POST-STROKE COGNITION AS A FALL PREDICTOR DURING INPATIENT REHABILITATION

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POST-STROKE REHABILITATION AS A FALL PREDICTOR

DURING INPATIENT REHABILITATION

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Accidental falls are common among persons admitted for inpatient stroke rehabilitation, and they can cause serious physical and psychological consequences. The role of post-stroke cognitive function in the occurrence of falls after stroke is not clear. The purpose of this dissertation was to evaluate the extent to which post-stroke cognition predicts falls during inpatient rehabilitation, and to explore the nature of the relationships among impaired balance, hemineglect, activities of daily living (ADL) performance deficit, executive cognitive dysfunction, and falls during inpatient rehabilitation after stroke.

Data were pooled from five simultaneously occurring studies at five of the UPMC Rehabilitation Institute's inpatient units. The Chedoke-McMaster Stroke Assessment Postural Control Scale (balance impairment), Line Bisection Test (hemineglect), motor Functional Independence Measure (ADL performance deficit), Repeatable Battery for the Assessment of Neuropsychological Status and Delis-Kaplan Executive Function System (non-executive and executive cognitive function, respectively) were administered to 180 participants shortly after admission to inpatient rehabilitation, and subsequent occurrence of participant falls was recorded.

Using logistic regression and controlling for relevant sociodemographic and clinical covariates, we found no significant predictive relationship between post-stroke cognition and falls, and no significant interaction between post-stroke executive cognitive function and other

risk factors for falls (balance impairment, hemineglect, and ADL disability). The most parsimonious predictive model of falls during stroke rehabilitation included educational level in years (p = .01), stroke severity (National Institutes of Health Stroke Scale, p = .04), use of fall prevention interventions during the inpatient rehabilitation stay (p = .01), and ADL disability (p = .04).

Future studies should address limitations of this dissertation, especially the lack of sample representativeness due to possible sampling bias and the need for remediation of large amounts of missing data through imputation. Future investigations are also needed to explore optimal methods for measuring cognitive domains most likely to be associated with falls, particularly when stroke-related communication deficits exist, and to further understand the strong association we found between use of fall prevention interventions and the occurrence of falls. Finally, exploration of mechanisms underlying associations between socioeconomic status and falls during inpatient rehabilitation is warranted.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

I am fortunate to have had a wonderful interdisciplinary team of dissertation committee members and consultants during my PhD journey, and I owe them many thanks. They have generously shared their time, expertise, and unparalleled scholarship with me. I am grateful to Dr. Judith Matthews, my chair, for deftly providing leadership, support, and encouragement through the ups and downs of this long journey; to Dr. Susan Sereika for patiently supporting me through many difficult data analyses; to Dr. Elizabeth Skidmore, for completely understanding the synergy between my clinical passion and my scholarship, and for being an extraordinary role model of a clinician-researcher; to Dr. Stephanie Studenski, for her pragmatic insights into research with vulnerable older adults; and to Dr. Ellen Whyte, for providing access to participants, data, learning experiences, and resources with which to complete my study—our serendipitous meeting early in my PhD program provided the springboard from which I launched this dissertation. In addition to my committee, I have benefitted immeasurably from the insights of Dr. Meryl Butters, an authority on cognitive assessment in older adults, and Dr. Mary Beth Happ, whose insights regarding hospitalized and medically complex older adults was invaluable.

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I could not have arrived at this point without the support of family and friends. I am grateful to my parents for making me the person I am today, through the values and ideals they instilled in me. Sadly, neither of them lived to see this day. They would have been so proud. I would also like to thank my husband, Tom, and my children, Kate and Zach, for their patience, support, and love through this process, and for understanding my need to do this. The past five years have not been easy for them. I also value the friendships I have made in the PhD program, and extend heartfelt thanks to my fellow students and friends, who always had time to lend an ear, a hand, a smile, or a shoulder.

This research would not have been possible without the generosity and engagement of the patients of the UPMC Rehabilitation Institute, and especially our research participants. Individuals with stroke are often tired, overwhelmed, and frightened, yet many gave unselfishly of their time and of their spirit to share with me, and to participate in this research. To all of our participants and to all the patients for whom I have been privileged to care throughout my career: Thank you for teaching me. I hope that I can 'pay it forward' by helping to improve the lives of those who come after you.

