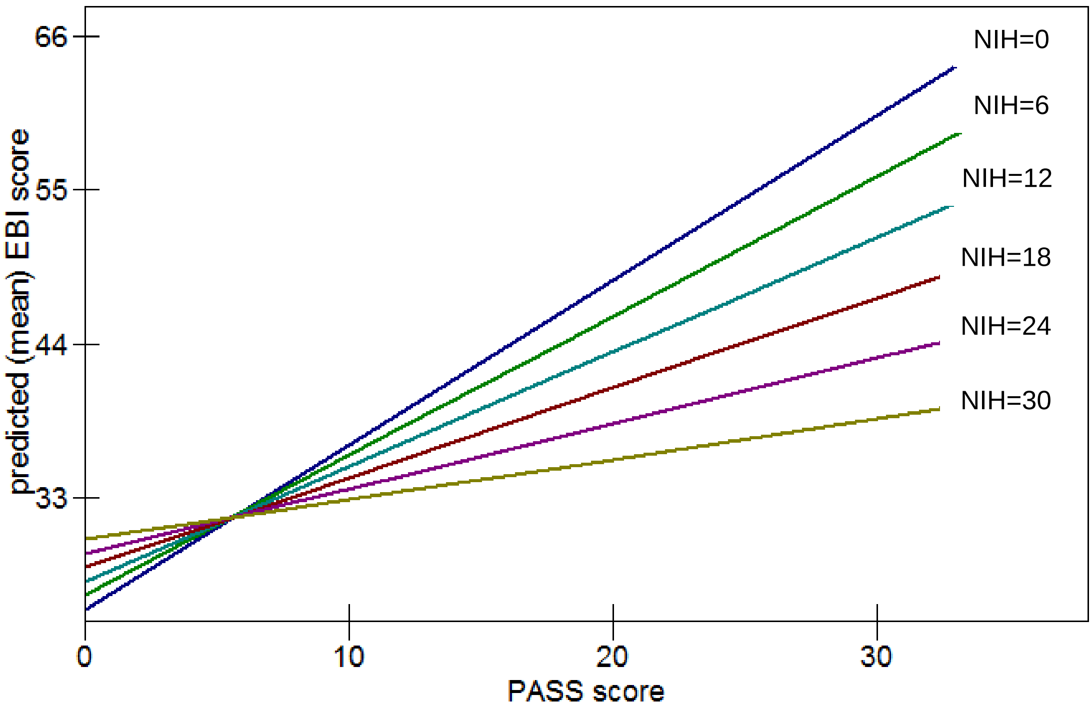
Time (since stroke) significantly contributed to functional change at the rate of 6.5 (linear) and 1.5 (non-linear) EBI units. This equates to 12.5% change in EBI score, of which 10% falls approximately within the active motor recovery phase (~ the 1st three months after stroke). The influence of time on functional ability decreases with time elapsed after stroke but it is still a statistically significant important contributor (p=0.0049) at 6 months. This finding supports an independent predictive role and implies that the effect of time should be taken into account in rehabilitation and stroke research.

5.3.2.2. Motor function and stroke severity

As already highlighted in figure 5.4, the effects of stroke severity and motor function are inter-dependent on one another and vary with time since stroke, which further complicates interpretation of the interaction. To this end, the graphs in Figure 5.5 show the predicted interaction effect on the DV (EBI scores) at selected NIHSS and PASS scale values. It is clear from these graphs that (i) the EBI predicted score depends on both PASS and NIHSS scores (ii) the lower the NIHSS score the bigger the predicted change in EBI score for PASS scores > 5 (characterised by very poor balance and posture control on the PASS scale) and (iii) that the rate of change in the PASS is disproportionate to the NIHSS score. This means that if X PASS = Y NIHSS score, 2X PASS ≠ to 2Y NIHSS score – if they were equal the slopes would be parallel.

Going back to Figure 5.4/lower 2nd graph, it would appear that those patients in whom the product of the interaction is differentially well below the mean (0 mark) have a higher rate of change in the EBI than in those whose interaction product is above the mean.

Figure 5.5 - Interaction between stroke severity and motor skills at selected scale values



Abbreviations: EBI=Extended Barthel Index, PASS=Postural Assessment Scale for Stroke,

NIH = NIHSS = Neurological Institute Health Stroke Severity Scale

Interpretation of interaction effects is notoriously complicated; in this case the milder the stroke the better the motor function and the larger the rate of change in the EBI score. This finding is consistent with clinical observations. There are likely implications for patients with severe stroke (NIHSS score >14). These are further elaborated on in the Discussion Chapter (ch6).

In addition to the interaction effect, motor function (balance and posture skills) has the largest influence on functional change relative to other predictor variables (refer to Figure 5.4, lower left graph). Corresponding estimates in Table 5.7(C3) indicate that for 1SD change in PASS, the EBI score changes by 0.45SD (=8.85 EBI units i.e. 13.8% of the EBI scale). In comparison, 1SD change in the NIHSS is equivalent to 3.54 EBI units or 5% of the EBI scale.

5.3.2.3. Cognitive ability

The effect size of cognitive function is an increase of 0.88 EBI units/ I unit increase in the MEAMS score. This equates to 10.5 EBI units (16% of EBI scale) when the MEAMS score is 12 i.e. no cognitive dysfunction. From Figure 5.4, upper 3rd graph, it can be deduced that on average, the higher the cognitive function, the higher the rate of change in functional ability over time even when all other factors present in the final model are accounted for. Conversely, given the MLM estimates, patients with very severe cognitive dysfunction are likely to remain considerably worse off functionally than those patients with milder cognitive impairment over the 6 months after stroke.

5.3.2.4. Self-efficacy

The effect size of self-efficacy is an increase of 0.27 EBI units/1 unit change in GSE score (0 to 40). In SD terms, this is 0.15 SD (EBI) per 1 SD change in GSE (which is comparable to that of stroke severity judging from the respective slopes in Figure 5.4). These results imply that on average, the higher the self-efficacy, the higher the rate of change in functional ability in the final model. The predicted change over time for patients with very high self-efficacy levels (GSE=40) is an increase of 10.8 EBI units equivalent to ~17% of the EBI scale. When plotted against time since stroke, all patients improve non-linearly but those with high self-efficacy levels remain functionally better off during the 1st six months after stroke. Relevant implications are further elaborated on in the main discussion (Ch6).

5.3.2.5. Bladder control

Bladder control showed a statistically significant effect on functional change in the order of 5.27 EBI units less for patients with abnormal versus normal control (illustrated in Figure 5.4). This is equivalent to 8.2% change in the EBI scale and is relatively less compared to other predictor factors in the final model. Nevertheless, according to the modelling analysis, bladder function exerts considerable influence on functional ability i.e. although all patients tend to gradually improve (non-linearly), those with persisting abnormal bladder control do not catch up functionally with their counterparts over the six month period.

5.3.2.6 Age

In the final model, age did not show a statistically significant relationship with functional ability (p=0.06) as evidenced by the shallowest slope in Figure 5.4. However, the result has to be interpreted with caution as follows;

The RC point estimate for age is -0.077 and is likely to have some clinical significance from these calculations; at 40 years the estimated drop in EBI score is ~3 EBI units, at 60 it is ~4.6, at 80 it is ~6.2, 90 it increases to ~7 and at 100 years it is ~ 8 EBI units, which is 12.5% of the EBI scale. This data supports the notion of a gradual decline in functional ability as a result of age in patients with stroke as modelled in Mf.

However, because the CI's (-0.18, 0.025) around the fixed regression coefficient-age overlap "0", theoretically it is possible that the slope for age may at any time become zero. In which case, there is no functional change. Consequently the effect of age in the final model is uncertain (at 95% CI) and has to be interpreted with caution.

5.3.2.7. Mean overall functional ability

In the final model, the estimated overall <u>mean</u> functional ability is 40 EBI units for a 75 year old patient with a borderline moderate to severe stroke (NIHSS=16), able to stand with support (PASS=20), has good cognitive function

(MEAMS=10), relatively high self-efficacy (GSE=29) and is continent irrespective of baseline HI status. For more severely impaired patients, the estimated overall mean will be less than 40 and vice versa.

5.3.3. Results - Random effects

Random effects are associated with variance parameters i.e. they estimate departure (above and below) from the fixed intercept and slope. Consequently, random estimates are indirect measures of how well the current model fits the data. Here are the results.

Level 1 – measurement level (within patient variation)

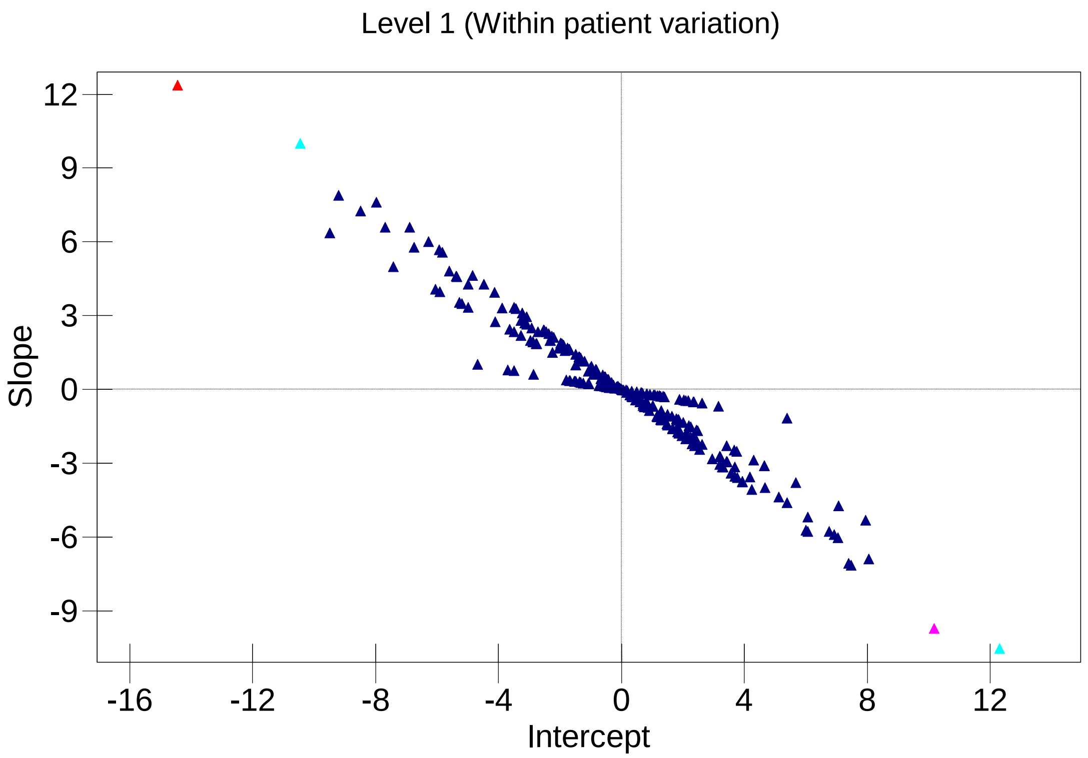
With reference to Table 5.7, the variance around the intercept at L1 is statistically significant - the RC (18.68) is more than twice its SE (3.79) but the variation around the slope is not significant (RC=18.91, SE=18.67). The extent of variation around the intercept is given by the standard deviation (SD) = square root of ~19 (4.4). This means that for a given patient, the highest or lowest points can vary by 4.4 variance units above or below their mean. Further the intercepts and slopes are negatively, significantly correlated as illustrated in Figure 5.6 – this shows a plot of the L1 regression residuals.

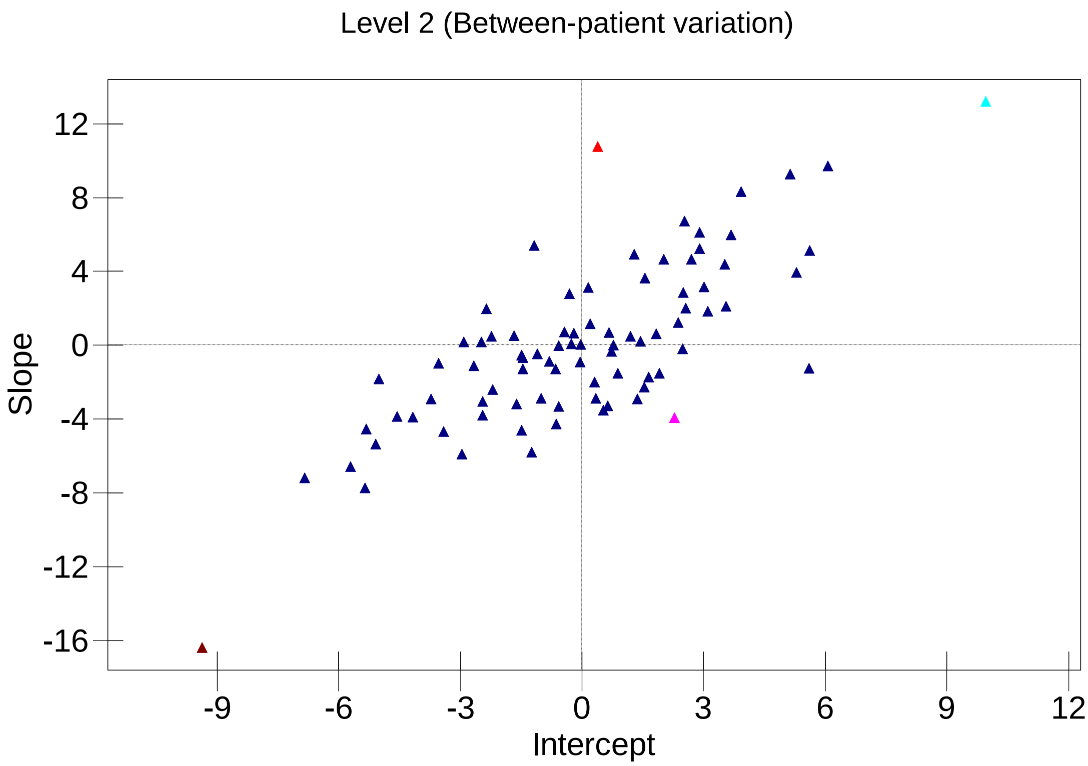
Collectively, L1 random results were interpreted as; individuals who started with extremely low functional ability progressed on measures at faster rates and vice versa. More than likely, the L1 variance is due to unmeasured pathological variables such as motivation/drive levels or executive components.

Level 2 - variation across patients

With reference to Table 5.7 (last two rows but one), it can be deduced that all variances are statistically significant (all coefficients are at least twice their SE).

Figure 5.6 - Relationship between random intercepts and slopes at level 1 and 2 (overleaf)





This indicates substantial variation around the overall intercept (SD = 4) and slope (SD = 6.0). The respective covariance is positively correlated and is illustrated in Figure 5.6 (L2 graph) albeit it can be seen that the association between individual intercepts and slopes is weaker than that in L1 graph.

The results at L2 support the existence of an important relationship between the amount and rate of progress in functional ability across patients in the 1st six months after stroke, which is likely to significantly impact on functional change and therefore outcome. The result is consistent with earlier findings which showed a tendency for variation to increase with time after stroke (refer to Figure 5.2), irrespective of HI status. More than likely, the source of L2 variance comes from unmeasured patient characteristics including contextual differences across patients in the 1st six months post stroke, as in socio-economic, educational status, faith and beliefs around stroke illness.

Extreme values in the data

With respect to Figure 5.6, the highlighted points represent extreme values from patients 44 (HI+) (red), 51 (HI+) (pink) and 91 (HI-) (light blue) who consistently departed from the mean above all other patients at both levels (L1 and L2); patient 87 (HI+) (dark red) differs extremely at L2 only. Estimation of the final model without the extreme values affected only L2 intercept/slope covariance which became statistically insignificant. All other coefficient estimates remained relatively stable (within 0.02 units of the original estimate). This suggests that extreme points 44, 51, 87 & 91 do not significantly influence average population estimates but they explain a proportion of the variance in the data. From the researcher's records, it is difficult to see how patients 44, 51, 87 and 91 differed from other patients in the sample. For this reason and given the moderate sample size (n=93), the extreme values were left in the data set. Overall, L2

MLM estimates support earlier results showing that L2 covariance is of significant importance to overall functional outcome (refer to Table 5.6).

5.3.4. Model fit

The goodness of model fit is given by IGLS deviance statistics (refer to Methods/section 3.4.9.1). When compared with model (M3), the difference in deviance is (M3-Mf) = 2407-1747 = 660 which is statistically significant (p=1.50e-145) in Chi distribution at 5df (this reflects the addition of 5 extra parameters in Mf compared to M3). Even though the number of cases differs in both models due to missing data (n= 270 & 338 in Mf & M3 respectively), the result represents considerable improvement in model fit when compared to M3. This finding is supported by a further 56% reduction in the amount of unexplained variance originally estimated in M3. Nevertheless, the author acknowledges that significant amounts of variance remain unexplained by the final model. The reasons for this are highlighted in the main Discussion Chapter (Ch6).

5.3.5. Section summary

The aim of section 5.3.5 was to identify the contribution of T0/HI status to functional ability when the factors brought over from section 5.2 were also taken into account. The factors were time since stroke, stroke severity, age and HI status, motor function, cognitive function, executive function, self-efficacy level, bladder control and nutrition status. During the modelling process, HI status, nutrition and executive function became statistically insignificant and were removed (p<0.05). On average, this result does not support an important explanatory or predictive role for HI status on functional change when the impact of more influential factors in the model is accounted for in the 1st six months after stroke.

Statistically significant contributions to functional change were made by motor (balance/postural abilities) and cognitive functions, self-efficacy levels, bladder control, time since stroke, age and stroke severity when modelled together. An interaction between stroke severity and motor skills was also identified in the same model (Mf).

Statistically significant important differences were found at the individual level i.e. within and across patients in the final model. These differences automatically limit the inferences that can be made from average progress trends i.e. they may not be entirely applicable to the individual level.

Presence of three extreme values (patients 44, 87 and 91) in the data was found not to exert undue influence on the regression line (specifically on fixed parameter estimates). Their presence in the model (Mf) explained a proportion of the residual variance.

5.4. *Overall summary and conclusion*

Following on from group (HI±) trends identified in Chapter four, an in-depth multilevel modelling study of the data highlighted considerable variation in functional progress in patients with and without HI i.e. at the individual level (in Figure 5.1). This variation was statistically accommodated by a two level random intercept and slope structural model which was used for all the models evaluated later on. The structure reflected variation at two levels; between and within the patients, at Level two (L2) and one (L1) respectively. Time was initially modelled as a (random) categorical variable which enabled direct interpretation of the impact of time from respective coefficient estimates in the model. In the final model (Mf) time was modelled as a quadratic trend to simplify the model but still capture the progress trend over time.

A basic working model (M1) consisting of time since stroke, stroke severity, age and the factor of interest (HI status) was first estimated. On its own, M1 explained ~ 47% of the variance in the EBI (of which time explained ~ 40%, stroke severity 5% and age 2%; the contribution of HI was not of statistical importance). M1 was later used to estimate the contribution of potential explanatory factors and HI status when the effect of time since stroke, stroke severity and age were accounted for (model details and MLM estimates (M2a-q) can be found in Table 5.4-6). Results from the analysis did not support a statistically important relationship between functional ability and HI status in any of the models evaluated (M2a-q) i.e. when the effect of stroke severity, age and time since stroke were accounted for. However, MLM results highlighted statistically important relationships between functional progress (gain) and motor function, basic and higher cognitive function, bladder continence, nutrition status and self-efficacy over time (1st six months since stroke). The identified factors were taken over to the next phase of the analysis together with time, stroke severity, age and HI status.

In regard to the residual variance, random parameters from the models (M2a-q) indicated statistically significant variance across patients, which was negatively associated with functional ability. This was interpreted as those patients who started with extremely low functional ability tended to progress at higher rates and vice versa but that differences stabilized over time.

Section 5.3 focused on the identification of a clinically and statistically sound model which optimally fitted the data (factors brought over from section

5.2) addressing the research question. The final model (Mf) consisted of time since stroke (modelled as a quadratic trend), stroke severity, age, motor and cognitive functions, self-efficacy, bladder control, and an interaction between motor function and stroke severity. At this stage, baseline HI status was dropped from the model as it was not statistically significant ($p=0.26$ at 95% CI) and unlikely to make an important contribution to change in functional ability over time. Mf explained an estimated 90% of the initial EBI variance in the unconditional model (section 5.1.3.1).

The random parameters associated with the final model indicated statistically significant unexplained variance which was associated with functional change. This residual variance limits the application of inferences based on fixed trends to individual patients in the data and irrespective of initial HI status. Further, the correlation between the individual intercepts and slopes across patients increases over time but decreases at the measurement level. This would suggest that differences across patients in the sample widened with time after stroke but narrowed within the patient as they progressed (irrespective of initial HI status).

To conclude this chapter and as far as research objective three is concerned (this was to study the dynamic relationships between early (T0) HI status and functional recovery when other associated factors were also considered) – on average, MLM results did not support a predictive or explanatory relationship between the factor of interest - baseline HI status and functional change in the first 6 months after stroke under considerable varied modelled conditions. A detailed discussion of the main findings including critical analysis of the study and future research recommendations can be found in the next chapter.

Chapter 6 - Discussion

Chapter six

Discussion

6.0. Introduction

This chapter contains an in-depth discussion on the results obtained from the PhD data and presented in chapters four (Ch4) and five (Ch5).

The primary research question is;

*"What is the relationship between early*** *HI status (HI±) and functional change in the 1st six months after right hemisphere stroke?"*

***(within 7 days since stroke)*

Layout of the discussion:

The key findings are summarised first, followed by the main body of the discussion which is sub-divided into four sections:

Section one discusses the results from this study when only HI status is considered and compared with functional outcomes (initial results in Ch4).