1.0 INTRODUCTION

Falls are among the most commonly occurring complications of stroke (Moroz, Bogey, Bryant, Geis, & O'Neill, 2004). Stroke affects 795,000 Americans annually (American HeartAssociation, 2009) and leads to some degree of permanent disability for an estimated 450,000 individuals (Salter, Foley, Jutai, & Teasell, 2007). Stroke-related falls occur at especially high rates in the inpatient rehabilitation setting, where incidence ranges from 20% to 48% (Suzuki et al., 2005). Almost one-third of those who fall sustain injuries such as fractures and hematomas (Teasell, McRae, Foley, & Bhardwaj, 2002). Other deleterious consequences include decreased physical activity related to fear of further falls (Suzuki et al., 2005), decreased falls self-efficacy (the belief that one can independently ambulate without falling), and a diminished sense of dignity (Rapport, Hanks, Millis, & Deshpande, 1998).

Empirical evidence to date suggests that stroke-related physical, perceptual, and functional risk factors including impaired balance (Nyberg & Gustafson, 1997; Olsson, Lofgren, Gustafson, & Nyberg, 2005; Rabadi, Rabadi, & Peterson, 2008; Stapleton, Ashburn, & Stack, 2001; Teasell, et al., 2002), hemineglect (Czernuszenko & Czlonkowska, 2009; Nyberg & Gustafson, 1997; Olsson et al., 2005; Webster et al., 1995), and difficulty performing activities of daily living, otherwise referred to as ADL performance deficit or ADL disability (Olsson et al., 2005; Sze, Wong, Leung, & Woo, 2001; Zdobysz, Boradia, Ennis, & Miller, 2005), increase

stroke survivors' risk of falling. However, the role of post-stroke cognition in relation to known risk factors and falls during inpatient rehabilitation is largely unexplored.

The domains of cognition can be divided into executive function (higher-order cognitive processes that control, integrate, and organize other cognitive abilities) and non-executive function (attention, immediate memory, delayed memory, language, visuospatial function, and psychomotor processing speed). Deficits may occur in any of these domains after stroke. Impaired executive function, otherwise known as *executive dysfunction,* is the most common post-stroke cognitive impairment (Cavanaugh, Hogan, Fairfax, Gordon, & Kopacz, 2002), affecting between 20% and 50% of persons with stroke (Jaillard, Naegele, Trabucco-Miguel, LeBas, & Hommel, 2009; Pohjasvaara et al., 2002; Zinn, Bosworth, Hoenig, & Swartzwelder, 2007). Executive dysfunction is manifested in several ways, including inability to inhibit inappropriate or unsafe behaviors; impaired ability to think abstractly or synthesize information; verbal or motor perseveration; inability to shift from one task, behavior, or construct to another; and difficulty sequencing thoughts and actions (Leeds, Meara, Woods, & Hobson, 2001). Two studies (Rapport et al., 1998; Rapport et al., 1993) that have directly examined the relationship between executive dysfunction and falls suggest that executive dysfunction may play a significant role in predicting falls during inpatient rehabilitation. However, these findings must be viewed with caution due to methodological limitations pertaining to sample size and instrumentation.

1.1 PURPOSE

Given the morbidity associated with post-stroke falls in inpatient rehabilitation settings, the frequency of executive dysfunction in individuals with stroke, and the lack of understanding of the relationships between cognitive factors and falls, we conducted this prospective observational investigation to further elucidate these relationships. Guided by the systems perspective of neurorehabilitation (Law et al., 1996; Mathiowetz, 2004; Shumway-Cook & Woollacott, 2001), which holds that performance of complex tasks and activities is under the simultaneous control of a variety of factors, we posited that post-stroke cognition influences falls in the inpatient rehabilitation setting and, more specifically, that executive impairment is a moderator of the associations among physical, perceptual, and functional abilities as they predict falls.

1.2 SPECIFIC AIMS

In a sample of rehabilitation patients recovering from stroke, we developed two aims:

Primary Aim: To evaluate the extent to which post-stroke cognition predicts falls during inpatient rehabilitation.

H1a: The severity of impairment in post-stroke cognition will significantly predict falls during inpatient rehabilitation among adults with either ischemic or hemorrhagic stroke, as indicated by a positive predictive relationship between post-stroke cognition and occurrence of falls in this setting and population.

H1b: Severity of executive dysfunction (i.e., difficulty with planning and problem solving, disinhibition, perseveration, and decreased cognitive flexibility) will be a stronger

predictor of falls during inpatient rehabilitation than severity of non-executive dysfunction (i.e., deficits in attention, immediate memory, delayed memory, language, visuospatial function, and psychomotor processing speed).

Secondary Aim: To explore the nature of the relationships among impaired balance, heminiglect, ADL performance deficit, executive cognitive dysfunction, and falls during inpatient rehabilitation after stroke.

H2 (exploratory): Executive dysfunction will significantly moderate the relationship between impaired balance, hemineglect, and ADL performance deficit and falls during inpatient rehabilitation.