Section two offers an in-depth interpretation of the main findings that address the research question. This begins with a comparison of the results from this study with those from past studies critically reviewed in the literature chapter (Ch2), then moves on to discuss the relative individual contribution of factors specifically modelled with HI status in the PhD study. Several interpretations are presented and supported by evidenced based arguments drawn from the wider stroke literature.

Section three offers a critical evaluation of the research study focusing on its strengths and limitations.

Section four elaborates on the implications for rehabilitation of RHS patients highlighted in the main discussion, offering suggestions for future research and recommendations in the area of stroke rehabilitation (RHS with or without HI).

A brief summary of the main points and findings concludes the chapter.

- *Key findings*

Data gathered in this study showed that both patient groups (with and without HI) demonstrated general positive non-linear trends in their functional recovery. This pattern of change was noted to be more prominent in physical rather than psychological factors associated with functional recovery. Substantial disparities were also found in between group median scores wherein patients without HI tended to outperform patients with HI in their overall functional ability and associated factors over time. This has important clinical and therapeutic implications which are borne out in the data; they are further elaborated on in the discussion.

Multi-level modelling (MLM) results supported a predictive/associative relationship between functional recovery and HI status only when no other influential factors evaluated in this study were taken into account; its impact greatly diminished (became statistically non-significant) when stroke severity, age and time since stroke were accounted for. Modelling results are discussed in depth later on in the chapter.

Another key finding was that 67% of the total variance in the Extended Barthel Index (dependent variable) could be attributed to characteristic and contextual differences between patients (such as nutrition status, carer status or unmeasured differences e.g. education level). The other 33% were attributed to (intrinsic) pathological changes within the patients as they improved over time.

However, those who scored lower initially tended to stay in the lower range (<30 EBI score at six months after stroke).

Section one

6.1.1. Comparison of the sample to past studies

An in-depth comparison of the sample to those used in past studies is presented in this section in order to facilitate interpretation of the results and check whether the findings can be fairly compared to those in previous studies.

The sample size (n=93; 58 HI+, 53 HI-) was comparable to that in the reviewed studies by Ring et al (1997) (n=84; 28 HI+, 56 HI-) and Odell et al (2005) (n=101; 60 HI+, 41 HI-). The proportion of HI+ patients was relatively higher (62%) in comparison to the 33-50% in the 13 studies (reviewed in Ch2). The higher representation of HI+ patients is probably explained by improvements in the PhD project design e.g. early recruitment (within the 1st week of stroke) and an assessment process which encouraged retention of patients with severe cognitive impairment including HI (Hadidi et al 2012). Indeed this is the first study to adopt an innovative practical approach to the assessment of severely stroke impaired patients, who tended to be excluded from past stroke/HI studies due to their limited ability to engage with the research protocol assessments at baseline (e.g. Buxbaum et al 2004, Gillen et al 2005, Nijboer et al 2013).

Secondly, as recommended in the stroke/HI literature, this study used a more sensitive HI diagnostic test battery (The Behavioural Inattention Test - BIT) versus the less sensitive single HI tests used in previous research; this is likely to have increased the detection of patients with different HI sub-types (Azouvi et al 2002 and Plummer et al 2003, Lopes et al 2007). The BIT also facilitated the correct categorical grouping of HI± patients which is of critical importance in comparative HI± group studies. This argument is further supported by the comparatively low rates (<50%) of HI+ patients in past studies that used single HI detection tests (Gillen et al 2005 and Nijboer et al 2013).

The average age was comparable in both HI± groups; 76 years (SD=10), and was the same as in reviewed studies by Kalra et al (1997), Stein et al (2009), Timbeck et al (2013), and similar to others e.g. 72 years in Gillen et al (2005) and 70 years in Odell et al (2005). Gender was not equally represented in the sample; twice as many female HI+ patients compared to HI-. In line with findings by Kalra et al (1997), Ring et al (1997), Odell et al (2005), gender was unrelated to functional ability levels in the first six months after stroke, once the effects of time since stroke, stroke severity and age were accounted for.

The majority (83%) of patients, equally distributed in both groups, had an informal carer at baseline. However, contrary to past findings by Norris et al (1990), Buxbaum et al (2004) and Klinedinst et al (2009), carer status in this study was not statistically significantly related to the patients' functional ability in the 1^{st} six months after stroke – possibly because of the high percentage of patients with severe stroke discharged to institutions where input from carers may be less important (physically).

Stroke severity was measured by the National Institute of Health Stroke Scale (NIHSS). More than half of patients in the sample (53%) (43 HI+, 7 HI-) were diagnosed with severe stroke. Of the others, 8.6% (0 HI+, 3 HI-) were mildly impaired and the rest were in the moderate range. These findings contrasts with two reviewed studies; Kalra et al (1997) and Paolucci et al (2001) in which the samples were of medium stroke severity (as measured by the Orpington Stroke and Canadian Stroke scales respectively). As remarked in the literature review

Chapter, this suggests that both past studies had poorer sample representation which limited generalisation of their results across the stroke severity range.

None of the reviewed studies reported the proportion of patients with different HI categories in their samples therefore this entity is not comparable. The sample in this PhD study was heavily weighted towards patients with severe HI levels; 48% (28/58) had BIT scores of 0 to 52. The other half were mild to moderate HI impaired (BIT score 53 to 128) (data in Table 4.1, Figure 4.1).

As a group, HI+ patients had twice as many (28%) complex lesions involving both cortical and sub-cortical areas, 46% had cortical lesions. In comparison, the HI- group had 14% complex and 46% cortical or sub-cortical lesions. However, these figures have to be seen in perspective of a high rate of unspecified lesions (40% HI- compared to 16% HI+) as reported in the medical notes. The tendency for complex strokes in HI+ patients is consistent with reports by Buxbaum et al (2004) and supported by Viken et al (2012); these figures would suggest a larger volume of infarcted cerebral tissue and probably a more diffused type of stroke (Teasell et al 2014). The high rate of unspecified lesions suggests that ordinary diagnostic imaging techniques may not be sophisticated enough to reliably identify less clearly defined (mild) strokes. Allternatively, interpretation by professional is poor. This is supported by inconsistencies in the MRI/CT scan reporting methods noted in the medical notes. Although this detracts from the diagnostic importance of the lesion site data, it does not lessen the observation that HI+ patients tended to have more complex, larger and severe strokes. This point needs to be kept in mind when comparing results from studies with heterogeneous stroke samples e.g. Nijboer et al (2013).

The frequency of pre-morbid conditions (36%) was in line with reports from epidemiological stroke studies (Jorgensen et al 1995, Di Carlo et al 2003, Ringman et al 2004) and similar in both HI± groups. In addition, HI+ patients had significantly higher rates of sensory dysfunction (91%) compared to 28% in the HI- group, which is consistent with findings from Buxbaum et al (2004). High rates of sensory impairment are often found in severe stroke conditions also associated with HI (Appelros et al 2007, and Orfei et al 2007).

Taking everything into account, the sample studied was considerably varied with respect to stroke severity levels and patient characteristics. Irrespective of gender or carer status, the findings are likely to be more applicable to patients with severe/very severe stroke and HI, who were relatively well represented in the sample (53%) compared to milder stroke conditions. This is one of the unique contributions afforded by the project to the field of stroke rehabilitation and research.

6.1.2. Differences between patient groups (HI±) in the PhD study

This section focuses on measured differences between patient groups in this study and based on HI status only (results in Ch4).

Due to differences in measurement tools and assessment time after stroke, differences in group scores are not directly comparable to those in past reviewed studies. However, they corroborate claims from all 13 studies (e.g. Kalra et al 1997, Katz et al 1999, Cherney et al 2001) that as a group patients with HI were on the whole more physically and cognitively impaired than HI. This tendency persisted throughout the 1st six months but the differences between groups tended to narrow with time after stroke. As a result, the HI+ participants were more disabled and dependent in activities of daily living which is further substantiated by longer LOS and a higher discharge rate to long term care institutions.

To illustrate, in the PhD study, on the EBI scale alone, the extent of group differences in the median scores at T0, T1, T2 and T3 were 19, 31, 35, 39 (HI+) compared to 36, 48, 55, 62 (HI-), respectively. This indicates that those HI+ patients who fell in the 5^{th} percentile were still considerably dependent in ADL basic tasks compared to HI-, who were functioning close to the higher end of the scale (EBI=64) by six months. The same data also suggests that the rate of progress was slower in HI+ patients in the six weeks after discharge (median LOS 59 days for severe stroke with HI). The pattern of differences seen in the EBI scores is consistent with that in PASS (motor) scores, which suggests a positive relationship between both factors.

As pointed out in the descriptive results (Ch4), poor balance and posture skills are not conducive to functional recovery which was further hampered by slow cognitive-motor processing speeds observed in HI+ patients. Poor efficiency is likely to compromise their safety and independence levels e.g. during washing, dressing and general mobility (walking, stairs, bed transfers). This is further supported by residual high rates of bladder/bowel dysfunction at six months (49% HI+; 12% HI-) in Figure 4.9, which may in part be due to *social incontinence* (i.e. not being able to get to the toilet on time). In turn this increases the risk of skin breakdown, infection and pressure sores which delay rehabilitation and compromise outcomes at discharge among those with HI, compared to those without HI.

Group differences based on HI+/- alone, were less apparent in relation to global cognitive function. Both group median MEAMS scores were within normal range at discharge albeit lower in HI+ group (MEAMS score 9 versus 12 in HI-) which is somewhat surprising, given the higher percentage of patients with initial severe stroke in both HI± groups. The cognitive recovery patterns in this study support those in reviewed studies by Kalra et al (1997), Di Monaco et al (2011), Nijboer et al (2013) but not others (Katz et al 1999, Gillen et al 2005).

Given the high cognitive levels found it is not surprising that self-efficacy levels (GSE) scores were also high in both HI± groups during the six month period, although the median HI+ group GSE score dipped slightly in the community – when most patients have to face the reality of living at home with residual stroke impairments. This result is interesting because denial levels also reduce in the community in both groups. However, considering the higher frequency of denial in HI+ patients throughout the study, one explanation could be the existence of an inverse relationship between self-efficacy and denial levels after discharge. Theoretically such a relationship is supported by Christiansen (1999) and Alaszewski et al (2006) who remark that realisation of stroke related dysfunction and consequences are accelerated in community living, wherein the demands imposed on the patient are very different to those experienced in a more sheltered and 'psychologically safe' stroke unit environment. Undoubtedly, the relationship between cognitive ability, self-efficacy, denial of illness and HI status is very interesting and not well known – it is further explored in section two.

To summarise, when groups are compared <u>on the hemi-inattention variable alone</u>, the under-achievement of HI+ patients compared to HI- is considerable, particularly in the ~1st three months after stroke. Consequently, HI+ patients appear predisposed to poor functional outcomes with associated increased risk of institution care and high disability levels in the community.

Section two

6.2. Comparison of modelled findings with those from critically reviewed studies

Although simple comparisons based on hemi-inattention status alone suggested disparities in functional outcomes, this comparison neglects the influence of other relevant variables. Such influences were further explored through the use of multi-level modelling.

The finding that HI status is not statistically related to functional progress in the 1st six months after stroke, when modelled together with other relevant variables, corroborates reports by Pedersen et al (1997) and the critically reviewed studies by Kalra et al (1997) and Odell et al (2005) but conflicts with findings by Katz et al (1999), Paolucci et al (2001), Buxbaum et al (2004), Gillen et al (2005), Di Monaco et al (2011) and Nijboer et al (2013). The most likely reason for this divergence in findings are improved features in the current design compared to that in reviewed studies. These are discussed next.

To recapitulate from the Methods chapter (Ch3), augmentation of past study designs was achieved by critically ensuring adequate representation of the RHS patient population in terms of stroke and HI severity and sample size. In contrast, past studies tended to automatically exclude patients with severe cognitive impairment through strict selection criteria. By accommodating their needs within the design (via interim observation time-points), it was possible to include and retain them in the PhD project (Blanton et al 2006, Hadidi et al 2012). In addition, a validated test battery (BIT) was used to increase detection of HI and facilitate the accurate grouping of HI± patients early on after stroke.

Furthermore, observations were standardised (at T0 and T3) and sufficiently far apart for progress to occur on cognitive-motor factors evaluated in this study. In comparison past studies tended to have shorter follow-up and limited number of measured factors, which may have reduced both the amount and quality of the data available for statistical modelling. This can impact on study power and in turn precision and accuracy of modelled results (Singer and Willett 2003, Royston et al 2009). Furthermore, the data was analysed by a robust statistical method appropriate for serial, hierarchical data compared to that in past studies. All these factors are likely to have contributed to the contrasting findings about the relevance of HI to functional outcomes.

Similar to this study, Odell et al (2005) did not find a statistically important relationship between HI status and functional ability on discharge despite important differences in their design (e.g. shorter follow-up of 30 days) and selective inclusion of patients with good rehabilitation potential – this is likely to have excluded those with severe cognitive impairment. However, Odell et al (2005) Rasch-transformed their data prior to modelling which may have contributed to increased precision of regression coefficient estimates and hence interpretation of the results (compared to ordinary multiple regression methods used by other past studies). Nijboer et al (2013) analysed their data by Random Coefficient Analysis (regression based method); their results were inconsistent with respect to the predictive role of HI, although they only modelled lower order terms i.e. the hierarchical structure of the data was ignored (statistically termed as ecological fallacy - Diaz Roux 2002). It is interesting that the three studies (inclusive of the current PhD project) which used advanced modelling methods obtained similar findings about the relevance of HI to functional outcomes despite substantial differences in design. This would suggest that the method of data analysis is of critical importance to the findings and conclusions drawn from modelling results (Tilling et al 2001, Ekstam et al 2007, Kollen et al 2005, Goedert et al 2013). Although Rasch model statistical techniques differ from MLM, their approach to data analysis bears some similarities in that contextual information about the patient is taken into account (Raudenbush 2003, Goldstein 2011). In this PhD study, patient characteristics and context alone were responsible for 67% of the variance in the EBI; variance which is unlikely to have been sufficiently accounted for in single regression analyses employed by past studies (e.g. Katz et al 1999, Gillen et al 2005, Di Monaco et al 2011).

A discussion on the differences between Rasch method and MLM is beyond the scope of this chapter, however Rasch models are based on item-response theory and more suited for analysis of self-reported measures whereas MLM principles are more suited for studying complex hierarchical relationships with inter-dependency in the data (Raudenbush et al 2003, Singer and Willett 2003). The strengths and limitations of the current study design are critically evaluated in section three.

Another factor that may have contributed to the differences in results is model specifications i.e. model size, complexity and combination of predictor variables included. For instance, Nijboer et al (2013) regressed FIM overall scores on FIM sub-scores (self-care, sphincter control, transfers, locomotion and cognition) whilst adjusting for sensory-motor deficits, BI, and depression at admission, time since stroke and HI status. In the current study, the closest model to Nijboer et al (2013) was the final one - consisting of time since stroke, HI status, stroke severity, age, motor function (balance and posture), global cognitive ability, bladder control and self-efficacy. Despite apparent similarities between these models, Nijboer et al (2013) did not find a relationship between FIM total score and cognition and/or bladder control whereas both factors were statistically significantly related to functional ability (EBI scores) in this study. This example reinforces the point made in the literature review (Ch2), that even apparently similar models are not as straightforward to compare. One reason is that the relationship between predictor variables in stroke are to an extent related to one another and therefore change accordingly depending on their combination in a specific model. There are numerous factors that can affect the final model estimates e.g. level of measurement of individual variables and entry order in a model (Twisk 2006, Royston et al 2009) - however this lack of comparability between models hinders comparison of results across studies and up to a point advancement of progress in this field.

Another reason for divergent findings with previous studies is the extent of statistical adjustment for important confounding factors undertaken during the analysis. Based on findings from the literature review, in the MLM analysis stroke severity, time since stroke and age were consistently adjusted for. This adjustment yielded very different results. When unadjusted for, HI status was clearly statistically significant but when stroke severity was added to the basic model, HI status became clearly insignificant (M1/Table 5.3). This result suggests that unless statistical control of stroke severity (in particular) is undertaken the likely finding is that HI status is of statistically significant importance – as is the case in studies by e.g. Katz et al (1999), Paolucci et al (2001), Buxbaum et al (2004), Gillen et al (2005), Di Monaco et al (2011) and Nijboer et al (2013).

Stroke severity accounted for a large proportion of unexplained variance (23% across patients) when modelled with age, time since stroke and HI status (M1/Table 5.3). This supports the importance of adjusting for stroke severity but also clinically estimating its contribution in models of functional recovery (Hakkennes et al 2011, Veerbeek et al 2011, Kwakkel and Kollen 2013).

From a statistical perspective, it could be argued that stroke severity and HI status are moderately correlated (Spearman's rho = 0.60, $p<0.0001$ based on n=372 cases) and should not be modelled together although Tabachnik and Fiddel (2007) and Field (2009) only caution about correlation between predictor variables of more than 0.8-0.9, which is not the case here. From a clinical perspective not including stroke severity in statistical models is likely to inadequately represent the RHS population and mislead comparison of patients in the sample. Furthermore, a degree of correlation between functional components in stroke recovery is inevitable because progress on one often depends on progress in other factor/s e.g. improvement in functional mobility depends on progress within cognitive domains. To this end, reasonable adjustments (e.g. centring predictors) were taken to reduce the effect of correlation (multicollinearity) between higher and lower order terms on the results (Twisk 2006, Field et al 2009).

In keeping with the importance of accounting for stroke severity effects, Buxbaum et al (2004), based on results from traditional multiple regression analysis, concluded that HI severity (versus lesion size) explained the discrepancy in functional ability of RHS patients in their sample (n=166). However, lesion size and stroke severity are also correlated; Schiemanck et al (2005) reported a correlation of R=0.61 with NIHSS after two weeks post-stroke onset, supported by findings from Ganesen et al (1999), Mihejeva et al (2012), Rehme and Grefkes (2013). This suggests that a different result and conclusion might have been obtained if stroke severity was adjusted for in the models evaluated by Buxbaum et al (2004). For example, MLM results in Ch5 indicated that neither lesion site nor type nor HI status contributed significantly to functional ability when time since stroke, stroke severity and age were accounted for (lesion site p=0.24, HI status p= 0.093, lesion type p= 0.38, HI status p=0.075).

The failure to sufficiently account for the confounding effect of 'time since stroke' in past studies on HI deserves further mention as it has been rarely reported and some studies did not control for the effect of time (since stroke) at all (e.g. Katz et al 1999, Paolucci et al 2001). Findings from this study indicate that time exerts a non-linear positive effect on functional progress, which is largest in approximately the first three months (supporting findings by Pedersen et al 1999, Tilley 2001 and Kwakkel et al 2006). The same trend is observed in progress within motor, cognitive and continence functions, denial status and HI levels.

In terms of effect size, the contribution of time since stroke was estimated at 12.5% in the final model compared to 42% change in the Barthel Index reported by Kwakkel et al (2006). The discrepancy in the estimates is probably explained by different model structure and predictor variable specifications i.e. Kwakkel et al (2006) modelled only progress in upper and lower motor recovery in a mixed patient sample using Random Coefficient Analysis (which tends to ignore the hierarchical structure of the data) whereas the variables (stroke severity, time, age, cognitive function, motor function, bladder function and self-efficacy) were included in the final MLM model. Nevertheless, both studies agree that the independent effect of time is more than 10% which is cited in the literature as a minimal requirement for a confounding factor of independent predictive importance (Twisk 2006, Field 2009). This evidence strongly suggests that future studies on HI and functional outcome should account for the effect of time post-stroke (Goedert et al 2013). The first 6 months are especially important because they are characterised by rapid gain in motor and functional recovery (Kollen et al 2005, Rehme and Grefkes 2013). To this end, another of the reviewed studies, Di Monaco et al (2011) controlled for time to 1st observation (average 23 days) but not for time to discharge (end of study) which varied substantially from 37 to 72 days, whereas Nijboer et al (2013) did not sufficiently control for time to 1st observation (55 to 63 days). Therefore one can appreciate why modelling results from different studies are inconsistent and often contradictory in this the field. Further support for modelling the effect of time comes from recent stroke reviews (by Barak and Duncan 2006, Langhorne et al 2011, Kwakkel and Kollen 2013). The impact of time has wider implications for rehabilitation where maximising the effects of therapeutic interventions is of paramount importance (implications are further discussed in section 6.4).

The rest of section two discusses the individual contribution of modelled factors in the PhD study starting with HI and draws mostly on the wider stroke literature to interpret the findings.

6.2.1. Relationship of HI status with functional change

When modelled with other factors evaluated in the study, HI status was statistically insignificant throughout the MLM analysis e.g. in Table 5.3, model M1c; p=0.061 and M1d; p=0.095. As will be shown later on, this finding provides substantial evidence that HI status is unlikely to reliably predict or explain functional change in the 1st six months after stroke when other influential factors in the final model (stroke severity, time (since stroke), motor and (global) cognitive functions, bladder control and self-efficacy) are considered. This result is further supported by findings from the sensitivity analysis in which HI status remained statistically insignificant ($p \geq 0.05$) whether modelled as individual BIT scores or a categorical variable (HI±). In this respect, categorical HI status showed similar sensitivity to BIT (interval) scores. The BIT published cut-off point (129) which was used to group RHS patients as with or without HI was also supported. Hence the diagnostic properties of the BIT as an assessment tool for HI are supported.

From a statistical, theoretical perspective, the main finding implies that <u>on average</u> a patient diagnosed early with RHS complicated by HI has an equal chance of making as good a recovery as one with RHS but without HI complications <u>under comparable</u> rehabilitative conditions; if motor, cognitive, bladder functions, self-efficacy, stroke severity and time since stroke are taken into account. The importance of advancing age is less clear cut. That being said, in practice equitable treatment and rehabilitation for all are difficult to guarantee judging by results from the Sentinel Stroke National Audit reports (ISWP 2012 & 2014), this is despite substantial ongoing improvements in service provision across the country.