1.3 DEFINITION OF TERMS

The following terms appear throughout this dissertation and are defined as follows:

Inpatient rehabilitation: a hospital-based or free-standing facility where patients who are considered to be "medically stable" (that is, not receiving cardiac monitoring or other intensive medical therapies, but still appropriate for inpatient care for medical management) are admitted for post-acute treatment after an illness or injury. Patients are seen daily by a physiatrist and receive around-the-clock rehabilitation nursing specialty care. They participate in a minimum of three hours per day of skilled therapy (including physical therapy, occupational therapy, and speech-language pathology), and they may receive other services including neuropsychology, counseling psychology, therapeutic recreation, orthotics/prosthetics, and rehabilitation engineering/assistive technology.

Fall: any unplanned contact with the floor of any body part, excluding the feet, as reported by the patient, his or her relatives, or the rehabilitation staff, as well as an incident in which a patient is caught in the middle of a fall and lowered to the floor by others (Mayo, Gloutney, & Levy, 1994; Sze et al., 2001). Falls may be conceptualized as the failure to successfully perform a complex functional task, such as transferring or ambulating. Our definition of falls includes those occurring on the nursing unit, in the therapy department, and in public areas of the hospital.

Fall prevention intervention: devices or care strategies aimed at minimizing the occurrence of falls during hospitalization. These may include devices such as bed and chair exit alarms that notify staff of patients attempting to walk or transfer without assistance, seat belts that remind patients to call for help before walking or transferring, positioning wedges and lap trays that prevent sliding or leaning out of a chair, and restraint devices such as net-enclosed beds or restraining belts or vests. Care strategies may include situating the patient in a room near the nurses' station, offering frequent toileting, performing hourly safety rounds, requiring a minimum of two staff to assist the patient with transfers, or providing constant observation for high risk patients.

Balance impairment: a disruption in the body's ability to maintain control of its posture, that is, of its position relative to the environment and to the forces of gravity, in order to remain upright and prevent falls (Winter, 1995).

Visuospatial hemineglect: impaired visuospatial perception of, and thus inattention to, one side of the visual field, resulting in a tendency to ignore stimuli presented to the visual field contralateral to the brain lesion (Schenkenberg, Bradford, & Ajax, 1980).

ADL performance deficit: a decrease in the ability to perform independently one or more basic activities of daily living such as bathing, dressing, grooming, toileting, and functional mobility, that is, ambulating and transferring.

Post-stroke cognition: disturbances or decreased performance in multiple domains of cognition, perception, and communication that are commonly seen after stroke (Nys et al., 2006; Pohjasvaara, et al., 2002; Sachdev, Brodaty, Valenzuela, Lorentz, & Koschera, 2004) including executive function, attention, immediate memory, delayed memory, language, visuospatial function, and psychomotor processing speed. For the purposes of this investigation, post-stroke cognition is further divided into two categories: non-executive cognitive impairment and executive cognitive impairment.

Non-executive cognitive impairment: decreased abilities in the cognitive domains of attention, immediate memory, delayed memory, language, visuospatial function, and psychomotor processing speed.

Executive cognitive impairment: an array of cognitive problems marked by decreased ability to engage in planning and problem solving activities that involve evaluating novel situations, generating alternative behavior strategies for engaging in the situation, and selecting and initiating the most appropriate strategy to meet that situation. Components include planning and implementing strategies for task performance, monitoring feedback to adjust one's performance of tasks and correct errors, allocating attention, inhibiting task-irrelevant information, and mental flexibility (set shifting) to respond to changes in situation and environment (Pohjasvaara et al., 2002).

1.4 BACKGROUND AND SIGNIFICANCE

Among hospitalized patients, falls constitute a significant problem (Rapport, et al., 1998) with potentially deleterious consequences that include fractures, decreased physical activity related to fear of further falls (Suzuki et al., 2005), and a diminished sense of dignity and self-efficacy (Rapport et al., 1998). Falls with resultant injury are particularly common in inpatient rehabilitation settings (Gilewski, Roberts, Hirata, & Riggs, 2007) where people with stroke form the largest group of fallers. Indeed, an estimated 20% to 48% of stroke patients fall during inpatient rehabilitation (Suzuki et al., 2005), and 13% to 29% of those who fall suffer injuries (Teasell et al., 2002). Given rehabilitation's goal of motivating patients toward independence by continually challenging their physical, cognitive, functional, and psychosocial capabilities, these prevalence data, though worrisome, are not entirely surprising.