Aside from practical issues of equity in rehabilitative provision, the main finding does not account for the impact of other potentially important factors not evaluated in this study. These factors include patient characteristics such as intelligence and educational level prior to stroke and attitudes towards health which were not measured as part of this PhD project. Their impact on stroke outcomes are acknowledged but tend to be relatively less known (Holmqvist and Von Koch 2001, Aben et al 2002, Roberts et al 2007). Evidence for this source of variance comes from statistically significant random (variance) parameters found in all the MLM models evaluated at the patient level (L2). They indicate substantial differences between patients across the sample which are related to functional progress and tend to widen with time elapsed after stroke (refer to Ch5/Figure 5.2). In clinical practice, this means that findings from average HI± group trends are less applicable to individual patients, which has important implications for the rehabilitation and management of patients with RHS and HI. It also reinforces what has been known clinically but anecdotally for some time that variation at the individual level limits the usefulness of statistical models in guiding individual rehabilitation i.e. without considering other circumstantial evidence available e.g. MRI/CT scan information.

In relation to causality, findings from this study indicate that on average, stroke severity rather than HI status is likely to be the cause of poor outcomes attributed to patients with HI (albeit both factors are associated with each other). This debate (about the relative impact of stroke severity versus HI) is not new in the literature and is revisited later on.

The importance of appropriate and equitable rehabilitative provision is illustrated by at least five patients in the study sample diagnosed with very severe stroke and HI. Despite substantial impairments and disability, they recovered sufficient functional ability to return to community living, assisted by family and outreach services. It is noted that the patients were relatively longer on the stroke unit and had more rehabilitation compared to other patients with severe stroke. In addition, three of the patients had a six week extended rehabilitation period in an Intermediate Care facility focused on returning home, which may have given them added advantages compared to the other two. Moreover, all five patients showed an unwavering commitment and determination to return home which was supported by strong family advocates on their behalf e.g. pushing for longer stroke unit rehabilitation rather early transfer to step-down facilities and/or discharge to institutional care. All five patients had high self-efficacy levels (GSE>30) which reflected a strong psychological belief in their abilities to cope at home. Similar ‘successful outcome’ case studies have been cited in the literature by Tham and Borrel (1996) Tham and Kielhofner (2003). Together, these illustrative cases suggest that under the right conditions patients with severe HI can thrive to levels comparable to patients without HI.

In relation to social support and home discharge, carer status showed a weak but significant relationship (p=0.028) with functional ability when adjusted for time, stroke severity, HI status and age but this was not maintained when other factors such as continence, cognitive and motor abilities were individually or collectively added to the model. These results suggest that on average carer status may not be of crucial importance to functional and discharge destination outcome compared to other factors such as basic cognitive and motor skills but as illustrated in the case studies, the finding is less applicable to individuals. For instance, had the families of the five patients described earlier not argued in their favour for longer rehabilitation time then they would have missed an important opportunity for continued rehabilitation.

In all probability, carer status may be of predictive importance in the long term or in situations where the carer is either in very good or poor health as suggested by the previous argument. To this end, evidence from the EXCITE project indicated that carer depression at stroke onset independently predicted mood and social participation of stroke patients at 12 months (Klinedinst et al 2009, Nijboer et al 2013). Their findings supported those by Lewis et al (2008) in that a spouse experiencing depressed mood negatively influenced the functioning of the person with an illness. Therefore it would seem that both the presence and the health of the carer may in some cases be linked to functional outcomes, although carer health was not evaluated in this study.

6.2.2. Relationship between self-efficacy, HI status and functional progress

In line with findings by Hellstrom et al (2003), LeBrassuer et al (2006) and Jones et al (2008), MLM results from this study indicated a significant positive relationship between self-efficacy levels and functional progress (p=0.00031). This held true irrespective of HI status and even when the effect of time since stroke, stroke severity, age, cognitive, motor and bladder function were taken into account. When plotted, the effect of self-efficacy appeared to extend beyond the 1st six months after stroke.

In comparison to other measures, the standardised effect equates to an increase of (~ 2.58) EBI units or 0.15 SD/1SD increase in GSE, which is comparable in size to that of stroke severity but in the opposite direction. Standardised effects have been criticised for not presenting an accurate picture because they are dependent on the standard deviation (SD) of specific samples (Cohen et al 1999, Field 2009, Baguley 2009). However, the GSE scores stabilised around 30 in the 1st six months after stroke which is expected to contribute 8 EBI units (1/8 total EBI scale) in the final model (not-standardised). This finding has relevant clinical and ethical implications because it suggests that those patients with high self-efficacy levels are functionally better off than those with lower levels even when the effect of core cognitive-motor function and age are accounted for (irrespective of HI status). The strength of this relationship may explain why some patients with severe residual cognitive and motor impairments go on to make unexpectedly good functional progress against the odds whereas others remain relatively incapacitated under comparable circumstances. Considering that HI+ patients were on average acutely more in denial about their stroke impairments than HI-, one would expect to find differences between groups (HI±) in GSE levels but on average this was not the case.

6.2.3. Relationship between denial status, HI and functional progress

In this study, it was assumed that increased awareness of stroke impairments would be reflected in lower percentage rates of denial across the sample which was supported by the results in Figure 4.8. They show a strong positive association between denial and HI status, which weakens over time. This finding also implies that RHS patients may become more receptive to therapy intervention delivered in the community suggesting that appropriate timing and delivery of services is important and especially at a time when stroke rehabilitation is moving faster into the community setting (Walker et al 2013).

When modelled, the lack of a statistically significant relationship (p=0.13) between denial status and functional change was surprising and not in line with earlier findings by Jehkonen et al (2001) and Gialanella et al (2005). Reasons for the difference could be variability in the duration of follow-up, different methods of data analysis and model specification (Gialanella et al 2005 did not model the data). For instance, Jehkonen et al (2001) used the number of days from stroke onset to returning home (up to one year follow-up) as the outcome variable (DV) and adjusted for age in ordinary regression analysis. In comparison, age, stroke severity and time since stroke were adjusted for in the MLM analysis and actual functional ability levels (versus LOS) were used as the DV. Consequently the results from Jekonen et al (2001) are confounded by stroke severity which makes it difficult to infer causality. In fact, as soon as stroke severity was modelled with denial status (M2j) both MLM-regression coefficients (denial and HI status) became statistically insignificant (when age and time since stroke were adjusted for). In terms of explanation, the dynamic in M2j provides further evidence that stroke severity is clearly the stronger predictor of the two (denial or HI status). However the exact relationship dynamic is difficult to tease out because of the interdependency between stroke severity, denial and HI status. Furthermore, HI status and denial status are associated with large infarcts and diffused multiple impairments (Appelros et al 2007, Orfei et al 2007). That being said, the confidence intervals (CI's) around both regression coefficients for denial status (-0.65; CI 1.71, -3.00) and HI status (-2.28; CI 1.97, -6.53) are relatively wide and therefore less reliable. This is indicative of considerable variation across patients, which is in turn supported by significant unexplained variance in the random part of the model (M2j).

The possibility that denial status lacked sufficient sensitivity to detect a significant effect when modelled as a binary categorical variable must also be considered. Denial is not an all-or-none phenomenon it is subject to time elapsed after stroke and cognitive ability at assessment time (Livneh 2009, Jenkinson et al 2011). Therefore it is possible that modelled as a continuous variable and with a different combination of factors (e.g. education level prior to stroke), it may exert greater influence on outcome.

An intriguing question arises as to why self-efficacy levels (discussed in section 6.2.2.) remained relatively stable whilst rates of denial changed markedly over time, irrespective of HI status. One would expect both factors to fluctuate in tandem since lower rates of denial hypothetically imply better stroke consequential awareness and hence a corresponding shift in self-efficacy levels. Psychologically, this picture tends to suggest that denial and self-efficacy operate quite independently of one another, possibly at different levels of consciousness. Theoretically, the perceptual distortion of reality associated with HI is likely to further predispose vulnerable patients towards denial especially when other contributing factors are present. This statement is supported by findings from Marcel et al (2004) and a series of publications on the subject by Fotopoulou (2012 &13) and Fotopoulou et al 2010 (a&b); in which supportive evidence is provided for the interference of unconscious, pathological processes (confabulation) in the absence of conscious representation, manipulated experimentally by the researchers.

In support of findings by Fotopoulou and colleagues another plausible explanation could be that a reduction in denial levels does not automatically result in increased self-efficacy levels without a corresponding increase in higher executive function. To this end, both patient groups (particularly HI+ patients) scored very poorly on the TMT (Trail Making Test) which suggest extremely slow cognitive-motor processing speeds. TMT results also suggest that HI+ patients in particular had poor mental flexibility, working memory and sequential thinking, which are requirements for good situational judgement, insight and future prediction of abilities. That is, executive dysfunction could be the missing link in patients deceived by manipulated experimental situations in the studies by Fotopoulou and colleagues. Consequently, specific executive dysfunction components are likely to affect the way that individuals perceive the world around them and their abilities to cope after stroke. The relationship between denial, HI, executive function and self-efficacy is not well known in stroke psychological literature but merits future interdisciplinary research attention. If the complex relationship dynamics were better understood then it may be possible to appropriately enhance self-efficacy levels, which in this study were of relative predictive importance.

From a rehabilitative perspective, denial (in RHS conditions) is an area of special interest both on its own and in association with other factors including the presence of HI because of its ethical, therapeutic and management implications. These are further elaborated on in section 6.4.

6.2.4. Relationship between age, HI status and functional progress

The literature review highlighted inconsistent findings about the relationship of age with stroke functional outcome (Kalra et al 1997, Ring et al 1997, Di Monaco et al 2011). On average, MLM results do not support an important relationship between age and functional recovery (p=0.062) irrespective of HI status and when the effect of other influential factors in the final model is taken into account (time since stroke, stroke severity, cognitive, motor and bladder function, self-efficacy).

However the presence of statistically significant variation in the models evaluated effectively limits generalisation of findings to individual situations.

Secondly, the MLM result contradicts reports by Jehkonen et al (2000), Ring et al (2004) and Gottesman et al (2008) who also controlled for stroke severity effects in the analysis but found that on average older stroke patients were more likely to show hemi-inattention.

Nevertheless, there is some evidence from MLM estimates that the impact of age becomes considerable after 80 years, (supported by findings from e.g. Bagg et al 2002, Bhalla et al 2004 and Black-Schaffer and Winston 2004, Saposnik et al 2008). Based on the final model estimates, the age-regression coefficient is -0.077. Calculation shows that at 40 years the estimated drop in EBI score is ~3 EBI units, at 60 it is ~4.6, at 80 it increases to ~6.2, at 90 to ~7 and at 100 years is ~ 8 EBI units which is 12.5% of the EBI scale. This data supports the notion of a gradual decline in functional ability as a result of age, which is likely to reflect natural increases in morbidity and risk of stroke (Feigin et al 2003, Nys et al 2007, Chen et al 2010, Ford et al 2010). The gradual decline may also be an important reason why findings from alteplase (the *clot busting* drug) therapy trials tend to be inconclusive for patients over 80 (Ringleb et al 2007, Lees et al 2010, Ford et al 2010, Mishra et al 2010). This is further supported by conflicting results in research studies on the impact of age on brain neuro-plasticity (Tombari et al 2004, Hermann et al 2012, Rehme and Grefkes 2013), which is very relevant to stroke recovery and rehabilitation. Despite inconsistency in the results, findings from the cited studies make compelling arguments in favour of the brain's preserved ability to functionally reorganise itself, even if changes are limited and more attenuated with increasing age. In turn, this is supported by findings that prior stroke health, genetic factors and rehabilitation provision can moderate the effect of age (e.g.

Kelly et al 2006, Sacco et al 2008, Sandercock et al 2012). Consequently there is little argument for not providing the same level of rehabilitation given to younger patients (< 80) with comparable pathology (Bagg et al 2002, Horn et al 2005, Kashihara et al 2011).

6.2.5. The impact of stroke severity on functional recovery

Stroke severity was modelled by one of the critically reviewed studies (Paolucci et al 2001), who did not report a predictive effect on functional outcome at discharge from in-patient rehabilitation (average/days HI+ (117± 61) & HI- (81± 38). In the current study, the effect of stroke severity was statistically significant in all the models evaluated. In the final model this was (p=0.00017). Overall, the finding supports that from past predictive studies with heterogeneous stroke samples and mixed pathology (infarct and haemmorhage) (Adams et al 1999, Schlegel et al 2003 and 2004, Weimar et al 2004).

Based on MLM results from the final model, a patient with severe stroke (NIHSS = 25) drops more than 10 EBI units (~17%) as a result (excluding the interaction effect with motor function). This is not surprising because 54% (n=50) patients had severe strokes which are associated with widespread neuronal damage beyond the focal lesion (Honey and Sporn 2008, Grefkes and Fink 2011, Rehme and Grefkes 2013). The resultant neurophysiological disturbances affect both direct and indirect cerebral networks, which sub-serve cognitive-sensory-motor function, including those networks associated with HI conditions (Chechlacz et al 2012, Jacobs et al 2012, Vandenberghe et al 2012). Further to the earlier debate (section 6.1.3) about the relative importance of stroke severity and HI status with respect to functional progress, the strength of evidence available would suggest prioritisation of therapeutic interventions aimed at reducing the overall impact of stroke severity. Theoretically, this should result in the reduction of HI (when present) and hence overall improvement in functional ability. It is possible that the mere focus on HI as the primary cause of poor functional outcomes in RHS patients in the literature, may in fact be undermining the importance of reducing stroke severity in order to enhance overall patient outcomes.

In the final model, the effect of stroke severity is subject to that of a significant, negative interaction (p=8.93e-006) between the NIHSS and PASS scores – graph in Figure 5.5). This means that the change in PASS score (motor abilities) is different for different stroke severity levels (mild, moderate severe and very severe). The same interaction effect weakens with time after stroke which implies that the interaction effect is strongest in the acute phase when patients are more likely to be motor impaired. The combined interaction effect is over and above that of the PASS and NIHSS effects although both factors are likely to be correlated with the interaction, which may have resulted in inflated estimates (Bauer and Curran 2005, Field 2009).

In summary, the presence of the interaction between stroke severity and motor function has potential clinical implications for patients with severe stroke conditions; these are discussed further in the implications section (6.4).

6.2.6. Relationship between functional progress, therapy exposure and length of stay

The duration of stay (LOS) (median 30 days) was significantly related to functional change (p=0.011) only when age, stroke severity, time and HI status were adjusted for - but it was not of statistical significant importance when other influential factors (cognitive, motor and bladder function and self-efficacy) were also accounted for in the final model. This suggests that, on average it is not the

LOS that is important in as much as what is functionally achieved in terms of progress during the stroke unit stay – irrespective of HI status. However, for patients who do not fit in with average progress patterns (e.g. slow progressing patients) there may be implications (discussed in section 6.4).

In regard to in-patient therapy recorded sessions there appears to be a mismatch between the median LOS (30 days) and median therapy figures (20 sessions). Although it is difficult to interpret the result due to limited information on therapy provision, the mismatch suggests that the middle quadrant of patients may not have received daily therapy. This is possible considering that stroke patients in the UK generally receive less in-patient therapy than other European countries such as Germany (CERISE study-De Wit et al 2006). The problem has also been recognised nationally (National Sentinel Stroke Audit ISWP 2012, Drummond et al 2012 and 2013, Forster et al 2013).

In this study, levels of therapy input may partly explain the lack of statistically significant relationship between HI and outcome, when cognitive and motor components are accounted for, since therapy amount is likely to be related to LOS. Other studies outside the UK reported significant relationships between LOS and outcome (Foley et al 2012, Wang et al 2013) but models are not directly comparable between studies.

Although intensity and amount of therapy provision are strongly debated in the literature, current expert consensus is that early intensive (functionally targeted) therapy leads to improved outcomes; the recommended dose is 45 minutes daily subject to patient tolerance (National Clinical Guidelines for Stroke 2012). There is ongoing research and debate in this area (at the time of writing). With respect to this study, patients with severe stroke may be disadvantaged by shorter LOS and possible reduced exposure to specialised stroke unit care, irrespective of HI status.

6.2.7. Relationship between motor function, HI status and functional change

Motor function showed a relatively strong, positive relationship with functional change ($p=4.63e^{-028}$) irrespective of HI status; even when other influential predictors (stroke severity, time, age, global cognitive function, self-efficacy and bladder function) were accounted for (supports findings by Katz et al (1999) and Nijboer et al (2013).

The effect of motor function is reflected in the NIHSS score (in the same cross-level interaction described in section 6.2.4). The standardised effect is more than twice that of stroke severity when calculated in EBI change scores; 1SD change in PASS (~ 12 units) and in NIHSS (~ 6 units) is equivalent to 13.8% (9 EBI units) compared to 5% (3 EBI units) respectively. This means that motor function components (balance and posture abilities) explained more change in functional ability for the same period than baseline stroke severity, irrespective of HI status. Hence, there is strong statistical evidence that motor recovery is crucial to optimising overall function in the 1st six months after stroke. This finding makes sense considering that stable sitting/standing balance and dynamic posture are prerequisites for the recovery and safe execution of basic ADL tasks - these include bed mobility, reaching, bending, turning, forward and backward stepping and retrieving items from different heights. The finding has implications in regard to the prioritisation of evidence-based intervention methods and approaches which promote early motor recovery and learning (see further comments in section 6.4).

6.2.8. Lesion size – Cause of poor functional outcomes in RHS

An interesting debate in the literature concerns the cause of poor functional outcome in HI+ patients i.e. whether this is due to larger stroke lesions in specific sites or the presence of HI *per se* (Appelros et al 2007, Kortte and Hillis 2009, Sampanis and Riddoch 2012).

In this study, lesion size (area/volume) could not be calculated from CT/MRI scans available. Alternatively, lesions were classified as cortical and/or sub-cortical assuming that severe strokes were more likely to involve both types of lesions. When modelled as a categorical binary variable, neither lesion site nor HI status made significant contributions to change in functional ability and when adjusted for stroke severity, age and time since stroke. This result does not corroborate reports by Buxbaum et al (2004) that the impact of HI on basic attention, functional disability, and family burden is significantly greater than that predicted by the number of lesion areas. Based on their finding, Buxbaum et al (2004) concluded that the 'neglect' syndrome rather than overall stroke predicted poor outcome in RHS conditions. However, there was no adjustment for stroke severity or time to 1st observation which varied from 5 to 1272 days (their sample included both acute and chronic patients with potential for rehabilitation). In relation to this PhD study, allowances must be made for the poor quality of radiographic reports describing affected brain areas. Aside from design issues, in Buxbaum et al (2004) lesion sites were meticulously measured and classified into 10 areas. - the inferior/mesial temporal, middle/superior temporal, inferior parietal, basal ganglia and occipital lobes were most likely to be involved in neglect/HI rather than non-neglect/HI patients. Perceptual neglect was more likely in lesions involving the temporal lobe (further supported by Parton et al (2004), Karnath and Rorden (2011).

In relation to the debate, causality cannot be confidently attributed to the presence of HI or lesion size but the argument is inherently weak because poor functional outcomes are unlikely to be caused by just two factors. Based on findings from this PhD study, initial stroke severity is the more likely explanatory factor. Future research studies interested in the debate should account for stroke severity effects and model the data by MLM so that covariance effects (between stroke severity, HI status and lesion size) can be accounted for. This would help tease out relevant relationships in the data.

6.2.9. Progress of patients with severe stroke and HI impairments

The interim observation data obtained from severely (NIHSS>15) affected patients is of particular interest. Aside from individual variation in progress patterns, it highlights a rather abrupt cessation of functional gain around the four week mark after stroke for patients with and without HI, especially in the very severe category (NIHSS>24) (see individual progress trajectories in Figure 4.3). It is also noted that the same point in time is consistent with the hypothetical duration of spontaneous neurological recovery processes which are associated with the extent of possible functional recovery and therefore outcomes (Rehme et al 2011, Hermann and Chopp 2012). It is recognised that outcome is modifiable by therapeutic activity (e.g. repetitive task training) and the rehabilitation environment (Teasell et al 2005, Rensink et al 2009, French et al 2010). Nevertheless, unless co-incidental, the sudden drop in functional progress noted in the results tends to suggest a poor interface between neurological and functional progress in patients with severe stroke, which is likely to have implications for discharge and destination outcome. This is further supported by the fact that in this study, 29 of the 33 severely affected patients were institutionalised due to the high functional dependency levels at discharge (the majority also had HI). There is also indication from the researcher's notes that they continued to deteriorate further up to six months after stroke regardless of their HI status. There is relatively little research in this area. These results support the need for focused research into the reasons why the progress of this sub-group of severely impaired stroke patients diminishes so early. The findings would inform how best to manage these patients therapeutically in order to enhance their outcomes. It is acknowledged that these patients have more medical complications than less severe patients. However medical complications alone are unlikely to provide satisfactory explanations for the results. Therefore research into the problem is important because currently there are few or no opportunities for skilled rehabilitation in longer term institutions. It is likely that some of the causative factors are modifiable and changeable within the current service provision e.g. unnecessary time delay, attention to continence and nutrition issues (which are discussed below).

6.2.10. Relationship between continence status, HI status and functional progress

In this study, bladder function showed a statistically significant (negative) relationship with functional outcomes which supports findings by Ersoz et al (2005) and Chamorro et al (2007). However, bladder control was unrelated to HI status in all the models evaluated when adjustments for the effect of time, stroke severity, age, and/or cognitive, motor function and self-efficacy were made. In contrast, Nijboer et al (2013) reported a relationship between HI status and bladder control but no adjustment for stroke severity was undertaken in their model. This could explain the difference in results.

Records from this study show that 50% of patients with HI were still impaired in terms of continence by discharge and only marginal progress was made by six months after stroke. Patients without HI had relatively lower rates of continence dysfunction but these were still substantial by six months. Overall, the rates are slightly higher than those reported in the literature for the same period but that is probably explained by the higher proportion of severely stroke impaired patients in the current sample.

The high continence dysfunction rates in patients with HI living in the community (refer to Figure 4.9) presumably impacts on the patients' independence levels, which are already jeopardised by poor mobility (median PASS score = 23/data in Figure 4.5). All these factors contribute to social incontinence which is not helped by poor continence management (National Sentinel Stroke Audit ISWP 2012). Continence dysfunction is a recognised poor diagnostic predictor but relatively under-researched in patients with HI.

Bowel dysfunction was less prevalent in the study sample but still relatively high in HI+ patients. On average, it was negatively related to outcome ($p < 0.0001$) and unrelated to HI status in adjusted models (time, stroke severity and age).

6.2.11. Relationship between Nutrition status, HI status and functional ability

In line with past study findings by Nip et al (2010) and Jones et al (2011), initial (T0) nutrition status was negatively, significantly related ($p=0.0030$) to functional recovery even when stroke severity, age and time were accounted for. HI status did not make a statistically significant contribution in the same model (M2m). This finding suggests that patients who were assessed as at risk of malnutrition on the MUST (Malnutrition Universal Screening Tool) shortly after stroke did less well functionally irrespective of their HI status - presumably due to an associated reduced strength, stamina and tolerance, which also have implications for therapeutic outcomes.

In comparison to other influential factors e.g. stroke severity, baseline nutrition status was not of significant importance in the final model. This is a positive finding because it implies hope for patients whose nutrition improves whilst on the stroke unit (supported by Nip et al 2010). Unfortunately this was not known because follow-up nutrition status data was unavailable to the researcher which suggests that practice guidelines and recommendations by the National Clinical Guidelines for Stroke (2012) were not adhered too.

More patients with HI (26%) were assessed as at higher risk of malnutrition compared to without HI (3%) soon after stroke. This finding is not surprising because HI+ patients who are also more likely to have severe stroke are automatically classified as high risk on the MUST measure. Furthermore, severely affected HI+ patients have greater difficulty locating food on their plate, eating, swallowing, poor appetite and other cognitive impairments which complicate the picture. Consequently the patient's problems are magnified by the presence of HI and will require appropriate management.

6.2.12. Relationship between Cognitive function, HI status and functional progress

This PhD study evaluated the contribution of both global cognitive and executive functions, they are separately discussed.

Consistent with reports by Katz et al (1999) and Gillen et al (2005), cognitive levels were positively, significantly related to functional outcome even when other influential factors were included in the final model and irrespective of HI status. This finding contrasts with that from Kalra et al (1997), Di Monaco et al (2011) and Nijboer et al (2013) who found no relationship. The inconsistency in results is probably due to confounding factors as in different sample mix, time to 1st observation and different assessment tools.

The assessment tools employed in the PhD project (MEAMS and BIT) overlap to some extent in their measurement of orientation and awareness, short/long term/working memory and spatial construction skills. The MEAMS is not an in depth assessment of hemi-inattention levels but is (100%) specific to memory and construction abilities (Cartoni and Lincoln 2005), whereas the BIT is an in depth measure of impairments associated with HI and gives an overall severity score. Based on MLM results from models (M2f & Mf), MEAMS scores explained significantly more of the dependent variable than T0/BIT scores, which supports the notion that HI is part of a much larger array of cognitive impairments. It also argues against treating HI as an isolated entity and is supported by findings from scientific reviews linking attention, HI levels, alertness and sensory-motor abilities (Hussain and Rorden 2003, Bowen and Lincoln 2007, Cicerone et al 2008, Lincoln et al 2008). Functionally, Walker et al (2011) also reported a reduction in HI following assessment and treatment of dressing problems in RHS patients by neuro-psychological versus traditional methods. In this respect, MLM results (M2f) argue for individual assessment and treatment of global cognitive dysfunction, since associated deficits not only differ considerably between patients and contextual environments but also have varying effects on outcome. This would suggest that individual tailored programmes are more likely to optimise outcomes considering that cognitive function is related to stroke severity, motor function, self-efficacy and bladder control - all of which showed important (statistically significant) effects.

Two executive function components - cognitive-motor processing speed and mental flexibility were measured by the Trail Making Test (TMT). TMT scores were significantly, negatively related to functional progress only when time, stroke severity and age were adjusted for but not in the final model. This result is irrespective of HI status and suggests that processing speed (efficiency) and mental flexibility (problem solving, sequential and lateral thinking) were less instrumental in bringing about change compared to other psychological factors e.g. global cognitive function or self-efficacy. It is also possible that other executive components not evaluated in this study are important in the 1st six months or that the TMT tasks lack sufficient sensitivity to detect small changes in function. Buxbaum et al (2004) assessed sustained and divided attention by means of SART (Sustained Attention Response Task) (Robertson et al 1997), which incorporates a secondary task load similar to the TMT (complex task). Their results also indicated that HI was associated with reduced sensory-motor speed and non-executive aspects of attention but was not associated with (frontal lobe) dysexecutive function (which is involved in mental flexibility as in performing dual attention tasks).

From a neuropsychological perspective, processing of incoming sensory information is slow in HI conditions which would be expected to delay the execution of appropriate cognitive-motor plans (Chica et al 2011, Finke et al 2012, Smith and Schenk 2012). Consequently more time is needed to finish everyday task components in patients with severe stroke (who are more likely to have HI) than less severe stroke conditions. That being said, there is some evidence that patients with HI become more efficient with time and evidenced based neuropsychological approaches to assessment and treatment of ADL tasks e.g. dressing (Walker et al 2012).

On average, severely impaired patients took a median of 280 & >300 seconds compared to 53 & 115 seconds in moderately impaired patients over the six month period to complete the simple and complex TMT tasks respectively. They were clearly slower and more rigid in their thought process which may have clinical implications in terms of functional progress but also individual risk and safety. These are addressed in section 6.4.

Section three - Critical evaluation of the study

This section addresses the methodological strengths and limitations of the study, starting with challenges to recruitment and data collection.

6.3.1. Practical challenges associated with data collection

There were several practical and logistic challenges associated with data collection from the two stroke units and community settings (home and care institutions); the most important of which are now described and commented upon.

Right from the outset, local organisational problems restricted planned recruitment from three to two stroke units and then to one unit for just over a year. This lengthened the recruitment period and reduced the patient pool available for potential inclusion. This challenge was partly overcome by extending the recruitment and data collection to 7 days a week for ~ 13 month period. In hindsight, the design is not ideal for a lone researcher due to the high fatigue levels involved and logistical problems (e.g. tight assessment schedules). On a more positive note, these were reasonably overcome by forward planning, high levels of organisation and assessment alongside MDT members where possible. Collectively, the measures taken enabled data collection to proceed with minimal interruptions and kept loss of data to a minimum. To put into perspective, the assessment of n=40 severely affected patients needed the physical assistance of more than one person which was provided by other health professionals such as e.g. nurses, occupational therapists and physiotherapists available on the stroke unit. Both recruitment and data collection schedules were very tight due to multiple assessments coinciding at different locations all being due within the same 7-day period. The full schedule was responsible for some data loss as it was not always possible to fit all assessments in, given the number of uncontrollable variables in the community e.g. traffic delay, patients not ready for their allotted appointment time, difficulty getting assistance in the community.

Attempts to overcome the above challenges were made by adopting pragmatic yet thorough ways of working with greater flexibility. For example, scheduling follow-up community visits when the main carer (who knew the patient well) was also present so could help with providing specific information on progress that the patient may have difficulty in recalling e.g. changes in patient abilities since the last visit. (Ethical approval for carer involvement had been formally granted). In the community, professional judgement was utilised when there was no other way of rating patient abilities. For the most part, these could be directly observed in high functioning patients. Indirect methods and clinical expertise were used to rate specific abilities in lower functioning patients; examples are provided:

Shaving and brushing teeth were judged from the person's cognitive and perceptual abilities, fine and gross motor movement, dexterity and co-ordination at assessment time i.e. the ability to grasp and manipulate shaver/toothbrush handle with available hand/finger grips and strength, likelihood of sustaining required movements for shaving/brushing teeth against gravity (taking into consideration fatigue levels, dexterity and ability to coordinate eye-hand-mouth/face movements at the time of visit) were all taken into account.

Eating, drinking, toileting and ambulation were for the most part directly assessed during the course of a morning or afternoon visit. Other indicators such as the presence of a urinary catheter, wet pants, smell of urine were also taken into account in the rating. Transfer abilities were directly observed apart from managing a flight of stairs. For safety and due to the high fatigue levels involved this task was assessed on the steps at the main access, also taking into account the patient's ability to balance safely, step and change posture safely. In order to reduce the likelihood of fatigue associated with multiple assessments within a short period of time, short breaks were provided or a return visit made when the person lived close-by. While this increased the workload for the researcher it ensured continuity in data collection.

Some equipment required for the PASS had to be improvised e.g. the patient's bed/chair/seating surface was used instead of an adjustable height plinth. It was also tricky to find suitable places with minimal distraction for table activities e.g. pen and paper assessments in relation to the MEAMS, TMT and BIT. The kitchen table was often used for this purpose.

An unforeseen challenge in the community was that 'desperate' patients and relatives expected the researcher to help and advise on their recovery and getting the ‘right therapy support’. For instance, some patients were not happy with generic therapy provision because they did not think it was specialised enough to help them achieve their rehabilitation goals. Several patients (~ 25%) were frustrated at delays in care package commencement and having to go to bed as early as 5:00 p.m. with the last care call. Some researcher time was spent listening and empathising with patients and family either prior to assessment or after. Recurring issues were noted because the frustration levels affected mood, focus, concentration and motivation levels. It may have inadvertently impacted on assessment results.

As for access to community records, there are no easy solutions until these are centrally and electronically available. Without such a system, it was impossible to collect data on type, content and time of service provision in the community. Incidentally, these details were also difficult to obtain from stroke unit records especially if patients were deceased or were transferred to other units at short notice. Inevitably there were incomplete data also on stroke units e.g. neurological information pertaining to stroke severity profiles was partly documented in the medical notes and partly on the NIHSS form. Another example was the apparent absence of follow-up MUST forms completed by dietetics. It is possible that this information was kept elsewhere. Furthermore data extraction from MDT records was complicated by illegible hand-writing and incorrect filing.

In terms of week-end working to collect data, this proved to be very successful as patients seemed more relaxed and were available for the researcher, in addition close family or informal carers were around if needed. Direct observation of the patient (e.g. being nursed, at meal times, engaging in social activities) was likewise possible. Weekend visits were also preferable in institutions, however patient access was not always forthcoming (e.g. getting permission to see the patient and observe personal care was difficult – despite the patient's verbal consent and the researcher having made a prior appointment to attend for this purpose. Sometimes, different staff on the shift insisted that permission was needed from sons/daughters who were not around. This was hugely disempowering to the residents who were mentally stable and healthy. These barriers to access caused unnecessary delay and reduced efficiency. In hindsight, a formal agreement with each institution may have expedited matters as soon as one is identified prior to discharge from the stroke unit.

As a general comment, more allowance should have been made in terms of time and research resources including travelling costs. A subsequent project would benefit from having a project team to share the workload. Other researchers such as Jeffries et al (2009), Wilkinson et al (2011) and Hadidi et al (2012) have realistically documented the multiple recruitment and data collection challenges encountered in serial, longitudinal stroke studies. On a more positive note, despite the barriers, the amount of missing data was minimal (<15%) compared to that in other longitudinal studies, which was reported at 33% by both Appelros et al 2003, and Di Carlo et al 2003. In fairness, it is difficult to directly compare, a relatively 'small' PhD study with only one researcher who was in control and seriously committed to data collection with a large scale RCT. Taking everything into account, the current dataset is substantial for the size of this project and research conditions described. This facilitated in depth statistical analyses and discussion in order to answer the research question. The results were supported by those from the sensitivity analyses which showed that estimating the final model with and without adjustment of missing data yielded comparable results).

6.3.2. Aspects of the design

The serial longitudinal design generated substantial amounts of data for the duration (~ 19 months), more than most of the critically reviewed studies (e.g. Kalra et al 1997, Gillen et al 2005, Odell et al 2005, Di Monaco et al 2011). The information collected provides a rich uninterrupted picture of the patient's natural progress patterns within specific functional components, HI levels and overall functional ability which are valuable in stroke rehabilitation research. The 1st six months are also very important because they are characterised by major functional change which forms the basis for subsequent progress and later life (including living with potentially long term residual stroke impairments) (Langhorne et al 2011, Kwakkel and Kollen 2012).

In the design, patients were screened for depression and anxiety whilst on the stroke unit. Ideally screening could also be carried out in the community phase (Barker-Collo 2006, Terroni et al 2012). Results from this PhD study could be replicated in larger scale studies on different RHS patient samples in order to rule out the potential impact of geographical differences in stroke service provision and management and to validate the results.

6.3.2.1. Number and position of observation points

Compared to past reviewed studies in (Ch2), the design was specifically augmented to capture change in progress (when it was likely to occur) whilst still respecting the natural time-line and progression of stroke in relation to the research question (i.e. HI± patient groups were compared at critically important stages – baseline (T0), discharge (T1), early post discharge (T2) and six months (T3). In this design the assessment needs and follow-up of a fully representative stroke-severity sample were accommodated by two interim observation points (TI1 & TI2). This was an important improvement on previous designs which tended to exclude severely cognitively impaired patients from the research (e.g. Gillen et al 2005, Odell et al 2005, Di Monaco et al 2011).

In contrast to previous designs, T0 and T3 (6 month post-stroke follow-up) were relatively fixed in time to enhance HI± group comparison at the beginning and end of the study period (supported by Kwakkel and Kollen 2013). Similar to previous studies (e.g. Kalra et al 1997, Paolucci et al 2001, Stein et al 2009) T1 & T2 (discharge early follow-up) were retained as key observation points because the research question required functional ability scores from a comparison group (HI±). Further, the alignment preserved a realistic sequence of events irrespective of when discharge occurred (Fisher and Walker 2011, Langhorne et al 2011, McAdam et al 2013).

6.3.2.2. Sample size and representation

As far as the author is aware, this is the 1st study in the field of RHS/HI to include patients with full range of stroke severity and severe HI. This necessitated retrospective estimation of baseline scores for five patients who were recruited and first assessed at (TI1) (later than other patients). Similar to other stroke studies (e.g. Viken et al 2012) professional judgement was used to estimate the missing data at baseline. Arguably, this was preferable to systematic bias that could have been induced by not doing anything about the missing data (Allison 2012).

Sample size is comparable to that of previous prospective stroke functional studies with similar design and data analysis method (MLM) (Kollen et al 2005, Kwakkel et al 2006). Although the sample size (n=93) at T0 proved sufficient to answer the research question, a larger sample size would have enabled the evaluation of slightly more complex functional models.

Although missing data was kept to a minimum by stringent data collection methods, there were 16 incomplete data sets due to deceased patients (n=16). In retrospect, the data was probably not missing at random because the deceased patients tended to also have very severe strokes and co-morbidity (e.g. cardiac conditions, hypertension and diabetes), which are associated with increased risk of mortality. Considering the predictive importance of stroke severity, this potential impact of this variance on the results was taken into account when making inferences from the data. Further, the deaths are not directly connected with the study.

Computer simulation of missing data could be considered in larger data-sets. This is a very complex procedure requiring the input from a professional statistician with an understanding of the project and the dynamic relationships between affected variables over time. Further, due to the associated costs it was not possible to undertake in the PhD project.

6.3.2.3. Measurement

The use of validated measurements (EBI, BIT, PASS, MEAMS, TMT, GSE, NIHSS, MUST) strengthen the findings from this study. The only exception was Denial of illness interview questions, adapted from Cutting's Anosognosia questionnaire (details in Methods/Ch3). Furthermore, potential order effects were minimised by changing assessment order between observations.

Some measurement limitations were also noted e.g. the BIT does not assess for HI in activities not performed within body reach and space (e.g. walking ahead). The EBI assesses ADL activities and instrumental ADL to a lesser extent (it covers ability to communicate and relate to others, which is one of the reasons why it was chosen instead of other BI versions). Consequently, the findings apply to functional abilities within the EBI remit.

6.3.2.4. Floor and ceiling effects

The PASS and the EBI showed acceptable floor and ceiling effects i.e. well within the conventional 20% cut-off recommended in the literature (Barak and Duncan 2006, Salter et al 2010); Ceiling effects were reached as follows - EBI (7.5% or 7 patients), PASS (4.3% in 4 patients) at T1 &/or T2; Floor; EBI (9% or 8 patients), PASS (15.1 % or 14 patients at T0). The GSE performed very well with an acceptable ceiling effect of 3% at T3. Overall, the results support the use of the PASS, EBI and GSE up to six months.

The MEAMS showed the highest ceiling effect at T3 (34%), T2 (24%), T1 (17%) which suggests that it may not have been very sensitive in detecting change at the upper end in mildly cognitively impaired patients. Floor effects for the MEAMS were well within the 20% acceptable cut-off at all times.

Although not a limitation as such, the performance of all measurements may have been affected by the assessment context. This varied in consistency and distraction levels between the stroke unit, community residences and care institutions – where a quiet place could rarely be guaranteed. Possibly also assessor reliability was in question with respect to a limited number of adjusted scores.

In terms of practicality, all measurements were easy to use in different settings with minimal improvisation needed in the community e.g. using the patient's bed instead of a plinth to assess sit to stand transfer. Encouragement and prompting were needed for cognitively impaired patients to complete the GSE. In some cases patients found questions ambiguous in which case, minimal assistance was provided to understand the requirements of the question. The TMT provoked anxiety in some patients who realised that they were unable to complete simple tasks against time but overall it was a practical measure. The two identical MEAMS versions were useful and well received by patients.

6.3.3. Data analysis method

The robust multi-level data analysis method is a considerable strength because of its statistical advantages over traditional methods such as single regression and ANOVA used in past critically reviewed studies. MLM features enabled the modelling of time-variant predictive factors in a two tier structural model which is commensurate with the hierarchical nature of stroke data and change in progress over time. The accuracy of the results was enhanced by using all the observations available which is expected to boost study power. This was important because of the higher attrition rates associated with serial designs. It was also possible to estimate the contribution of at least two sources of variance associated with differences between and within patients over time.

Although MLM is very versatile and precise with accuracy of regression coefficient estimates, its mathematical complexity presents considerable challenges for those new to the approach and lack training in the method. It is difficult to apply MLM concepts without having a thorough understanding and mastery of modelling techniques appropriate for the requirements of the research question. Further, it is challenging to explain, write and help other readers (not statistically minded) follow the rationale behind complex decisions made prior to undertaking the actual analysis. In this case, expert statistical advice was sought from the National Centre for MLM based at the University of Bristol. The author of the thesis attended several of their MLM courses on site. The method of analysis and the findings were recently presented in the European congress of research methodology held at Ultrecht University (Netherlands) in July 2014, and favourable received.

6.3.4. Models evaluated in the PhD study

The extent and complexity of models evaluated in this study was guided by statistical theory (sample size, standard error, random variance estimates and goodness of fit statistic (-2loglikelihood test) and evidence based findings from relevant stroke-literature reviews (e.g. Cicerone et al 2011, Teasell et al 2012, Kwakkel and Kollen 2013). The data available was sufficient to appropriately model between six to nine factors (in a given model e.g. M2 model series and Mf). More data may have allowed for the inclusion of additional predictor variables and possibility of explaining more of the residual variance left in the models and putative interactions, which are likely to exist between inter-dependent functional components and factors.

Arguably, the relationship between factors evaluated in this study is not as straightforward as it looks. For example, the statistical assumption of “all other conditions, being equal” in functional recovery models is fundamentally flawed because clinicians know that patient ‘conditions’ and life circumstances may be comparable at most but not equal. This means that it is very difficult to simulate stroke recovery by complex (let alone simple) statistical models. Complicated models are of limited practicality, because they are difficult to interpret by clinicians and apply in everyday clinical settings. (Cheng et al 2010). Therefore a balanced approach between statistical accuracy and clinically relevant models was adopted to increase the interpretation and application of MLM findings in practice. Statistically, the data was sufficiently modelled to answer the research question under investigation.

6.3.4.1. Choice of factors

The factors modelled were specifically chosen because of their evidence-based links to functional progress in the literature. However, it is acknowledged that less well known and under-researched factors (not modelled) could also be important explanatory factors e.g. socio-economic status, psychological factors such as personality traits and past life experiences, attitudes to health and stroke.

Some loss of information may have occurred in binary variables e.g. denial of illness, lesion site, control of bladder and bowel and nutrition status. Results from the sensitivity analysis effectively ruled out this possibility in regard to HI status which increases confidence in the findings from this study.

Section four - Implications and suggestions for rehabilitation

Results obtained in this study imply that when HI status is considered in isolation then the more marked functional difficulties associated with HI+ require additional care and rehabilitation. Consequently, regular assessment of the patient's needs is warranted in order to promote independence within an adequate support system.

In addition, MLM results indicate that stroke severity is a key contributing factor to the poor functional recovery found in patients with RHS and HI. Due to its importance, stroke severity should be included in future research designs so that its effect can be accounted for and estimated. In combination with other measures, such as the BIT, comprehensive stroke severity profiles (as the NIHSS) could serve as early indicators of multiple impairments (Kwakkel et al 2010). They can up to an extent, acutely guide the management of RHS patients (with HI) who tend to miss out on opportunities to improve compared to other patients without HI (Edwards et al 2006, Menon-Nair et al 2006, Lopes et al 2007, Chen et al 2012).