Complete recovery from stroke is rare. Many patients face long term physical, functional, and emotional impairments (Ekstam, Uppgard, von Koch, & Tham, 2007; Pohjasvaara et al., 2002). In light of these challenges, preventing further devastating impairments, such as those that may occur from injurious falls, is crucial. Yet current science provides little direction to guide practice with respect to effective fall risk assessment and fall prevention measures in this population and setting. Indeed, despite the frequent occurrence of post-stroke falls during inpatient rehabilitation, surprisingly little empirical literature exists related to this topic. According to this sparse literature, selected physical, perceptual, and functional impairments have been associated with fall risk post-stroke. These include balance impairment (Olsson et al., Nyberg & Gustafson, 1997; Olsson, et al., 2005; Rabadi, et al., 2008; Stapleton, et al., 2001; Teasell, et al., 2002), visuospatial hemineglect (Czernuszenko & Czlonkowska, 2009; Nyberg &

Gustafson, 1997; Olsson et al., 2005; Webster et al., 1995), and ADL performance deficit (Olsson et al., 2005; Sze et al., 2001; Zdobysz et al., 2005).

The fall prevention interventions most frequently used in clinical practice include bed and chair alarms, side rails, restraint belts, lap trays, and enclosure beds. These measures, though well intended, may actually discourage independent functioning and be detrimental to patients' dignity and sense of self-efficacy (Rapport et al., 1998). Such measures may also contribute to fall-related injuries, rather than preventing falls and resultant injuries (Dunn, 2001), primarily because patients attempt to climb over bedrails, or disentangle themselves from alarm belts.

Filling the critical gap in rehabilitation science regarding the influence of cognitive dysfunction on falls, controlling for known risk factors, during post-stroke rehabilitation will enable development of targeted therapeutic interventions designed to prevent or mitigate the incidence of falls among stroke inpatients. Without new, more effective interventions, clinicians will have no choice but to continue to rely on restrictive measures such as restraints and alarm belts to prevent falls, rather than rehabilitative techniques that may facilitate recovery of cognitive and functional skills.

1.4.1 Impaired balance.

Several studies have explored the relationships between various measures of balance and the occurrence of stroke-related falls. Balance impairment, more specifically postural instability, is a frequent and often long lasting consequence of stroke, present in at least twice as many stroke survivors as in healthy age-matched controls (Harris, Eng, Marigold, Tokuno, & Louis, 2005; Nichols, 1997). Impaired balance can cause gait disturbances as well as the inability to safely perform dynamic tasks such as reaching from both standing and seated positions. The

relationship between balance impairment and falls makes intuitive sense, and this relationship is also well supported in the literature on post-stroke falls during acute hospitalization and in long-term care and residential settings (Cheng et al., 1998; Harris et al., 2005; MacIntosh, Hill, Dodd, & Goldie, 2005; Nyberg & Gustafson, 1996, 1997; Olsson et al., 2005; Rubenstein & Josephson, 2006).

1.4.2 Hemineglect.

Impaired visuospatial perception of one side of the visual field, known as hemineglect, is common in stroke. One population-based study found hemineglect in 23% of stroke patients overall, and in 42% of patients with right hemisphere lesions (Webster et al., 1995). Falls often occur during some type of functional activity (e.g., while attempting to transfer, ambulate, or use the toilet) when individuals with hemineglect fail to acknowledge half of their person or environment. Hemineglect has been associated with poor rehabilitation outcomes (Webster et al., 1995) and post-stroke falls (Godlewski, Webster, Beissel, & Abadee, 1990; Nyberg & Gustafson, 1997; Olsson et al., 2005), though findings for the latter have been mixed. For example, Nyberg and Gustafson (1997) and Olsson et al. (2005) noted significant predictive relationships between visuospatial hemineglect (measured by the Line Bisection Test) and falls during post-stroke rehabilitation. In contrast, Stapleton, Ashburn, and Stack (2001), using a different measure (the Star Cancellation Test), did not find this same relationship, although their results must be interpreted with caution, as this study was greatly underpowered to identify significant effects.

Rapport and colleagues (1993) also assessed hemineglect as a predictor of falls among patients in stroke rehabilitation. These researchers did not find a direct relationship between

hemineglect and falls, although lack of association may have reflected a measurement issue. That is, the study assessed hemineglect using an investigator-developed laboratory tool named the "Bilateral Scanning Task" that was designed to assess hemineglect and "failure to inhibit" scanning behavior during task performance. The authors found that poor overall test performance was related to falls, but the part of the task designed to measure hemineglect was not related to falls (Rapport et al., 1993). Moreover, the construct validity, sensitivity, and specificity of the Bilateral Scanning Task has not been established and may explain the lack of significant association found between hemineglect and falls in this investigation.

1.4.3 ADL Performance Deficit.

Performance of basic ADLs has been examined in many studies of falls during post-stroke rehabilitation (Mayo, Korner-Bitensky, & Kaiser, 1990; Nyberg & Gustafson, 1997; Olsson et al., 2005; Suzuki et al., 2005; Sze et al., 2001; Teasell et al., 2002; Zdobysz et al., 2005). Virtually all of these studies support an association between ADL performance and falls, yet the precise nature of this association is unclear at present. Zdobysz et al. (2005) demonstrated that selected domains of ADL performance (specifically, transfers) are related to falls, while Nyberg and Gustafson (1997), Olsson et al. (2005), Sze et al. (2001), and Mayo, Korner-Bitensky, and Kaizer (1990) found that overall scores of general ADL performance were related to falls. Suzuki et al. (2005) found that performance of motor ADLs (e.g., dressing, transferring, and ambulation) and cognitive ADLs (e.g., social cognition, or the ability to appropriately communicate and interact with others) were related to falls, whereas Teasell et al. (2002) found that a single global score of ADL performance was not related to falls. Common among many of these studies has been measurement of ADL performance using the Functional Independence

Measure (Hamilton, Granger, Shwerwin, Zielezny, & Tashman, 1987), or FIM, which yields both individual ADL item scores as well as summary scores for motor, cognitive, and total (global) ADL performance.

1.4.4 Post-Stroke Cognition.

It seems logical clinically that falls are related to poor cognitive abilities. Yet, results of studies testing whether cognitive impairment predicts falls are equivocal. For example, Nyberg and Gustafson (1996, 1997), Olsson et al. (2005), and Sze et al. (2001) found no association between cognitive deficit and falls in various samples of patients receiving post-stroke rehabilitation, while Suzuki et al. (2005), Teasell et al. (2002), and Rabadi, Rabadi, and Peterson (2008) found that cognitive deficit was associated with falls. These conflicting results may be because of differences in measurement of cognitive function among the studies. The studies that found no relationship between cognitive status and falls used general cognitive screening tests such as the Mini Mental State Exam (MMSE) or the Abbreviated Mental Test, whereas two of the three studies linking cognitive impairment with falls used the cognitive FIM. (The third study, by Rabadi's group, found that an MMSE score indicative of cognitive impairment, i.e. < 24 was associated with falling; however, they did not exclude persons with aphasia, and they admit that MMSE scores are lowered by concomitant language impairment.)

Stroke can result in deficits in multiple domains of cognition (Nys et al., 2006; Pohjasvaara et al., 2002; Sachdev et al., 2004) comprising executive function (i.e., planning, selecting and implementing strategies for task performance, monitoring task performance and adjusting strategies accordingly, and inhibiting irrelevant information) and non-executive function (i.e., attention, immediate memory, delayed memory, language, visuospatial function,

and psychomotor processing speed). However, studies thus far have primarily examined associations between general cognitive function and falls, or memory and falls. In most of the studies finding no association between cognitive deficit and falls, cognitive deficit was operationalized as a low score (<24) on the Mini-Mental Status Examination (MMSE), whereas studies that measured cognitive deficit using functional performance criteria were more likely to find a relationship between cognitive impairment and falls. Since the MMSE is a screening test for Alzheimer's-type dementia, it is heavily weighted to items assessing memory and language but contains no items evaluating executive dysfunction (Liu-Ambrose, Pang, & Eng, 2007; Sachdev et al., 2004). Thus, the MMSE may not be the most appropriate cognitive measure for the post-stroke population. Indeed, the reason why the relationship between cognitive function and post-stroke falls has not been definitively established may be that this relationship has not been sufficiently investigated using valid measures that are sensitive to post-stroke cognitive deficits. Most studies to date have not measured executive dysfunction specifically, nor have they parsed out the influence of executive dysfunction versus non-executive dysfunction on falls during inpatient stroke rehabilitation.

Impaired executive function is one of the most common post-stroke cognitive impairments (Cavanaugh et al., 2002; Pohjasvaara et al., 2002); various authors estimate its prevalence at between 20% and 50% of persons with stroke (Jaillard et al., 2009; Pohjasvaara et al., 2002; Zinn et al., 2007). Component executive functions include planning and implementing strategies for task performance, monitoring feedback to adjust one's performance of tasks and correct errors, allocating attention, inhibiting task-irrelevant information, and having the mental flexibility (set shifting) to respond to changes in situation and environment (Pohjasvaara et al., 2002). These executive functions need to be intact for an individual to complete non-routine

complex activities of daily living such as preparing a meal, selecting and donning clothing appropriate to the weather, or obtaining help in an emergency (Leeds et al., 2001; Pohjasvaara et al., 2002).