Given its importance it seems prudent to think that stroke severity should be a prime target of acute stroke rehabilitation. Although stroke severity as such cannot be directly treated in the same way as cognitive or motor dysfunction can, recent evidence-based neurological reviews emphasise the need to harness the brain's natural recovery processes in order to maximise functional outcomes (Langhorne et al 2011, Hermann and Chopp 2012, Chollett 2013, Teasell and Hussein 2014). They advocate use of neuro-protective and restorative therapies (e.g. tPA – Tissue Plasminogen Activator) which target viable brain tissue after stroke but also specific therapeutic interventions e.g. early repetitive task training within meaningful functional tasks (Rensink et al 2009, Kwakkel and Kollen 2013).

However, evidence-based practice is notoriously slow to effectively implement into the clinical setting (Meyer et al 2012, Korner-Bitensky 2013, Walker et al 2013). Radical changes are likely to require a major shift in thinking through current rehabilitative practice with special focus on the management of severely stroke impaired patients, irrespective of their HI status. Some of these changes in practice are further elaborated on. By doing so, it is hoped that they provide food for thought as well as spark debate on how clinical practice can become more aligned with emerging evidence on brain tissue healing, neuro-plasticity and functional recovery after stroke (Grefkes and Fink 2011, Hermann and Chopp 2012, Chollett 2013, Rehme and Grefkes 2013).

In a nutshell, rehabilitation professionals need to work more closely, efficiently and effectively with a growing body of evidence in support of a critically important interface between neurological and functional recovery - especially given the importance of time since stroke in this study and in relation to physiological processes (angio and neurogenesis) which are known to impact on neurological and subsequent functional recovery. There is some evidence that pure neurological recovery eventually results in a more refined quality of movement after stroke, than would otherwise be possible with an early focused traditional functional approaches used on their own e.g. compensatory methods used in the treatment of HI (Johansson 2011, Kitago and Krakauer 2013, Maxton et al 2013). The downside is that pure neurological recovery is slower and takes longer to achieve than functional recovery and may have more potential in healthy, milder stroke severity conditions than less healthy, severe survivors (Corbett et al 2014). In any event, if the aim is to optimise functional outcome, then specialised stroke rehabilitation would need not only to start early and intensively after stroke onset but also to continue well beyond discharge into the community phase (Bernhardt et al 2013, Korner-Bitensky 2013).

In light of the above comments, there are basic treatments that clinicians can do very early on within the current service provision and stroke pathway. This is not an exhaustive list but practising simple motor patterns used in everyday activities such as, hand to mouth in feeding, hand to neck/head/hair in grooming, hand to arm/thigh/leg in washing and dressing, flexion/extension of weight bearing joints with or without assistance of a helper. For instance, cognisant patients can use their unaffected upper limb to assist the affected limb to go through simple movement patterns. Recent studies such as Periera et al (2012) and Petzold et al (2014) have found that evidenced based training such as early repetitive task training is currently the exception rather than the rule with severe stroke conditions; who probably stand to benefit from practice of simple movement patterns most (Stinear et al 2007, Teasell et al 2014).

It is well accepted that the frequency and intensity of therapy matters and that patients should receive daily practice, depending on how much they can tolerate. This is particularly relevant to patients with severe stroke but to wait for a miracle to happen (until patients can do more for themselves) is no longer an option given substantial evidence in support of early, intensive and repetitive task practice (Walker et al 2012, Fletcher-Smith et al 2014, Teasell et al 2014). Simple exercise programmes can be done in bed, in sitting and by trained, rehabilitation technicians. It is thought that machine operated robots and virtual reality methods can help deliver realistic amounts of training on a daily basis. Currently their feasibility and use has sparked a lot of research (Johansson 2011, Rossini et al 2012, Soekadar et al 2014). They may be appropriate for selective patients.

Where appropriate, advances in wearable technology have now made it possible to monitor overall physical activity and resistance training by means of small wearable devices such as, the ActivPAL and the ActiGraph also in clinical conditions. Their use in stroke has not been well explored but the devices can be worn on the wrist, waist or embedded in shoes and provide a means of ensuring that patients are receiving the recommended doses and adhereing to treatment regimes. They may also increase patient compliance and accountability for their own recovery especially when rehabilitation professionals are not around and when therapeutic support is limited.

There is also strong evidence that a combination of therapies and interventions particularly for HI is more effective in optimising functional recovery than just one at a time (Johansson 2011, Corbett et al 2014). This makes sense given the fact that the brain uses multi-modal cognitive, sensory-motor feedback and integration to produce meaningful movement patterns which collectively lead to specific behaviour and pre-determined outcome (Sampanis and Riddoch 2013, Kitago and Krakauer 2014). Consequently, a reductionist approach of researching and clinically applying one or two interventions at a time needs to be challenged sooner rather than later (Rossini et al 2012, Hara 2015). Subsequently, it is very important for clinicians to stay abreast of new developments but also consider less traditional methods of treatment alongside traditional ones for which limited evidence exists especially in HI conditions (Singh-Curry and Husain 2010, Maxton et al 2013, Petzold et al 2014). The rest of this section considers implications as a result of specific findings from the study other than those asspciated with overall neurological and functional recovery.

MLM (random) results suggest that modelled average trends are considerably less applicable to individual patients whose abilities deviate from the average population mean. As a result, rehabilitation professionals should continue to assess individuals in their own right and plan treatment accordingly.

The presence of significant residual variance is not atypical in stroke functional recovery MLM models and has been reported by Tilling et al (2001), Stinear (2010), and Goedert et al (2013). Unexplained variance attests to the wide range and individuality of stroke conditions. Robust statistical modelling approaches such as MLM can at least yield an objective measure of the extent of population variation from average tendencies and the likely source of differences. They are therefore much more informative than traditional regression methods used in past studies. This statistical evidence could serve as justification for appropriate action e.g. request for more specialised resources such as skill mix or policy change. For instance, where the source of variance is pathological (i.e. emanating from within the patient) this would necessitate a medical/therapeutic oriented approach to problem solving, whereas if it is at a population level (e.g. a considerable proportion of patients in this study found it difficult to stay active in the community because they could not afford a club/gym membership), then this would require a different solution. The point made here is that the likely source of unexplained variance is of interest as much as fixed effects.

A complex interaction was identified between motor function and stroke severity which significantly impacted on functional change. As a result, functional progress is likely to be accelerated by targeting motor recovery in the acute phase irrespective of HI status (Kollen et al 2005, Kwakkel et al 2006, Kitago and Krakauer 2013, Takeuchi and Izumi 2013). To this end, collaborative future research (e.g. between rehabilitation and psychology) should tease out the relationship between cognitive and motor function in severe stroke conditions. Both factors are intricately intertwined and were critically important contributors to functional outcome in this study.

In regard to ‘assessment of rehabilitation potential’ arising from the discussion in section 6.2.1, it is recommended that health professionals listen and pay attention to detail provided by close family/relative perspectives on the individual’s ‘would be’ capacity to improve. As evidenced by examples from this study, close relatives often know the patient’s history, attitudes, characteristics and life circumstances best. That may put them in a better place to advocate and make certain decisions (e.g. risks involved in a home discharge) on behalf of the patient if need be, than the MDT. This is particularly relevant to patients who are unable to advocate for themselves and their interests whilst still recovering from severe stroke impairments (e.g. denial of illness and executive dysfunction). Similar observations and recommendations were made by previous researchers (e.g. Jehkonen et al 2001, Tham and Kielhoffner 2003).

Findings from this study showed that HI+ patients were extremely slow to complete even the simplest of assessed executive function (TMT) tasks. Such in-efficiency is likely to increase the vulnerability of severely impaired patients (e.g. with poor insight and impulsive behaviour) and pre-dispose them to accidents and personal injury especially in the community. Therefore, whilst promoting independence in ADL tasks they may need closer monitoring from relatives, support and assistance (e.g. when cooking with gas, electricity, microwave meal preparation, handling of electrical or sharp appliances, mobility in/outside, road crossing, driving and self-medicating).

In this study, when present together, borderline cognitive function, executive dysfunction, poor mobility and continence dysfunction resulted in high discharge to nursing home institutions (45% of HI+ compared to 8% HI-). As already stated, the interdependency of relationships (and potential interactions) known to exist between important components of function (e.g. cognitive-motor-executive-self-efficacy) still needs to be elucidated in future research studies. Such detail is likely to be an important link in understanding how complex dynamic relationships interact together in order to bring about change in functional progress, which is key to rehabilitation practice especially in severe stroke conditions (irrespective of HI status) (Cumming et al 2012, Terroni et al 2012).

As evidenced from the main discussion, time (since stroke) has a considerable effect on change in functional ability, especially in the acute phase. Its relative importance cannot be over-emphasised in terms of both neurological and functional recovery, which is likely to translate into positive functional gain. Consequently, it is of crucial importance that fundamental (core) therapeutic practices are not only evidence- based but also closely aligned with functional recovery trends and critical time-windows to optimise functional outcome.

More research is needed into the attenuated recovery patterns of patients with severe stroke (irrespective of HI) (30/50 in this study) and how best to support these patients therapeutically (refer to earlier discussion on neurological and functional recovery). They are in double jeopardy situation, in that they are likely to be severely disadvantaged by trends for shorter length of in-patient stay and then further disadvantaged by inappropriate, untimely and/or insufficient therapeutic provision in the community (supported by Young and Forster 2007, Kalra and Walker 2009, Langhorne et al 2011, Hickey et al 2012).

Findings from this study tend to support the negative (controversial) effect of age on functional outcome after 80 years, irrespective of HI status. However, evidence from neuro-physiological studies (Grefkes and Fink 2011, Chollet 2013) suggests that the ageing brain retains at least some capacity for healing and functional reorganisation after stroke. This knowledge is important in order to ensure parity with therapeutic service provision across all ages and irrespective of HI status (Reed et al 2006, Luker et al 2008 and 2011, Centre for policy on aging 2009 and Hickey et al 2013).

Self-efficacy proved to be an important positive contributor to functional change in this study irrespective of HI status. Consideration and formal assessment of self-efficacy are indicated for RHS with or without HI. In addition, the relationship between self-efficacy and denial status warrants further rehabilitation research because of the challenges that high rates of denial present to treatment and ultimately outcome (e.g. at discharge denial was still evident in HI+ 73%, HI- 45%). The negative impact of prolonged denial states is well acknowledged in the literature, in that an individual with considerable denial may be reluctant to engage in therapy, difficult to motivate and ethically hold accountable for their actions (Barrett et al 2006, Jenkinson et al 2013, Besharati et al 2014). Patients in denial may present as a safety hazard to themselves and others especially if they are behaviourally challenged (Katz et al 2001, Cherney 2006, Barrett et al 2010) due to poor executive function. In terms of psychological defence and coping mechanisms, denial also serves a good purpose which is clearly recognised in counselling-psychology reviews (e.g. Telford et al 2006, Livneh 2009) but less so in rehabilitation literature. Although every situation has to be risk assessed, it is recommended that rehabilitation professionals consider both the negative and positive impact of denial in their decision making i.e. how well the person would cope with stroke if they were not in denial at the time. Health professionals could educate themselves in constructive ways of managing challenging patients and associated ethical dilemmas that can arise when patients have poor cognitive situational awareness (Katz et al 2001, Cherney 2006, Barrett 2010).

The same behavioural problems (described above) have the potential to increase stress and burden in the carer and the family (Buxbaum et al 2004, Ilse et al 2008). Therefore, appropriate rehabilitative provision should be made in the community for patients recovering from associated psychological impairments. This is supported by denial rates which fell appreciably after hospital discharge in this study, suggesting that affected patients may become more receptive to therapy when living in the community rather than the stroke unit setting. Further, therapists could use the clinical information gained from individual case studies to work with researchers and find out more about how denial influences outcomes particularly with time after stroke.

The essence of the recommendations made in this section culminates in the experience of five patients from this study who were relatively mobile at baseline despite considerable impairment associated with severe HI. These patients progressed faster than others in basic ADL whilst in the facilitative therapeutic environment offered by the stroke unit (e.g. where occupational therapists would lay out dressing garments in sight and ready oriented to go on the body, use of bright colour coding of small object such as tooth brush and tooth paste). The five patients were consequently discharged home much earlier than other patients (two self-discharged), even though they still had significant residual cognitive impairment including poor judgement and HI. Unfortunately, they were not sufficiently supported in the home environment and struggled to cope (two of whom lived on their own). Follow-up research records document how they struggled with simple problem solving and memory recall tasks, reading, writing, and figuring out familiar cooking recipes. They often got lost inside their home trying to locate keys, reading glasses and magnifying lenses or worse figuring out how to get inside specific storage places and drawers where they thought the objects were. This was a constant source of palpable frustration during assessment as was the fear of having to go into care despite their high level of independent mobility.

In principle, these case studies support the timely and appropriate provision of evidence-based therapeutic rehabilitation in RHS patients with residual cognitive impairment (inclusive of but not limited to significant HI). This is supported by evidence from other studies e.g. Teasell et al (2005) who reports that even cognitively impaired patients stand to gain functionally if they are appropriately supported and provided with the opportunity to do so.

6.5 Conclusion

In regard to the research question, it can be concluded that, on average, (initial) HI status is unrelated to change in functional ability in the first six months after stroke when other factors evaluated in this study are taken into account. This means that it is unlikely to predict or importantly explain functional progress unless modelled in isolation but this would not be a true representation of an RHS patient. It can also be concluded that modelled average trends are less applicable to individuals whose abilities and/or characteristics differ considerably from those of the average RHS population. Preliminary indications from this study point to characteristic differences across patients as being the main source of variance in the data. These characteristics probably include less well known factors associated with stroke functional recovery but not measured in this study e.g. contextual influence such as life experiences, attitudes, educational, and social resources.

Based on findings and indications from this study, the likely cause of group disparities observed between patients with and without hemi-inattention (Ch4) is stroke severity, rather than the presence of HI *per se*. This is supported by larger stroke-related neurological disturbances in patients with HI and higher impairment levels compared to patients without HI. Consequently, patients with severe stroke (who are also more likely to have HI) appear not to catch up with less severely affected patients who tend not to have HI or mild HI. As a result, they are at high risk of being institutionalised, more vulnerable to injury and harm especially when not adequately supported in the community.

The wider contribution of the project to knowledge in the field of stroke forms part of the concluding chapter (Ch7).

Chapter seven

Conclusion of the thesis

The importance of this project, specific achievements and contribution to the field of stroke, hemi-inattention and rehabilitation research are highlighted in this concluding chapter. The author takes a look back at the whole project, summarising the main points, including specific challenges and personal learning, generation of new knowledge, key implications from the findings, followed by a sense of what might be next i.e. future recommendations.

Chapter one highlighted the reasons for the project and its importance in the field of understanding functional outcomes in stroke patients with right hemisphere dysfunction (RHS) which is frequently accompanied by hemi-inattention (HI) complications. It laid down the extent of the problem and striking features of the HI condition i.e. its unpredictability, and heterogeneity in patients' behavioural presentation which is typically marked by reduced awareness of self and others, reduced attention to salient detail in the environment and apparent resilience to known treatments. All these factors have the potential to compromise patient safety besides poor functional outcomes in RHS patients as reported in the stroke literature. The adverse implications of poor functional outcomes are well known and acknowledged i.e. increased levels of dependency and disability, high risk of long term institutional care with associated socio-economic ramifications, and poorer quality of life.

Given the traditional assumption that HI is a principal contributory factor to poor functional outcomes and the argument that if the condition of HI is resistant to known treatments, the current prognosis for stroke patients with this clinical phenomenon is likely to be poor. Evidence was presented in support of this belief, which arguably could be damaging in itself (because of the consequential reluctance to rehabilitate these patients). In fact as apparent in the critical literature review (Ch2) there is little by way of robust evidence which attributes the cause of functional problems to HI.

Chapter two offered an in-depth, critical narrative review of 13 past studies which compared the functional abilities of RHS patients with and without HI. The findings highlighted significant methodological differences and lack of robust research methods which threatened the validity of the results and hence generalisation of findings across studies. Consequently, it was not possible to establish a clearly important relationship between the presence of HI and poor functional outcomes in RHS patients from the data available. The evaluation of a relationship between both factors now became the subject of this study which addressed the research question:

"What is the relationship between early* HI status (HI±) and functional change in the 1st six months after right hemisphere stroke?"

*(within 7 days since stroke)

Chapter three focused on the methods used to address the research question, collect and statistically analyse data. It also addressed ethical issues arising as a result of the project. A serial, prospective design was chosen to answer the research question. A cohort sample of 93 RHS patients consisting of 58 with and 35 without HI was recruited from two stroke units from May 2008 to September 2009. A full range of stroke and HI severities was represented in the sample. The assessment protocol involved a series of one-off and repeated measures on each subject at baseline, discharge, 6 week post-discharge and 6 months since stroke, in all the patients who were grouped by initial HI status (refer to Diagram 3.1). This enabled comparison of the data by group. A set of clinical and patient-related factors associated with HI and functional ability were measured by means of validated tools (refer to details in Table 3.1-2). The study design was feasible but challenging to implement in both research settings (stroke unit and community). Despite a number of challenges as described in Ch6/critical evaluation section, a considerable amount of data was collected. The design itself was original in that;

- It accommodated patients with severe stroke and cognitive impairment who were excluded at the recruitment stage in past studies on HI (reviewed in Ch.2). Two interim observation points were placed between baseline and discharge which allowed for delayed enrolment of 5 eligible patients and thorough assessment of 31 more severely cognitively affected patients with the assessment protocol.
- Age, time elapsed after stroke and stroke severity were consistently adjusted for and estimated in the subsequent multi-level modelling (MLM) analysis. Time was modelled as a quadratic trend in which the regression coefficient was allowed to vary (supported by non-linear trends identified in the exploratory analysis and statistical evidence from the model fit indices).
- An advanced statistical method of analysis (MLM) was used to model the data because of its distinct advantages (including greater precision and accuracy of estimates) compared to traditional methods of regression and ANOVA (analysis of variance) employed by past studies (reviewed in CH2). The coefficient estimates were later used to calculate statistical

significance and confidence intervals. The two-level structural model used enabled the identification of different sources of variance in the data (differences between or within individuals) which would not have been possible with traditional methods of data analysis. Furthermore, allowing time since stroke to vary improved the model fit, reliability and stability of the coefficient estimates.

For the author, the complexity of MLM presented a steep learning curve which required several advanced statistical courses to sufficiently understand the theory, apply it to the data set appropriately and interpret the results.

The quality of this study benefitted from the amount of data generated by the serial design and longer follow-up compared to past study designs with smaller data sets and shorter duration. Aside from demographics (age, gender, carer status), data on key functional components was collected, some of which (the underlined) had not been evaluated or modelled in past studies (stroke severity, cognitive, executive and motor functions, self-efficacy, continence control, denial (versus reality) of stroke impairments and functional important indicators e.g. nutrition status, duration of in-patient stay, amount of recorded therapy, and discharge destination outcome). Specific challenges associated with data collection were successfully overcome; others such as access to outreach data in the community remained problematic (contributing to missing data, albeit as a small proportion of the total collected).

Chapter four offered a descriptive summary of the data and initial results from simple comparisons of group median scores (based on hemi-inattention variable alone) on factors evaluated in the study. Correlation between the variables was not accounted for at this stage. The findings confirmed earlier reports that as a group, HI+ patients tended to have an attenuated functional recovery in the 1st six months since stroke. The disparity in group scores (HI±) tended to be larger in this study compared to that reported in the reviewed studies (Ch2), probably because the current sample included patients with severe stroke. As a group, patients with HI did not catch up with progress made by patients without HI at six months i.e. when the rate of motor and physical recovery tends to slow down. This implied that patients in the HI+ group were relatively more disabled than HI- group in the long term.

Overall this chapter contributed valuable serial data on a range of physical and pscyho-social factors associated with HI and functional abilities at varies stages of recovery in the 1st six months after stroke. This provided a comprehensive picture of patient progress not previously seen in past studies on HI.

Chapter five focused on the identification of important relationships in the data when HI status (the factor of interest) is considered on its own and when other associated factors (e.g. stroke severity, time elapsed after stroke and age) are also considered. For all the models, the dependent variable was change in functional ability levels.

A stepping up approach was used to model the data, starting with an unconditional model, followed by a basic model (consisting of stroke severity, HI status, age and time since stroke) on which subsequent models were built. This led to the identification of the final model consisting of stroke severity, time since stroke, motor, cognitive and bladder functions and self-efficacy, which best explained the variance in functional ability in which HI status was not statistically significantly related to functional change. The final model was subject to a sensitivity analysis which supported the validity of the results and hence inferences made from them even when ‘missing’ data were left unadjusted in the original data-set. Overall this chapter contributed a robust analysis consisting of modelled, average progress trends and importantly an estimate of how well they could be generalised across patients in the RHS population sampled. The MLM analysis also contributed statistical information such as means, variances and covariances required by sample size estimation software such as PINT (Snijders and Bosker 1993).

Chapter six offered an elaborate discussion and a rich interpretation of the results from chapters four and five. Potential explanatory reasons supported by research evidence were offered in regard to the deviation of findings from those in past studies. In addition, the dynamic interplay between HI status, associated factors and their individual contribution to functional ability over time was discussed. Arguably, although MLM is a statistically robust method which in this study provided greater insight into the relationships in the data (than would have otherwise been possible using past methods e.g. single multivariate regression), additional theoretical and clinical evidence from the literature was needed to interpret the results and answer the research question. With this in mind, it was concluded that:

On average, HI status is unlikely to be an important explanatory or early predictive factor compared to other influential factors affecting functional outcome such as, overall stroke severity, age or time elapsed since stroke.