Rapport and colleagues (1998; 1993) are among the few investigators who have examined executive dysfunction in relation to falls during inpatient rehabilitation in general, or stroke rehabilitation in particular. In a study of 90 rehabilitation patients with orthopaedic, spinal cord injury, and traumatic brain injury diagnoses, they showed that certain aspects of executive function (cognitive flexibility and response disinhibition) and visuospatial impairment explain as much variance in fall risk—approximately 30%--as do other common, empirically supported, fall risk factors including balance impairment and functional disability. They postulate that these cognitive variables moderate the influence of other fall risk factors such as age, postural instability, and functional impairment. The types of cognitive impairments identified by Rapport et al. (1998) as predictive of falls in a mixed rehabilitation population are similar to the types of cognitive impairment often seen in stroke rehabilitation patients, with executive dysfunction ranking as most common (Liu-Ambrose et al., 2007; Pohjasvaara et al., 2002; Sachdev et al., 2004). Rapport's group achieved similar results in a study of 32 stroke rehabilitation patients (1993). Their results suggest that behavioral impulsivity, theoretically an aspect of executive dysfunction, was predictive of falls in this small sample of right-hemisphere stroke patients. It should be noted, however, that these researchers used laboratory measures that relied on investigator-developed equipment which is neither available nor practical for general clinical use. Further, their ability to draw inferences to the larger population of stroke survivors undergoing inpatient rehabilitation was hampered by lack of statistical power in both studies. It is likely that executive dysfunction may be related to falls in the inpatient rehabilitation

population, but such an association has not yet been explored using clinically available instrumentation in a sample large enough to yield sufficient power. A detailed discussion of the potential role of post-stroke cognition among risk factors for falls during post-stroke inpatient rehabilitation can be found in the published integrative review (Campbell & Matthews, 2010) provided in Appendix A.

1.5 GUIDING FRAMEWORK

No specific theory guiding the study of risk factors for falls in general, or falls during inpatient stroke rehabilitation in particular, is evident in extant literature on the subject. Systems models such as those used in neurorehabilitation, including the Person-Environment-Occupation model developed by Law and associates (1996) and the Person-Task-Environment model proposed by Shumway-Cook and Woolacott (2001), may provide guidance. Models derived from the systems perspective recognize that neurobehavior (i.e., responses resulting from central nervous system processing that lead to task performance in daily functioning) is the result of the combination of many systems and subsystems (Mathiowetz, 2004). Performance of complex tasks and activities is under the simultaneous control of a variety of factors. Physical, sensory/perceptual, and cognitive factors as well as environmental considerations combine to determine the individual's task performance in any given situation. Neurobehavior, and thus task performance, constantly changes in response to changes in the individual's physical, sensory, and cognitive status, as well as changes in the individual's environment.

Post-stroke falls may be conceptualized as the failure to successfully perform a complex functional task, such as transferring or ambulating. Guided by a systems perspective, we posited

that falls during inpatient rehabilitation after stroke are related to a variety of factors, not simply a single factor such as impaired balance. That is, falls may occur in relation to physical, perceptual, and functional abilities, and the addition of cognitive dysfunction confounds the association between these three types of abilities and falls, even within the relatively constant environment of the inpatient rehabilitation setting. Specifically, impaired balance, hemineglect, and decreased functional performance of ADLs together contribute to falls; disruptions in higher level cognitive processes worsen the effect of these factors. We posited that these factors in combination are related to post-stroke falls during inpatient rehabilitation, and the severity of executive dysfunction significantly increases fall risk, compared to the absence of executive dysfunction (see Figure 1).

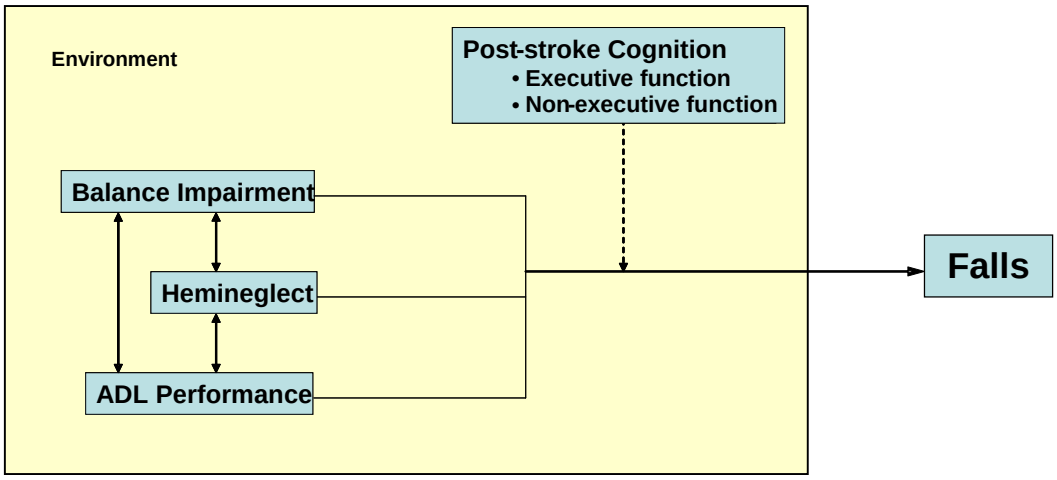

Figure 1. Conceptual framework.

1.5.1 Significance.

In light of the many persons with stroke who fall during inpatient rehabilitation, their likelihood of incurring injury and further functional deficit after falling, and the prevalence of executive dysfunction in the post-stroke population, we undertook research designed to generate new knowledge about the relationships among impaired balance, hemineglect, ADL performance deficit, post-stroke cognition, and falls. Using more precise measures of cognitive function (executive and non-executive) than have been used in prior studies, we evaluated the role of post-stroke cognition, among other known risk factors, in predicting falls. Our hope in pursuing this line of inquiry is eventually to enable improved quality of life among persons with stroke by preventing further disabling complications, and to spawn design of more acceptable alternatives to restrictive interventions such as physical restraints and alarm devices in inpatient stroke rehabilitation settings. The knowledge gained from this investigation will inform a future program of research that ultimately may result in novel, interdisciplinary, therapeutic interventions which can be implemented by clinicians with patients who are at high risk of falling during stroke rehabilitation.

1.5.2 Preliminary Studies.

1.5.2.1 Evaluation of the sampling pool.

To gauge the feasibility of obtaining the target sample for this dissertation, we examined historical admissions data at five sites (Mercy, Montefiore, Passavant, Saint Margaret, and McKeesport) within the UPMC Health System, a large university-affiliated health system in western Pennsylvania. Based on admission trends (see Table 1) and fall occurrence trends, we

estimated that the five study sites would admit between 700 and 900 post-stroke patients during our planned 18-24 months of recruitment, yielding ample numbers of participants with stroke and an adequate number of fall events for meaningful analysis.

Table 1. Stroke Admissions, by Site, 2008

UPMC Site	Number (%) of Facility Rehabilitation Admissions with Stroke Diagnosis
Montefiore	121 (21.5%)
Mercy	201 (24.2%)
Passavant	95 (27.6%)
St. Margaret	75 (17.6%)
McKeesport	103 (25.4%)

1.5.2.2 Clinical evidence of risk factors.

Several clinical quality improvement investigations conducted at our study sites have indicated that the variables of interest in this dissertation are likely to be related to falls. For example, in a 2008 study of a small sample of stroke patients enriched for fallers (N = 47, ~25 of whom had fallen) analyses were performed to identify factors related to falls. Hemineglect and impairments in balance, transfer capabilities, and problem solving (based on clinical charting by nurses, physicians, and therapists) were observed in greater proportions among fallers than non-fallers (see Table 2). These findings were used to develop a new Stroke Assessment of Fall Risk (SAFR) tool for clinical use during inpatient stroke rehabilitation. The accuracy of this new tool was compared to the accuracy of the currently used Fall Risk Screen (FRS) in the same sample, using ROC analysis. The area under the curve of the FRS was .50, whereas the area under the curve for the newly developed SAFR was .75, and mean total SAFR scores were significantly higher among persons who fell, M = 30.71, SD = 9.18, than for persons who did not fall, M = 23.15, SD = 5.56 (Breisinger & Campbell, 2011). Presence of these risk factors was ascertained

largely from clinical observation by nurses and therapists who staffed the rehabilitation unit, rather than by administration of established measures as part of a research protocol. These findings support the need for further examination of these risk factors, using valid and reliable research instruments in a larger sample of stroke rehabilitation inpatients.

Table 2. Percentage of Fall Risk Factors in a Sample of Stroke Patients Enriched for Fallers at UPMC

	Balance Impairment	Hemineglect	Transfer Impairment	Impaired Problem Solving
Fall	76%	33%	80%	95%
No Fall	81%	15%	34%	61%

1.5.2.3 Fall rates among stroke patients.

Quality monitoring data from UPMC South Side, the site with the largest census of stroke patients prior to relocating its stroke rehabilitation services to UPMC Mercy, indicated that during 2008 the trend for falls among stroke patients mirrored those reported in the literature. That is, stroke patients constituted the most common diagnostic group to fall at this facility, and fall rates for the stroke unit ranged from 7.0 falls to 12.5 falls per 1000 patient days (Campbell, 2006 ,unpublished report). More recent quality improvement data provided by the UPMC Mercy Rehabilitation Institute stroke rehabilitation service show that fall rates for that site that roughly correspond to our data collection period, from July 2009 through May 2011, ranged from 4.44 to 16.05 falls per 1000 patient days. Fall rates at the other three sites were similar, consistent with estimates documented for stroke rehabilitation patients by Nyberg and Gustafson (1995).