Average progress patterns (fixed effects) are less applicable to a considerable proportion of patients whose characteristic stroke profile and social circumstances differ significantly from those found in the average (mean) RHS population. That is, generalisation of the findings is limited at the individual level. As a result, RHS patients would benefit from a regular individualised client-centred assessment in which all clinical and circumstantial evidence is considered. Such a comprehensive assessment is more likely to reliably guide treatment and expected functional outcome of individual patients over time. This is well supported by statistical evidence from the MLM analysis which points to individual patient factors (characteristics/context) as the likely source of the variation. Only a small proportion of these factors were evaluated in the current project (e.g. age, carer status, nutrition status, stroke severity, discharge destination). Future research is warranted into other contextual factors such as educational level, personality traits, and socio-economic and cultural factors whose impact on patient progress in functional recovery is less well known (irrespective of HI status).

Another important contribution is additional insight into the relationship dynamics of key functional components (cognitive, motor and bladder functions and self-efficacy) and patient characteristics defined in the study (stroke severity, age, HI status). To this end, an interaction between stroke severity (NIHSS scores) and motor function (PASS scores) was identified in the final model. The interaction effect weakened over time elapsed after stroke and was interpreted as the moderation of motor function by stroke severity levels. This is likely to accentuate functional impairment levels in patients with severe stroke (irrespective of HI status) at the acute phase (< 3 months post-stroke onset) where effect size is largest. Another critical relationship is that of age (over 80 years old) which is likely to considerably slow down the rate of functional recovery (albeit not detrimentally) irrespective of HI status (supportive by neurophysiological evidence presented in the discussion).

A further contribution to knowledge was in regard to clinical data, which clearly showed the poor functional recovery trajectories of severely affected patients with and without HI (n=33). Relevant practical and ethical issues were discussed in relation to the overall management of these patients (e.g. bladder control and cognitive awareness) - although the causes and reasons underlying their apparent lack of progress could not be identified from this study. This area warrants urgent research in order to ameliorate the problem and possibly modify contributing factors which may be controllable even in the present stroke service provision e.g. continence dysfunction, basic cognitive dysfunction and prolonged immobility after stroke, with adverse consequential effects (Cumming et al 2013).

Substantial practical challenges were highlighted in the critical section of the discussion. These were reasonably well overcome but will need to be taken into account in future study designs in order to facilitate a smoother and efficient data collection process in serial studies.

Lastly, there were relevant implications for the training and practice of rehabilitation professionals in the area of stroke/HI and functional outcomes). This may require additional justification for resources to adopt individualised assessment and treatment evidenced-based practices (supported by MLM random coefficient results).

To conclude, the findings from this study challenge traditional beliefs and assumptions in the literature that HI status is an early predictive or important explanatory factor of functional progress and recovery in the 1st six months after stroke. Such a relationship is only seen when HI is considered alone rather than as one aspect of a complex array of influences on functional progress and outcome (Kerkhoff and Schenk 2012).

At the same time, the findings raise awareness to the reality of poor patient outcomes in severe RHS stroke conditions, which tend to be more accompanied by HI than milder conditions (Appelros et al 2007, Orfei et al 2009). In light of the findings, the author recommends focusing research on interventions which minimise the adverse impact of stroke severity in order to magnify the positive effects of motor (balance and posture skills), cognitive functions (e.g. attention, awareness, reality orientation, spatial and working memory) and self-efficacy over time.

Ongoing advances in stroke practice, especially hyper-acute stroke interventions are leading to more people with severe impairments surviving the initial insult. Therefore, it is hoped that findings from this PhD study, which purposively had a maximally inclusive design, will inform the future treatment of this important sub-group of stroke patients that paradoxically are often excluded from research studies due to the inherent complexities that they present.

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Appendix A

MLM methods were applied in three studies which are briefly described.

Kwakkel et al (2006), Ekstam et al (2007) and Nijboer et al (2013) evaluated stroke functional outcomes as assessed by the BI, AMPS (Assessment of Motor and Process Skills) (Fisher 2003) and FIM respectively. Random coefficient analysis (RCA) was used to analyse data in a single level model in Kwakkel et al (2006) and Nijboer et al (2013) and in a two level model in Ekstam et al (2007) which is proposed for the PhD data analysis (see diagram 3.1)

Kwakkel et al (2006) studied the effects of time on observed improvements in motor strength, synergisms, and activities of daily living during the first 16 weeks post stroke in n=101 patients. Time was categorized into 8 biweekly intervals and modelled with age, gender, hemisphere, stroke type, and intervention type. The total number of IV's in the same model varied from 11 to 15, depending on how time was entered as a categorical or continuous variable in the models.

Ekstam et al (2007) examined the relationship between awareness of disability and occupational performance in a group of elderly persons during the first year after stroke. Data was collected at 1, 3, 6 & 12 months from a sample of 34 patients. Three to five factors including time post stroke were modelled together as independent variables (IV's).

Nijboer et al 2013 was critically reviewed in the literature (section 2.5, study 13). The authors used random coefficient analysis to compare the functional outcomes of two patient groups (53HI+ & 131HI-) at 6, 12 and 36 months after stroke. In the 2^{nd} model FIM scores from 53 HI+ patients were regressed on seven IV's.

Appendix B

Copies of assessment tools included in the research protocol

Behavioural inattention test scoring sheet

Section A Subject's details

Number

Name

Age

Date of birth

Years of education

Sex

Estimated IQ

Occupation

Hand preference Left Right Ambidexterous

Marital status

Location status Inpatient Outpatient

Present diagnosis

Date of onset

Date of admission

Medication

Previous significant illnesses Head injury

Operations

Encephalitis

Hypertension

Diabetes

Cardiac disease

Other (specify)

Observations

Language deficits

Sensory deficits

Motor deficits

Visual field deficits

Eye movements

ADL score

Aetiology of lesion Stroke

Head injury

Neoplasm

Other (specify)

Section B Details of test

Date

Name of examiner

Assessment First Second

Version A B

Comments

Results of test Conventional score 146

Behavioural score 81

1

Section C

Conventional sub-test scores

	Scores (maximum indicated in each box)						Total score
1 Line crossing							
Score the total number of lines crossed in each column (do not include the central column)	6	6	6	6	6	6	36
2 Letter cancellation							
Score the total number of E's and R's cancelled in each column	10	10	10	10			0
3 Star cancellation							
Score the total number of small stars cancelled in each column (do not include the two small) stars immediately above the centralising arrow.	8	8	11	11	8	8	54
4 Figure and shape copying							
(a) Figure copying Score one for each figure drawn complete	Star	1	Cube	1	Daisy	1	3
(b) Shape copying Score one if all the shapes are drawn complete							1
5 Line bisection							
Score each line according to the amount of deviation shown on the scoring template	Left line	3	Centre line	3	Right line	3	9
6 Representational drawing							
Score one for each drawing completed	Clock face	1	Man/ woman	1	Butter-fly	1	3

Total conventional test score 146

Appendix B

Denial interview questions

Buxbaum et al (2004) used a method adapted from Cutting's anosognosia questionnaire (1987) in order to identify this factor in patients with HI. The method consisted of five questions aimed at eliciting denial in the patient's response which were also used in the PhD study.

1) Why are you here?
2) How did the stroke affect you?
3) Is there anything wrong with your arm or leg?
4) Is it weak, paralysed or numb?
5) How does it feel?

If denial is elicited by any of the questions, (1) is recorded and if not elicited (0) is recorded.

No. [ ]

Appendix B: EXTENDED BARTHEL INDEX

A patient can be scored as independent only if a task can be completed without assistance and within a reasonable time span. If this reasonable time span is exceeded the score must reflect the degree of assistance required by the patient to complete the task within the reasonable time span. A guideline as to reasonable time spans is given in parentheses beside those items for which it is deemed necessary.

	date			
	Score			
I. Eating & drinking (~ 1hr)				
• Not possible or needs PEG/nasogastric tube that cannot be operated independently	**0**			
• Food has to be prepared (e.g. meat & vegetables have to be cut up).	**2**			
• Eating possible without human assistance but with the use of aids (e.g. special wooden platter, thick handles on cutlery) OR needs PEG/nasogastric tube that can be used without assistance.	**3**			
• No assistance or aids required	**4**			
II. Grooming (~ 20 min.) (face washing, combing, shaving, brushing teeth)				
• Not possible	**0**			
• Help needed from an assistant with some but not all procedures	**1**			
• Needs minor assistance (e.g. unscrewing of toothpaste, help with shaving) OR no direct assistance required but patient needs to be reminded/told/supervised in respect to some procedures	**2**			
• Personal care possible without as assistant but with the use of aids (e.g. extension for comb, face cloth, brush)	**3**			
• No assistance required (in all the above areas; *even those patients who are not able to braid or style hair properly are also classified as being independent)*	**4**			
III. Dressing/undressing (~30 min) (includes tying shoe laces, buttoning/unbuttoning, fastening fasteners)				
• Not possible	**0**			
• Needs physical assistance in putting on or removing most but not all items of clothing	**1**			
• Needs physical assistance only with few procedures (e.g. needs help with tying shoe laces, buttoning, putting on elastic stockings or orthotic/prosthetic devices) OR patient does not require physical assistance but in the case of a few procedures needs to be reminded/told/supervised	**3**			
• No assistance required (the use of stocking pullers/aids is allowed)	**4**			

IV. Bathing (~30 mins.)(includes taking a shower or washing the whole body)				
• Not possible	**0**			
• Needs physical assistance of one other person in some but not all aspects (e.g. cleaning upper body parts without assistance, but needs assistance for cleaning lower body parts; needs help with transfer or with drying)	**1**			
• Possible with slight assistance (e.g. unscrewing bathing utensils OR patient does not require physical assistance but in the case of a few procedures needs to be reminded/told/supervised	**2**			
• Needs aids (e.g. bath or shower seat), which patient uses without assistance	**3**			
• No assistance required	**4**			
V. Moving from wheelchair to bed and return (~ 10 mins.)				
• Not possible	**0**			
• Needs physical assistance of one other person in some but not all aspects	**1**			
• No physical assistance required but needs to be reminded/told/supervised with respect to some aspects of the transfer process (e.g. putting on the brakes)	**2**			
• No assistance required	**4**			
VI. Locomotion (~ 2 mins. for 50 meters) (stair climbing not included)				
• Not possible (either walking or with the aid of a wheelchair)	**0**			
• Needs wheelchair or rollater that patient can operate without assistance for the most part (e.g. covers long distances, does not knock against objects in the path, can negotiate bends, turn etc; and requires only minimal assistance in rare cases) OR is able to walk short distances (<50m) but not without physical assistance or hand rails	**1**			
• Is able to walk short distances (<50m) without physical assistance or handrails, but for longer distances (>50 m) needs a wheelchair, rollater or supervision	**2**			
• Walks long distances (>50m) without handrails or rollater but needs a stick/cane or crutch or other orthotic devices	**3**			
• Can walk long distances (>50m) without assistance or aids	**4**			
VII. Ascending and descending stairs (~ 1 min. for one floor)				
• Not possible	**0**			
• Needs major physical assistance of one person (e.g. needs help with lifting a leg)	**1**			

• Needs minor assistance or supervision (e.g. assistance of a person in holding patient's balance)	**2**			
• Possible without assistance (*the patient is allowed to hold on to hand rails, to use stick/cane, crutch etc.)*	**4**			
VIII. Toilet (~ 20 mins.) (transfer, handling clothes, wiping, flushing)				
• Not possible	**0**			
• Needs physical assistance of one other person in some but not all aspects (e.g. transfer without assistance; however needs help with undressing/dressing)	**1**			
• No physical assistance required; however, in some procedures needs to be reminded/told/supervised.	**2**			
• No assistance required OR unnecessary as the patient wears continence pads or is supplied with a suprapubic catheter, so that the patient does not have to use the toilet at all	**4**			
IX. Controlling bowels				
• Not possible	**0**			
• Occasionally at least once a week, but not daily) incontinent and needs assistance with changing pads or cleaning OR occasional assistance (at least once a week but not daily) by one person is required to ensure regular bowel evacuation (e.g. enema)	**2**			
• Problems in bowel control, but needs no assistance in changing continence pads, cleaning self or applying bowel regulating measures	**3**			
• Normal bowel control (also includes incontinence occurring less frequently than once a week)	**4**			
X. Controlling bladder				
• Complete or very frequent incontinence (several times a day and unable to change continence pads unassisted) OR needs indwelling urethral catheter, supra-pubic catheter or self-catheterisation and needs assistance with managing those devices	**0**			
• Partially incontinent (at most once a day) and needs assistance in changing continence pads and cleaning self	**1**			
• Fully or partially incontinent but needs no assistance in changing continence pads and cleaning self OR needs indwelling urethral catheter, supra-pubic catheter or self-catheterisation, but needs no assistance with managing those devices	**3**			
• Normal bladder control	**4**			
XI. Comprehension				
• Not possible, even simple instructions or questions are not understood, also unable to follow written instructions or to comply with instructions given by the use of facial expressions or gesture	**0**			

• Understands simple instructions (e.g. contents relating to situations of daily living:" take this pill") either in verbal written or gesture form	**1**			
• Understands complex contents (e.g. "take this pill before your meal"); however, comprehensions unreliable OR depends on written form to achieve full comprehension	**3**			
• Normal comprehension (includes patients relying on hearing aids but does not include patients who only understand written, e.g. content instructions)	**4**			
XII. Expression				
• Totally or almost totally unable to make self understood	**0**			
• Is able to express only simple content. Understands complex content relating to situations of everyday life such as hunger, thirst, etc; with or without aids (e.g. written notes, communicator)	**1**			
• Able to make self understood in relation to almost all subjects, but only with the use of aids (e.g. written notes, communicator)	**3**			
• Able to make self understood in relation to almost all subjects without aids *(grammatical mistakes, mild word finding difficulties or slightly slurred speech are allowed)*	**4**			
XIII. Social interaction				
• Behaves most of the time is an uncooperative manner (e.g. refuses to cooperate with helpers) or in an aggressive, obtrusive or withdrawn manner	**0**			
• Behaves occasionally in an uncooperative, aggressive, obtrusive or withdrawn manner	**2**			
• Normal social interaction	**4**			
XIV. Problem solving				
Examples of disturbed everyday problem solving behaviour are: impulsive actions (e.g. leaving wheelchair without putting on the brakes), stubborn behaviour(e.g. difficulties in adapting to changes in the order of the day): difficulties in keeping to schedule; difficulties in taking medication (that are not the result of motor impairment): has lack of insight into his/her impairments or lack of concern about the consequences resulting from his or her impairments				
• Arising from the above disorders, needs major assistance to deal with everyday problem solving situations	**0**			
• Arising from the above disorders, needs minor assistance to deal with everyday problem solving situations	**2**			
• Arising from the above disorders, needs no assistance to deal with everyday problem solving situations	**4**			

XV. Memory, learning orientation				
• Is mentally confused or disoriented with a strong tendency to run away and to leave the clinic or patient's dwelling	**0**			
• Is mentally confused or disoriented and has no tendency to leave the clinic/dwelling, but patient has difficulty finding way around the clinic OR is unable to retain new information (e.g. patient does not remember cares even after several meetings, forgets content of conversation, appointments, places where belongings are kept) and is unable to use external memory aids (e.g. notebook, calendar)	**1**			
• Needs frequent reminding	**2**			
• Requires reminding only occasionally OR uses external memory aids effectively	**3**			
• No impairment affecting everyday situations OR despite memory deficits, patient does not needs extra care (e.g. completely immobile patient with serious disorientation problems)	**4**			
XVI. Memory, learning orientation				
• Has difficulties finding way in familiar (e.g. own room or ward) and unfamiliar environments (e.g. parts of the clinic outside ward) because of visual disturbances or neglect OR overlooks or collides often with obstacles or persons	**0**			
• Finds way in familiar environment and never or rarely collides with obstacles or persons; has difficulties finding way in unfamiliar environment (e.g. parts of the clinic outside ward)	**1**			
• Finds way in familiar environment with or without aids (e.g. dog, stick) and has major difficulties with reading OR depends on special aids for reading (e.g. large print ruler, magnifying glass, special reading lamp)	**3**			
• Normal vision *(people who achieve good visual performance with glasses included)* OR despite visual deficits or neglect, patient does not need extra care (e.g. completely immobile patients with serious visual problems**)**	**4**			
TOTAL score				

Appendix B

Hospital Anxiety and Depression Scale (HADS)

Name: date:

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings, then he/she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and underline the reply which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies; your immediate reaction to each item will probably be more accurate than a long, though out response.

A	D			A	D
3☐ 2☐ 1☐ 0☐		**I feel tense or wound up:** Most of the time A lot of the time From time to time Occasionally Not at all	**I feel as If I am slowed down** Nearly all the time Very Often Sometimes Not at all		3☐ 2☐ 1☐ 0☐
	3☐ 2☐ 1☐ 0☐	**I still enjoy the things I used to:** Definitely as much Not quite so much Only a little Hardly at all	**I get a sort of frightened feeling like 'butterflies' in the stomach.** Not at all Occasionally Quite often Very Often	3☐ 2☐ 1☐ 0☐	
3☐ 2☐ 1☐ 0☐		**I get a sort of frightened feeling as if something awful is about to happen:** Very definitely and quite badly Yes but not too badly A Little, but it doesn't worry me Not at all	**I have lost interest in my appearance:** Definitely I don't take as much care as I should I may not take quite so much care I take as much care as ever		3☐ 2☐ 1☐ 0☐
	3☐ 2☐ 1☐ 0☐	**I can laugh and see the funny side of things:** As much as I always could Not quite so much now Definitely not so much now Not at all	**I feel restless as if I have to be on the move:** Very much indeed Quite a lot Not very Much Not at all	3☐ 2☐ 1☐ 0☐	
3☐ 2☐ 1☐ 0☐		**Worrying thoughts go through my mind:** A great deal of the time A lot of the time Not too often Very little	**I look forward with enjoyment to things:** As much as I ever did Rather less than I used to Definitely less than I used to Hardly at all		3☐ 2☐ 1☐ 0☐
	3☐ 2☐ 1☐ 0☐	**I feel cheerful:** Never Not often Sometimes Most of the time	**I get sudden feelings of panic:** Very Often indeed Quite often Not very often Not at all	3☐ 2☐ 1☐ 0☐	
3☐ 2☐ 1☐ 0☐		**I can sit at ease and relax:** Definitely Usually Not often Not at all	**I can enjoy a good book/radio or television programme:** Often Sometimes Not often Very Seldom		3☐ 2☐ 1☐ 0☐
☐	☐	***TOTALS***	***TOTALS***	☐	☐

No.

Date:

Appendix B

The General Self-Efficacy Scale (GSE)

English version by Ralf Schwarzer & Matthias Jerusalem 1993

PLEASE put an X in the box with the most appropriate answer

		Not at all true	**Hardly true**	**Moderately true**	**Exactly true**
1.	I can always manage to solve difficult problems if I try hard enough.				
2.	If someone opposes me, I can find the means and ways to get what I want.				
3.	It is easy for me to stick to my aims and accomplish my goals in therapy and rehabilitation after stroke.				
4.	I am confident that I could deal efficiently with unexpected events, such as the effects of my stroke.				
5.	Thanks to my resourcefulness, I know how to handle unforeseen situations.				
6.	I can solve most problems if I invest the necessary effort.				
7.	I can remain calm when facing difficulties because I can rely on my coping abilities.				
8.	When I am confronted with a problem, I can usually find several solutions.				
9.	If I am in trouble, I can usually think of a solution.				
10.	I can usually handle whatever comes my way including ill health.				

N.B. Questions 3, 4 & 10 had "health condition" replaced by "stroke".

Appendix B

MEAMS Scoring sheet

Subject and test details

Name

Date of birth

Reason for assessment

Version A B

Date of assessment

1 Orientation

Score

Name

Age

Date of birth

Today's date

Address

Total

Pass or fail (pass score = 5)

2 Name learning

2a Presentation (test and score later)

3 Naming

A Watch B Pen

A Strap B Nib

A Buckle B Clip

Total

Pass or fail (pass score = 3)

4 Comprehension

Score

A Mirror B Ash

A Shell B Vase

A Microphone B Bee

Total

Pass or fail (pass score = 3)

5 Remembering pictures

5a Presentation (test and score later)

6 Arithmetic

A 10 B 8

A 12 B 13

A 5 B 5

Total

Pass or fail (pass score = 3)

7 Spatial construction

Square

Four-pointed star

Total

Pass or fail (pass score = 2)

5 Remembering pictures

5b Identification

A	N	N	Y	Y	N	Y	N	Y	N	N	Y	N	Y	N	N	Y	Y	Y	N	Y
B	N	Y	N	N	Y	Y	Y	N	N	Y	N	Y	N	N	Y	N	Y	N	Y	Y

Score 1 for each correct 'yes' response

Subtract the number of false positives

Total

Pass or fail (pass score = 5)

Appendix B

8 Fragmented letter perception

A t B n	
A m B f	
A h B b	
A d B e	
Total	
Pass or fail (pass score = 3)	

9 Unusual views

A Screwdriver B Paintbrush		
A Toilet paper B Case		
A Knitting B Stool		
Total		
Pass or fail (pass score = 2)		

10 Usual views

Only to be administered if the patient scored less than 3 in sub-test 9 'Unusual views'

A Screwdriver B Paintbrush		
A Toilet paper B Case		
A Knitting B Stool		
Total		
Pass or fail (pass score = 3)		

11 Verbal fluency

A Animals
B Things to eat

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
Total	
Pass or fail (pass score = 10)	

12 Motor perseveration

A 2 B 1	
A 1 B 2	
A 1 B 2	
A 2 B 1	
A 1 B 2	
Total	
Pass or fail (pass score = 3)	

2 Name learning

2b Recall

Score 2 for each name (ie first name and second name) recalled without prompt
Score 1 for each name recalled with prompt
Otherwise score 0 for each name

A Mary Carter
B Peter Watson

First name		
Second name		
Total (possible of 4)		
Pass or fail (pass score = 2)		

34/36 High Street
Titchfield
Fareham
HANTS PO14 4AF
England

Appendix B

THE POSTURAL ASSESSMENT SCALE FOR STROKE PATIENTS *(PASS)*

☐ KCH
☐ QEQM
☐ WHH

Hospital Admission ☐ | Community ☐

Stroke unit ☐ Ward ☐ | Home ☐ Res home ☐

PATIENT DETAILS:

Name: ☐ DOB ☐ Gender m/f
Address: ☐
☐ Postcode: ☐

Date of scan ☐
CT Scan report
Affected Side: LEFT / RIGHT
☐ ☐

Please X in box

PASS ITEMS AND CRITERIA FOR SCORING	Date:	Admission	Discharge	Post Discharge
Maintaining a posture:				
1. **Sitting without support** (sitting on the edge of a 50 cm high examination table (a Bobath plane for instance) with the feet touching the floor. 0 = cannot sit 1 = Can sit with slight support 2 = can sit for more than 10 seconds without support 3 = Can sit for 5 minutes without support		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3
2. **Standing with support**, (feet position free, no other constraints) 0 = Cannot stand, even with support 1 = can stand with strong support of 2 People. 2 = can stand with moderate support of 1 Person. 3 = can stand with support of only 1 hand.		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3
3. **Standing without support** (feet position free, no other constraints) 0 = Cannot stand without support 1 = can stand without for 10 seconds or leans heavily on one leg. 2 = can stand without for 1 minute or stands slightly asymmetrically. 3 = can stand without support for more than 1 minute and at the same time perform arm movements above shoulder level.		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3
4. **Standing on unaffected leg** (no other constraints). 0 = Cannot stand on nonparetic leg 1 = Can stand on nonparetic leg for a few seconds. 2 = Can stand on nonparetic leg for more than 5 seconds. 3 = Can stand on nonparetic leg for more than 10 seconds.		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3
5. **Standing on Affected Leg** (no other constraints) 0 = Cannot stand on nonparetic leg 1 = Can stand on nonparetic leg for a few seconds. 2 = Can stand on nonparetic leg for more than 5 seconds. 3 = Can stand on nonparetic leg for more than 10 seconds.		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3

Appendix B

CHANGING POSTURE Scoring of items 6 – 12 is as follows: (items 6 – 11 are to be performed on a 50 cm high examination table, like a Bo bath plane; items 10 – 12 are to be performed without any support; no other constraints). 0 = Cannot perform the activity 1 = can perform the activity with much help 2 = Can perform the activity with little help 3 = Can perform the activity without help				
6. Supine to affected side		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3
7. Supine to non-affected side		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3
8. Supine to sitting up on the edge of the table		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3
9. Sitting on the edge of the table to supine		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3
10. Sitting to standing up.		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3
11. Standing up to sitting up		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3
12. Standing, picking up a pencil from the floor		☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3	☐0 ☐1 ☐2 ☐3
TOTALS				

ANY OTHER COMMENTS:

Signature OT...

Appendix B: Trail Making Test (TMT) Parts A & B

Instructions:

Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed.

Step 1: Give the patient a copy of the Trail Making Test Part A worksheet and a pen or pencil.
Step 2: Demonstrate the test to the patient using the sample sheet (Trail Making Part A – SAMPLE).
Step 3: Time the patient as he or she follows the “trail” made by the numbers on the test.
Step 4: Record the time.
Step 5: Repeat the procedure for Trail Making Test Part B.

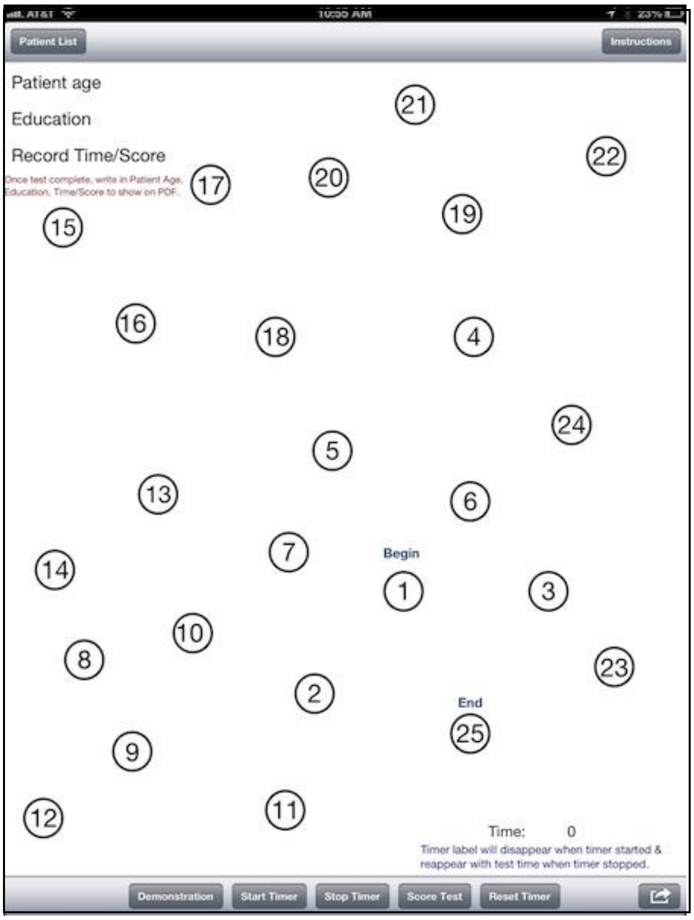
Scoring:

Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment.

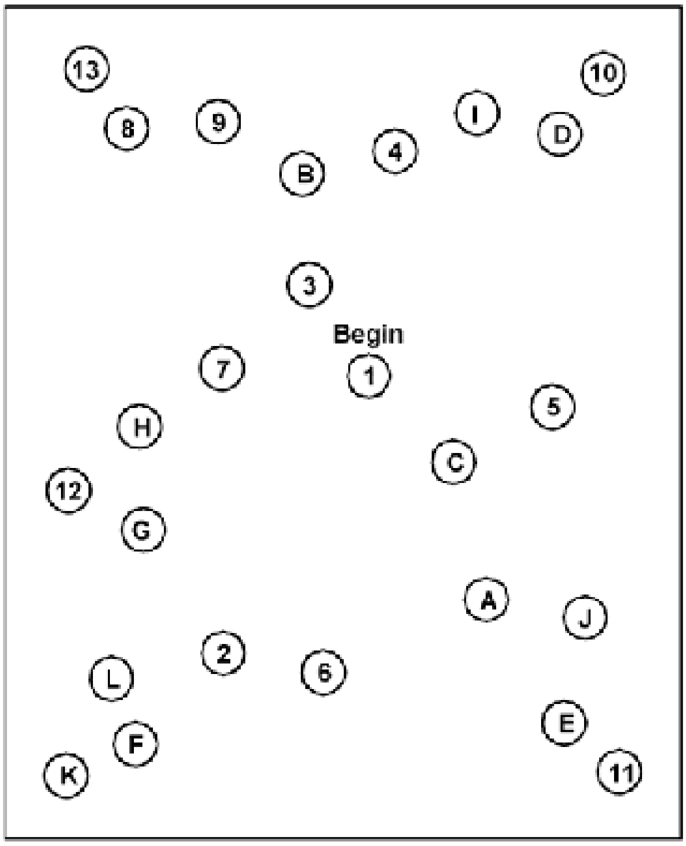
Average Deficient Rule of Thumb
Trail A 29 seconds > 78 seconds Most in 90 seconds
Trail B 75 seconds > 273 seconds Most in 3 minutes

Sources:

Corrigan JD, Hinkeldey MS. Relationships between parts A and B of the Trail Making Test. J Clin Psychol. 1987;43(4):402–409.
Gaudino EA, Geisler MW, Squires NK. Construct validity in the Trail Making Test: what makes Part B harder? J Clin Exp Neuropsychol. 1995;17(4):529-535.
Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4th ed. New York: Oxford University Press; 2004.
Reitan RM. Validity of the Trail Making test as an indicator of organic brain damage. Percept Mot Skills. 1958;8:271-276.



Trail Making Test



Appendix C (supplementary data)

Research protocol assessment tools, abbreviations, level of measurement, interpretation of scores and supplementary data on psychometric properties

Assessment tool	Abbreviation	Level of measurement & range	Interpretation of scores	Reliability***	Validity***
Behavioural inattention test (HI levels)	BIT	Interval* 0 to 136	< 129 denotes clinically significant HI; the lower the score the higher the intensity	test-retest reliability (r = 0.89, Inter-rater-Pearson Correlation Coefficient (r = 0.99) (Halligan et al 1991)	Convergent, r=0.64 when compared to BI in stroke (Cassidy et al 1999) Pearson r=0.77 compared to ADL checklist Hartman-Maier and Katz (1995)
Extended Barthel Index (functional ability DV)	EBI	Interval* 0 to 64	64 = max. independence	Internal consistency; cognitive less reliable than the physical part. It is a 3-dimensional scale as calculated by factor analysis (factor 1 with eigen value 8.2, factor 2 with eigen value 2.7 & factor 3 with eigen value 0.9) (Jansa et al 2004).	Criterion validity to the BI & Fugl-Meyer Motor Impairment Scale was supported (P=0.1-0.001). External validity to the Self-Assessment scale was also supported (P<0.001) (Jansa et al 2004)
Postural assessment scale for stroke (balance & posture for ADL skills)	PASS	Interval* 0 to 36	36 = max. control of posture	Test/retest ICC=0.84, Internal consistency Cronbach's α = 0.96 (Chien et al 2007); Inter-rater, Spearman's rho r=0.77 to 0.99 & intra-rater (r=0.88 to 0.98) (Persson et al 2011)	Predictive R^2 = 0.39, p<0.001 (Yu et al 2012); Convergent & discriminant validity, Pearson correlation coefficient with FIM total score (r=0.73), transfer tasks (r=0.82) and locomotor tasks (r=0.73) in n=58, 30 days PSO (Benaim et al 1999).

Border in view of binding					
Middlesex Elderly Assessment of Mental State (Basic cognitive function)	MEAMS	Interval** 0 to 12	0 to 7 indicates clinically significant cognitive impairment, 8 to 9 borderline and 10 to 12 - no clinically significant impairment	Internal Consistency Chronbach's α = 0.82 (Kutlay et al 2007)	Construct Validity With FIM (Functional Independence Measure) r = 0.571 (Kutlay et al 2007)
Trail Making Test (Higher cognitive function)	TMT	Continuous 0 to 500 seconds	The longer the time, the greater the level of impairment	Excellent test-retest reliability for both Part A and Part B were found (0.94 and 0.86 respectively) in the sub-group of patients with stroke (Goldstein & Watson 1989)	Convergent validity, Pearson r=0.44 with Paced Auditory Serial Addition Task & r=0.38 with category test (O'Donnell et al 1994)
General self-efficacy scale adapted for stroke	GSE	Interval* 0 to 40	The higher the score the higher the self-efficacy level	Internal consistency 0.75 to 0.91 (Scholz et al 2002), test/retest correlation coefficient of 0.83, internal reliability, Cronbach α = 0.89 (Sanders & Wolley 2005)	Item response theory shown uni-dimentional construct (Scherbaum et al 2006) Good construct validity – factor analysis, all items loading > 0.6 (Tarihi 2006)
Hospital anxiety and depression scale	HADS	Interval** 0 to 42	0 to 7 = normal, 8 to 10 = borderline, ≥ 11 abnormal level on each scale	internal consistency Cronbach's α = 0.85 (Aben, Verhey, Lousberg, Lodder, and Honig 2002)	Criterion – correlations with Montgomery Asberg Depression Rating Scale r = 0.62 to 0.81, with Hamilton Anxiety Rating Scale (r = 0.34 to 0.44) Bjelland et al. (2002).
The National Institute of Health Stroke Scale	NIHSS	Interval* 0 to 42	The higher the score, the more severe the stroke; mild ≤ 5, moderate 6 to 14, severe 15 to 24, very severe 25 to 42	Interrater reliability acute stroke; ICC = 0.95 (Goldstein & Samsa, 1997) Interrater r^2 = 0.98, p < 0.001), test-retest r^2 = 0.94, p < 0.001 (Williams et al 2000)	Concurrent Validity Correlations with diffusion weighted MRI lesion volumes (r = 0.48 right, r = 0.58 left); and perfusion-weight hypoperfusion volumes (r = 0.62 right, r = 0.60 left) (Fink et al, 2002)

Abbreviation: R^2 = proportion of variance explained by the regression model, ICC = intra-class correlation coefficient

* Ordinal treated as interval scale, ** one dimensional (Rasch analysed scales)

*** Tests for reliability & validity - Scale for coefficient α (Cronbach's α), test/retest & inter-rater reliability is 0.8+ is good, 0.7 to 0.79 is acceptable, 0.6 to

Appendix D

Models suitable for analysis of serial data – additional information

Statistical literature considers the following models suitable for serial, longitudinal and repeated measure designs. These are now described together with equations and accompanying notation taken from CMM – Introduction to MLM in MLwiN 2013. Further details can be obtained from specific MLM literature sources including Goldstein 1999, Twisk 2006, Rasbash et al 2008, Singer & Willet 2003, Snijders 2005

- *Basic linear growth model & Random intercept model - figure 3.3 (a)*

This model allows for individual variation in the level of Y and is characterised by the equation;

$$Y_{ti} = \beta_{0i} + \beta_1 t + e_{ti}$$

$$\beta_{0i} = \beta_0 + u_{0i}$$

$\mathbf{Y_{ti}}$ is the response at occasion t (t = 1 to 4) for individual i (i = 1 to 93).

$\boldsymbol{\beta_{0i}}$ = random intercept; $\boldsymbol{\beta_0}$ = intercept; $\mathbf{u_{0}}_{i}$ is an individual specific residual (or random effect) representing unmeasured individual characteristics that are fixed over time; $\mathbf{e_{ti}}$ are measurement occasion – level residuals.

$\boldsymbol{\beta_1}$ is the growth rate (coefficient of t) which is fixed across individuals.

Assumptions

u_{0i} and e_{ti} (random parts) are assumed to be normally distributed and uncorrelated. Covariance ($e_{ti,}$ $e_{si\ (slope)}$) = 0 i.e. correlation between individual's Y- values over time is explained by $u_{0i.}$

This model can be viewed as a ***'random intercept'*** where $\mathbf{u_{0i}}$ allows the level of y (intercept) to vary across individuals and is viewed as a conceptual necessity in MLM (Twisk 2006, Field 2009, p724). The same model can be used to estimate variance between levels by means of the *Intra-class correlation coefficient (ICC),* details in chapter four (Kreft & De Leeuw 1998, Singer & Willet 2003,Twisk 2006)

- *Random slope model*

The random slope model assumes that individual growth rate changes as a function of time (Centre for multilevel modelling – University of Bristol). This assumption is reasonable in stroke based on known individual variation and recovery trends reported in the literature (Kalra et al 1997, Appelros et al 2002, Buxbaum et al 2004, Ringman et al 2004, Gillen et al 2005, Jehkonen et al 2006, Kashihara et al 2011). Consequently it was important to allow for a random slope (and intercept over time as described earlier).

Equation for a random slope model

$$Y_{ti} = \beta_{0i} + \beta_{1i}t + e_{ti}$$

$\beta_{0i} = \beta_0 + u_{0i}$ (individual variation in level of Y)

$\beta_{1i} = \beta_1 + u_{1i}$ (Individual variation in growth rate = random coefficient)

$$\begin{pmatrix} u_{0i} \\ u_{1i} \end{pmatrix} \sim N\left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma^2_{u0} & \\ \sigma_{u01} & \sigma^2_{u1} \end{pmatrix}\right] \quad e_{ti} \sim N(0,\sigma^2_e)$$

$\mathbf{Y_{ti}}$ = $\beta_{0i} + \beta_1 t$ is the average trajectory (but may not represent trajectory of any individual)

$\mathbf{u_{0i}}$ = individual specific residual (departure from the average intercept)

$\mathbf{u_{1i}}$ = individual specific residual (departure from the average slope)

$\boldsymbol{\sigma^2_{u0}}$ = between-individual variance in the mean of y at t=0 (baseline)

$\boldsymbol{\sigma^2_{u1}}$= between-individual variance in the growth rate

$\boldsymbol{\sigma_{u01}}$= covariance between the intercepts and slopes of the individual linear trajectories

N = assumed normal distribution of residuals

References

National Centre for Research Methods (NCRM) (January 2013). Introduction to Multilevel modelling in MLwiN, University of Bristol, http://www.ncrm.ac.uk/research/ accessed on 24/01/2015

Appendix E

South East Research Ethics Committee
South East Coast Strategic Health Authority
Preston Hall
Aylesford
Kent
ME20 7NJ

Telephone: 01622 713097
Facsimile: 01622 885966

11 February 2008

Ms. SM Stein
Lecturer in Occupational therapy
Brunel University
School of Health Sciences and Social Care
Brunel University
Uxbridge, Middlesex
UB8 3PH

Dear Ms. Stein

Full title of study:	**The functional status of patients with stroke and neglect pre and post- hospital discharge and impact on carer stress.**
REC reference number:	**08/H1102/6**

Thank you for your letter of 25 January 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair and named members of the Committee who were present at the meeting.

Confirmation of ethical opinion

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

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA) There is no requirement for Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application		10 December 2007
Investigator CV	Stella Stein	
Protocol	1	16 April 2007
Covering Letter		11 December 2007
Summary/Synopsis		
Letter from Sponsor		04 December 2007
Statistician Comments		10 December 2007
Questionnaire: 6-months post discharge	Validated	
Questionnaire: Following patient discharge	Validated	
Questionnaire: Discharge Stage	Validated	
Questionnaire: Admission Stage	Validated	
Questionnaire: Multi-Disciplinary Team (MDT) Survey	Validated	
Participant Information Sheet	3.0	25 January 2008
Participant Information Sheet: Caring	3.0	25 January 2008
Participant Information Sheet: Multi-Disciplinary Team Survey	1.0	26 November 2007
Participant Consent Form: Caring	1.0	26 November 2007
Participant Consent Form	3.0	25 January 2008
Response to Request for Further Information		25 January 2008
Behavioural inattention test		
MEAMS Scoring Sheet		
The General Self-Efficacy Scale (GSE)		
Supervisor CV	David Maskill	
Supervisor CV	Daniel Reidpath	
Geriatric Depression Score		
Hospital Anxiety and Depression Scale (HADS)		
Caregiver Strain Index (CSI)		
The Barthel Index		
The Postural Assessment Scale for Stroke Patients (PASS)		26 January 2005
Trail Making Part A & B		
Denial status assessment		
Letter of Approval from School Research Ethics Committee		04 December 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk .

08/H1102/6	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr L. Alan Ruben
Chair

Email: nicki.watts@nhs.net

Enclosures: *Standard approval conditions*

Copy to: Mrs. Elizabeth Cassidy

Ethics approval letter will be included

Appendix F

N.B The font has been reduced from 18 to 12

East Kent Hospitals
NHS Trust

PATIENT INFORMATION SHEET

Title of the study:

"The functional status of patients with stroke and hemi-inattention pre and post-hospital discharge and impact on carer stress".

You are invited to take part in a research study investigating strokes on the right side of the brain. Besides physical weakness, this type of stroke may affect attention and awareness of objects in the affected parts of space.

Details of the study

In this study, we are interested in the inattention (known as hemi-inattention) present on the affected side and in particular how it impacts on your independence and functional abilities. In other words, what and how much you can do for yourself whilst you are in the hospital and after discharge from hospital. It is important to identify these difficulties when they exist and assess their severity. Such information contributes towards the management of patients with this type of stroke and the organisation of rehabilitation services delivered to patients recovering from the condition.

Participant sample

Sixty patients will be recruited for this study, 30 with inattention difficulties and 30 without these difficulties. This allows for comparison of abilities between patients with and without hemi-inattention. All participants with and without hemi-inattention will contribute valuable data to the research study.

What will happen to the participants?

All participants will be required to undertake six short assessment measures at admission to hospital, then every four weeks leading up to discharge from hospital. The same measures will then be repeated at six weeks and six months after discharge, which is also the end of the study. Most of these assessments take about 8-15 minutes each to complete and are carried out routinely for people with stroke.

As per usual practice, a copy of the results will be in the medical records and thus available to other members of the team who have access to these records.

The assessments consist of pen and paper tasks, some tabletop activities and movement related skills e.g. changes in body posture and walking. Similar skills are required in order to carry out essential activities of daily living on a regular basis. Once discharged, the researcher will take these measurements at your home during two visits; one at six weeks and six months. The visits will be arranged at a convenient time for you, generally mornings or afternoons.

How will the data contribute to the study?

The researcher will be able to evaluate the progress made at various stages and whether this has been maintained up to 6 months following discharge from hospital. The results and an overall summary of the findings from this study will be made available to you on request.

Participation in the study

Participation is entirely voluntary and you may withdraw at any time without giving a reason. This would not affect the standard of care that you receive. Should you decide to participate; written consent will be requested within the next two weeks. The researcher will then be able to use the results for the purpose of this study. All information will be stored confidentially and according to the data protection act.

Independent advice can be sought at *INVOLVE* website about participation in research studies (www.invo.org.uk).

Should any concerns arise during the conduct of the study, you can discuss these with the principal researcher (details given below) and if you remain unhappy you may wish to complain formally through the NHS complaints procedure, details of which can be obtained from the hospital.

This study is being undertaken as part of a PhD. It has been reviewed and approved by the School of Health Sciences and Social Care Research Ethics Committee at Brunel University.

M. S. Stein
Principal researcher

Kent and Canterbury Hospital, 01227 766877 ext. 73076
Brunel University 01895 268692

Supervisor details:

Dr. Sally Spencer (01895 268843) and Mr. David Maskill (01895 268684)

Brunel University, Health and Social Care, Mary Seacole Building, Uxbridge, Middx. UB8 3PH

Appendix G

EAST KENT HOSPITALS
NHS Trust

Study Number
Patient Identification Number:

PATIENT CONSENT FORM

The functional status of patients with stroke and hemi-inattention pre and post-hospital discharge and impact on carer stress

Name of Researcher: Ms. SM Stein

Please initial box

1. I confirm that I have read and understand the information sheet dated……………. for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. I agree to take part in the above study.

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Name of patient	Date	Signature
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Name of person taking consent	Date	Signature
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Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix H

Summarized median statistics for patients with severe stroke at baseline interim and discharge by group

HI-	T0 (n=5)		TI1 (n=5)		TI2 (n=3)		T1 (n=3)	
Factor	Median	Range	Median	Range	Median	Range	Median	Range
Hemi-Inattention (BIT)	136	9	136	14	135	10	135	10
Stroke severity (NIHSS)	18	4						
Functional ability (EBI)	13	12	34	31	36	6	36	3
Balance (PASS)	9	3	19	19	20	13	22	7
Cognitive (MEAMS)	10	3	9	3	10	3	10	3
Higher cognitive	58	260	52	267	87	267	87	267
Higher cognitive	275	173	300	121	300	225	300	225
Self-efficacy (GSE)	36	36	36	8	31	6	31	6
*Denial present	3		3		3		3	

HI+	T0(n=25)		TI1(n=25		TI2(n=11		T1 (n=11	
Factor	Median	Range	Median	Range	Median	Range	Median	Range
Hemi-Inattention (BIT)	11	127	49	140	80	119	86	146
Stroke severity (NIHSS)	22	17						
Functional ability (EBI)	14	30	23	34	30	36	29	41
Balance (PASS)	4	21	5	29	12		13	27
Cognitive (MEAMS)	1	11	7	11	9	9	10	11
Higher cognitive	300	275	300	50	300	36	249	263
Higher cognitive	300	300	300	155	300	224	253	215
Self-efficacy (GSE)	29	37	32	37	30	16	30	
*Denial present	20		20		18		20	

Abbreviations: n = number of observations, HI+ and HI- = with and without hemi-inattention respectively. T0 = discharge, TI1 and TI2 = interim observations at 30, 60 days since stroke respectively, T1 = discharge.

*raw figure

Appendix I

Baseline summarized mean statistics for patients with and without HI by group (HI±) on normally distributed variables.

Factor	HI- (n=35)		HI+ (n=58)		Statistical test	p-value at (0.05, 95% CI)
	mean	SD	mean	SD		
Stroke severity (NIHSS)	10.9	4.6	18.6	5.3	t-test	*<0.0001*
Functional ability (EBI)	36.4	14.1	20.4	14.1	t-test	*<0.0001*
Balance (PASS)	20.3	9.3	11.5	10.8	t-test	*<0.0001*

Abbreviations: n = number of observations, HI+ and HI- = with and without hemi-inattention respectively, SD = standard deviation, CI = confidence interval

Appendix J

MLM- results from the streamlined model (M3) (n=338)

Fixed effects	RC	SE		
HI status	-4.31	2.34		
Time (linear)	15.02	1.76		
Time (non-linear)	-4.15	0.58		
Stroke severity (NIHSS-16)	-1.66	0.18		
Age-75	-0.29	0.09		
HI status x linear time	-5.30	2.26		
Regression intercept				
HI- patients	38.78	1.74		
HI+ patients	34.47	1.74		
Random effects	*Intercept (SE)*	*Slope (SE)*	*Covariance(SE)*	
Level 1 (within patient)	30.47 (5.60)	15.30 (28.41)	-24.91 (5.08)	
Level 2 (between patient)	66.47 (11.42)	77.6 (18.72)	36.28 (10.35)	
IGLS deviance	2704.17			

Abbreviation: HI = hemi-inattention, RC = regression coefficient, SE = standard error

Appendix K

Comparison of multi-level and single level regression estimates from the final model (Mf)

Predictor	Multi-level			Single level		
Variable	RC	SE	p-value	RC	SE	P-value
Time (linear)	6.54	1.08	7.24e-010	5.54	1.01	2.13e-008
Time (non-linear)	-1.52	0.59	0.0049	-1.35	0.83	0.053
NIHSS	-0.43	0.12	0.00017	-0.35	0.096	0.00014
Age	-0.077	0.052	0.062	-0.077	0.041	0.031
PASS	0.71	0.065	4.63e-028	0.80	0.063	4.93e-037
MEAMS	0.88	0.18	5.042e-007	1.03	0.17	7.24e-010
GSE	0.27	0.079	0.00031	0.23	0.07	0.00058
Bladder control	-5.27	1.18	3.91e-006	-4.19	1.19	0.00022
PASS x NIHSS	-0.03	0.007	8.93e-006	-0.032	0.006	4.92e-008
Overall Intercept	39.54	0.84	<0.0001	39.04	0.74	<0.0001
Residual variances						
Intercept (I)	18.68	3.79	4.11e-007	34.45	5.095	6.90e-012
Slope (S)	18.91	18.67	0.16	42.85	19.83	0.015
Covariance (IxS)	-14.58	3.70	4.074e-005	-4.11	4.39	0.17

Abbreviations: RC=regression coefficient, SE=standard error

Confidence intervals (CI) are not calculated but these depend on the magnitude of the SE in the formula RC+ (1.96 x SE), RC- (1.96 x SE), therefore the CI width is affected.

Appendix L

Comparison of MLM results from the final model with and without adjustment to missing data

Predictor	Adjusted (n=269 cases)			Not adjusted (n=267 cases)		
Variable	RC	SE	p-value	RC	SE	P-value
Time (linear)	6.54	1.08	7.24e-010	6.05	1.08	1.06e-008
Time (non-linear)	-1.52	0.59	0.0049	-1.63	0.57	0.0021
Stroke severity NIHSS	-0.43	0.12	0.00017	-0.39	0.11	0.00019
Age	-0.077	0.052	0.062	-0.074	0.052	0.077
Balance/posture PASS	0.71	0.065	4.63e-028	0.76	0.067	4.16e-030
Cognitive ability MEAMS	0.88	0.18	5.04e-007	0.87	0.18	6.83e-007
Self-efficacy GSE	0.27	0.079	0.00031	0.25	0.08	0.00087
Bladder control	-5.27	1.18	3.91e-006	-5.008	1.15	6.81e-006
Interaction PASS x NIHSS	-0.03	0.007	8.93e-006	-0.030	0.007	8.93e-006
Overall Intercept	39.54	0.84	<0.0001	39.32	0.82	<0.0001
Residual variance – level 1(within patient change)						
Intercept (I)	18.68	3.79	4.11e-007	18.58	3.67	2.074e-007
Slope (S)	18.91	18.67	0.16	15.88	17.95	0.19
Covariance (IxS)	-14.58	3.70	4.07e-005	-16.12	3.64	4.71e-006
Residual variance – level 2 (between patient change)						
Intercept (I)	15.17	3.71	2.16e-005	14.52	3.59	2.63e-005
Slope (S)	35.83	12.27	0.0017	37.32	12.083	0.0010
Covariance (IxS)	13.11	4.73	0.0027	12.85	4.59	0.0027

Abbreviations: RC=regression coefficient, SE=standard error, p-value=significance level at alpha=0.05

Appendix M

Comparison of MLwin (version 2.28) and SPSS (20.0) output for the final model (Mf)

Predictor	MLwin (n=269 cases)			SPSS (n=269 cases)		
Variable	RC	SE	p-value	RC	SE	P-value
Time (linear)	6.54	1.08	7.24e-010	6.79	1.01	9.08e-012
Time (non-linear)	-1.52	0.59	0.0049	-1.58	0.57	0.0028
Stroke severity NIHSS	-0.43	0.12	0.00017	-0.45	0.12	8.84e-005
Age	-0.077	0.052	0.062	-0.079	0.053	0.068
Balance/posture PASS	0.71	0.065	4.63e-028	0.68	0.064	1.14e-026
Cognitive ability MEAMS	0.88	0.18	5.04e-007	0.87	0.18	6.83e-007
Self-efficacy GSE	0.27	0.079	0.00031	0.30	0.08	8.84e-005
Bladder control	-5.27	1.18	3.91e-006	-5.61	1.13	3.52e-007
Interaction PASS x NIHSS	-0.03	0.007	8.93e-006	-0.028	0.007	3.16e-005
Overall Intercept	39.54	0.84	<0.0001	34.02	0.97	<0.0001
Residual variances						
Intercept (I)	18.68			10.93		
Slope (S)	18.91			22.32		
Covariance (IxS)	-14.58			-15.62		
IGLS deviance	1746.77			1741.60		

Abbreviations: RC=regression coefficient, SE=standard error, p-value=significance level at alpha=0.05, IGLS deviance = estimate of model goodness of fit.

Appendix N

Comparison of estimates from the final model with and without baseline (interval) BIT scores

Predictor	Without T0-BIT scores			With T0-BIT scores		
Variable	RC	SE	p-value	RC	SE	P-value
Time (linear)	6.54	1.08	7.24e-010	6.56	1.08	9.08e-012
Time (non-linear)	-1.52	0.59	0.0049	-1.58	0.60	0.0028
Stroke severity NIHSS-16	-0.43	0.12	0.00017	-0.32	0.13	8.84e-005
Age-75	-0.077	0.052	0.062	-0.079	0.053	0.068
Balance/posture PASS-20	0.71	0.065	4.63e-028	0.71	0.065	1.14e-026
Cognitive ability MEAMS-10	0.88	0.18	5.04e-007	0.76	0.20	6.83e-007
Self-efficacy GSE-29	0.27	0.079	0.00031	0.24	0.08	8.84e-005
Bladder control	-5.27	1.18	3.91e-006	-5.18	1.17	3.52e-007
Interaction PASS x NIHSS	-0.03	0.007	8.93e-006	-0.032	0.007	3.16e-005
T0-BIT scores-129 (HI level)	-	-	-	0.025	0.016	0.06
Overall Intercept	39.54	0.84	<0.0001	40.24	0.92	<0.0001
IGLS deviance *(n=269 cases)*	1746.77			1744.60		

Abbreviations: RC=regression coefficient, SE=standard error, p-value=significance level at alpha=0.05, IGLS deviance = estimate of model goodness of fit.

Appendix O

Table 5.3 – Estimates from the development of the basic model (1a to 1d)

N=338/372		C1	C2	C3	C4	C5	C6	C7
Model	Variables	HI status	T1	T2	T3	NIHSS	age	IGLS
1a	HI status	-18.81 (2.76) CI (-14.1,-23.5) p=5.2e^{-012}						2712
1b	Time-T0	-16.63 (2.60) CI (-11.5,-21.7) p=7.8e^{-011}	10.13 (1.21) CI (12.5,7.8) p=2.2e-^{017}	14.64 (1.35) CI (17.3,12.0) p=1.7e-^{027}	16.12 (1.64) CI (19.3,12.9) p=5.6e^{-023}			2476
1c	NIHSS-16	-3.64 (2.36) CI (0.98,-8.3) p=0.062	10.25 (1.21) CI (12.6,7.9) p=9.5e^{-018}	14.79 (1.35) CI (17.4,12.2) p=3.0e^{-028}	16.29 (1.63) CI (14.5,13.1) p=7.7e^{-024}	-1.68 (0.19) CI (-1.3,-2.05) p=6.8e^{-019}		2421
1d	Age-75	-2.95 (2.25) CI (1.5,-7.4) p=0.095	10.21 (1.20) CI (1.3,7.9) p=9.5e-^{018}	14.74 (1.35) CI (17.4,12.1) p=5.8e^{-028}	16.27 (1.63) CI (19.5,13.1) p=9.3e^{-024}	-1.66 (0.18) CI (-1.3,-2.0) p=1.5e^{-020}	-0.29 (0.088) CI (-0.1,-0.5) p=0.00048	2411

Abbreviations; C = column, NIHSS-16 = stroke severity, IGLS = IGLS deviance = model fit statistic = the smaller the deviance the better the fit. Regression coefficients and their standard error in brackets are in the first line of each cell, confidence intervals (CI) in the second row and significance levels (p-values) in the third row of each cell. All results are at α = 0.05, 95% CI, e^{-x} denotes 10^{-x}

HI status – estimates represent difference between HI+ and HI- groups (estimates provided are with respect to the HI+ group). 'Time' – estimates provided are in comparison to baseline (T0) which was the reference category

Appendix P

Table 5.4 - Random coefficient estimates for model series (M2a-q)

Series	C1	NIHSS		AGE		T1		T2		T3	
M2	Predictor variable (x)	RC (SE)	P-value	RC(SE)	P-value	RC(SE)	P-value	RC(SE)	P-value	RC(SE)	P-value
a	Stroke (infarct vs haem)	-1.66(0.18)	1.49e-020	-0.28(0.09)	0.00094	10.21(1.20)	8.70e-018	14.74(1.35)	4.63e-028	16.27(1.63)	9.32e-024
b	Lesion (cortical vs all other)	-1.66(0.18)	1.49e-020	-0.29(0.09)	0.00094	10.20(1.21)	8.70e-018	14.74(1.35)	4.63e-028	16.28(1.63)	9.32e-024
c	Carer	-1.65(0.17)	9.31e-021	-0.28(0.09)	0.00094	10.23(1.21)	1.46e-017	14.77(1.35)	6.43e-028	16.31(1.63)	6.89e-024
d	Gender	-1.66(0.18)	1.49e-020	-0.31(0.09)	0.00028	10.22(1.20)	7.98e-018	14.75(1.35)	4.63e-028	16.28(1.63)	9.32e-024
e	Motor function	-0.68(0.15)	3.40e-006	-0.18(0.07)	0.0051	5.62(1.01)	1.27e-008	8.94(1.12)	7.32e-016	10.05(1.31)	8.60e-015
f	Cognitive function	-1.47(0.16)	1.96e-020	-0.17(0.08)	0.017	8.27(1.20)	2.60e-012	12.36(1.35)	2.60e-020	14.17(1.58)	1.49e-019
g	Executive function	-1.52(0.18)	1.46e-017	-0.22(0.09)	0.0071	9.91(1.12)	4.38e-019	14.40(1.36)	1.66e-026	15.76(1.61)	6.22e-023
h	Executive function	-1.62(0.18)	1.13e-019	-0.23(0.09)	0.0071	10.05(1.22)	7.92e-017	15.04(1.38)	5.76e028	16.26(1.67)	3.88e-010
i	Self-efficacy	-1.38(0.18)	8.60e-015	-0.24(0.08)	0.0014	9.71(1.28)	1.60e-014	15.53(1.38)	1.16e-029	18.08(1.62)	2.06e-031
j	Denial	-1.66(0.18)	1.49e-020	-0.28(0.09)	0.00094	9.51(1.17)	2.15e-016	13.92(1.43)	1.12e-022	15.25(1.82)	2.65e-017
k	Bladder control	-1.26(0.17)	6.32e-014	-0.19(0.08)	0.0087	8.84(1.22)	2,08e-013	13.38(1.32)	1.84e-024	14.87(1.56)	7.87e-022
l	Bowel control	-1.20(0.16)	3.19e-014	-0.18(0.08)	0.0087	8.71(1.15)	1.87e-014	13.05(1.27)	4.34e-025	14.23(1.55)	2.16e-020
m	Nutrition	-1.36(0.19)	4.03e-013	-0.20(0.09)	0.013	10.03(1.24)	2.75e-016	14.59(1.37)	8.72e-027	16.07(1.66)	1.83e-022
n	Duration of stay	-1.45(0.19)	1.17e-014	-0.31(0.09)	0.00029	10.30(1.20)	4.74e-018	14.85(1.35)	1.91e-028	16.40(1.63)	4.15e-024
o	Therapy contacts	-1.63(0.19)	4.74e-018	-0.28(0.09)	0.00094	9.83(1.20)	1.20e-016	14.33(1.35)	1.20e-026	15.80(1.63)	1.66e-022
p	Discharge	-1.48(0.21)	8.95e-013	-0.22(0.09)	0.0073	9.70(1.21)	5.29e-016	14.17(1.36)	4.80e-026	15.66(1.64)	6.49e-022
q	Stroke unit (A vs B)	-1.74(0.17)	6.56e-025	-0.25(0.09)	0.0027	10.16(1.18)	3.65e-018	14.70(1.34)	6.38e-011	16.25(1.61)	3.06e-024

Abbreviations: RC = regression coefficient, SE = standard error, CI = confidence interval, NIHSS = National Institute of Health Stroke Scale, T1 = stroke unit discharge, T2 = 6 weeks after discharge, T3 = six months since stroke

Appendix Q

Table 5.6 - Random coefficient estimates for models (M2a-q)

model	Factor	Between individual variation / Level 2					Within individual variation/ Level 1				
(M2)		I	S	I x S	I x S p-value	I x S CI	I	S	I x S CI	I x S p-value	I x S CI
a	Stroke type	87.6 (26.0)	16.8 (3.9)	-25.3 (9.1)	0.0027	-7.5,-43.1	104.4 (37.5)	3.0 (5.7)	-18.5 (15.1)	0.11	11.0,-48.1
b	Lesion type	89.0 (26.2)	16.8 (3.9)	-25.8 (9.1)	0.0023	-7.9,-43.6	105.0 (37.5)	3.1 (5.7)	-18.8 (15.1)	0.11	10.8,-48.4
c	Carer status	88.3 (26.3)	16.7 (3.9)	-26.2 (9.2)	0.0023	-8.2,-44.2	110.7 (37.7)	3.9 (5.7	-21.1 (15.1)	0.082	17.6,-57.0
d	gender	87.2 (25.8)	17.0 (3.9)	-25.6 (9.0)	0.0023	-8.0,-43.2	100.2 (37.1)	2.4 (5.7)	-16.9 (15.0)	0.13	17.6,-51.5
e	Motor function	44.8 (15.9)	8.9 (2.3)	-13.4 (5.5)	0.0074	-2.6,-24.2	58.3 (24.2)	0.71 (3.8)	-8.1 (10.0)	0.21	13.2,-29.4
f	Cognitive function	64.3 (21.9)	14.3 (3.5)	-20.9 (7.8)	0.0038	-5.6,-36.2	91.3 (33.5)	2.0 (5.2)	-15.0 (13.6)	0.16	15.0,-45.0
g	Executive function-TMTA	89.6 (26.4)	15.5 (3.8)	-24.7 (9.0)	0.0031	-7.1,-42.3	91.6 (39.2)	0.52 (6.0)	-12.6 (16.0)	0.22	21.4,-47.2
h	Executive function-TMTB	87.4 (26.2)	17.2 (4.0)	-26.4 (9.2)	0.0021	-8.4,-44.4	97.8 (36.4)	1.2 (5.6)	-14.7 (14.7)	0.22	20.6,-50.0
i	Self-efficacy	84.9 (28.8)	11.9 (3.7)	-21.5 (9.5)	0.012	-2.9,-40.1	111.9 (40.5)	4.5 (6.0)	-22.5 (16.0)	0.081	14.0,-59.0
j	Denial status	111.4 (29.7)	20.3 (4.6)	-36.1 (10.7)	0.00038	-15.2,-57.1	67.9 (35.7)	0.34 (5.8)	-7.1 (14.9)	0.32	22.1,-36.3
k	Bladder control	65.3 (23.0)	13.6 (3.5)	-20.2 (8.1)	0.0064	-1.3,-39.1	110.0 (36.3)	3.8 (5.4)	-20.8 (14.4)	0.075	7.4,-49.0
l	Bowel control	74.6 (23.2))	13.5 (3.4)	-22.8 (8.1)	0.0025	-6.9,-38.7	194.0 (33.0)	5.2 (4.9)	-22.3 (13.0)	0.044	3.2,-47.8
m	Nutrition status	91.4 (27.3)	16.8 (4.0)	-27.8 (9.5)	0.0017	-8.9,-46.4	116.0 (38.5)	4.5 (5.8)	-22.9 (15.3)	0.067	7.1,-52.9
n	Duration of stay	83.7 (25.2)	17.3 (4.0)	-26.0 (9.0)	0.0019	-8.4,-43.6	97.2 (36.6)	1.8 (5.6)	-15.3 (14.8)	0.15	13.7,-44.3
o	Therapy contacts	79.2 (24.4)	17.3 (3.9)	-24.1 (8.7)	0.0028	-7.1,-41.2	91.9 (36.5)	1.2 (5.7)	-13.6 (14.9)	0.18	15.6,-42.8
p	Discharge destination	87.5 (26.0)	16.7 (4.0)	-26.1 (9.1)	0.0021	-8.3,-43.9	103.0 (37.3)	2.9 (5.7)	-18.2 (15.0)	0.11	11.4,-47.8
q	Stroke unit (A or B)	29.0 (25.9)	17.4 (3.9)	-28.4 (9.1)	0.00090	-10.6,-46.2	86.8 (35.9)	0.4 (5.6)	-11.4 (14.6)	0.22	18.2,-41.0
M1	Basic model estimates for comparison purposes	88.2 (26.0)	16.9 (3.9)	-25.5 (9.1)	0.0026	-7.7,-43.3	102.8 (37.3)	2.8 (5.7)	-17.9 (15.1)	0.12	11.7,-47.5
	Abbreviations: I=intercept. S=slope, I x S = intercept, slope covariance (standard error shown in brackets), CI = confidence interval. All estimates are at α = 0.05, 95% CI										