1.5.3 Research Design and Methods.

For this dissertation we employed a prospective, observational design with stroke patients engaged in inpatient rehabilitation. We ascertained participants' physical, perceptual, functional, and cognitive status at baseline, along with data for relevant covariates. We also followed participants during their inpatient rehabilitation stay to determine the occurrence of falls. For participants who sustained a fall, we ascertained the circumstances surrounding the fall through chart review and by interview, when practical, to gain information regarding the location and type of fall.

1.5.3.1 Setting and Sample.

Setting—The five sites from which participants were recruited were hospital-based, acute rehabilitation units comprising the UPMC Rehabilitation Institute, which is part of a 19-hospital University of Pittsburgh Medical Center (UPMC) health system in western Pennsylvania.

Sample— Through collaborative recruitment efforts for all studies conducted on the stroke service at the Rehabilitation Institute, we accrued 180 participants from the inpatient rehabilitation units at UPMC Mercy, UPMC Montefiore, UPMC Passavant, UPMC Saint Margaret, and UPMC McKeesport. One hundred sixty two participants involved in one of four co-occurring stroke studies consented to falls follow-up and provided data for relevant predictor (physical, perceptual, functional, and cognitive) and outcome (falls) variables. These four studies included 'Enhancing Rehabilitation after Stroke,' also referred to as 'Enhance,' and 'Web-Based Stroke Education' (PI: E. Whyte) and 'Co-operative Training for Stroke Rehabilitation' and 'Neurobehavior and Activity Interactions after Stroke' (PI: E. Skidmore). Another 44 inpatients who did not meet the more stringent inclusion criteria for these four studies but met the criteria

for the present study were approached for participation, yielding an additional 22 consented participants. One of these consented patients was later disqualified because she had been discharged to a skilled nursing facility between hospitalization for acute stroke and admission to inpatient rehabilitation, resulting in 21 additional participants enrolled. A diagram depicting the sources of study participants appears in Figure 2.

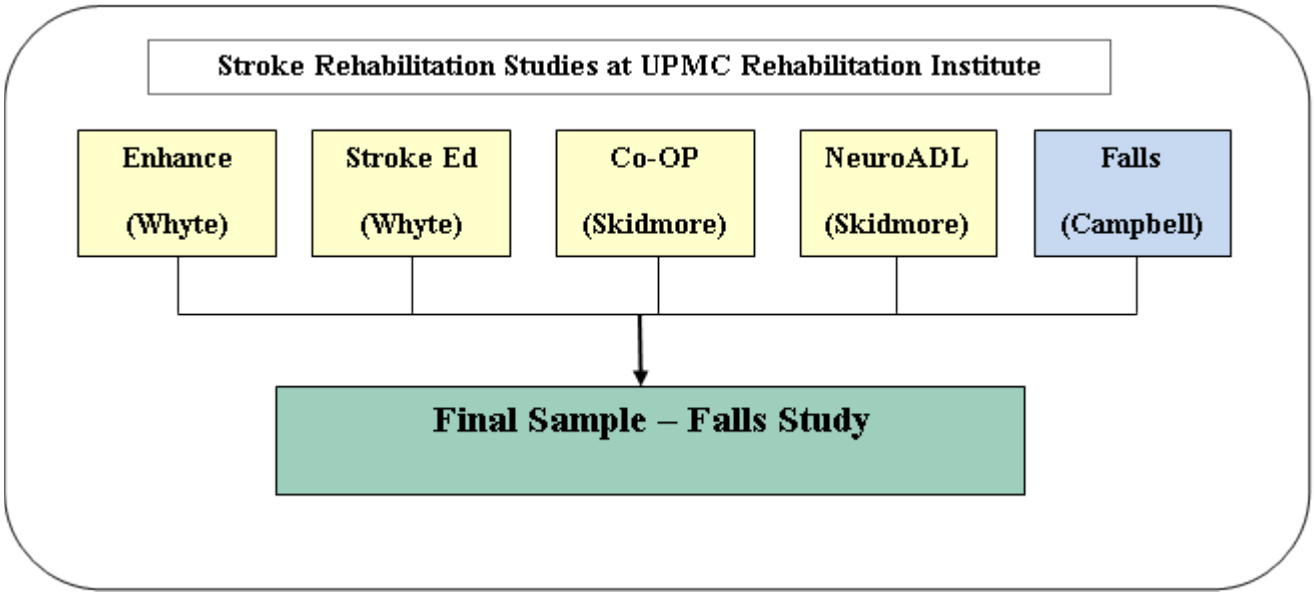

Figure 2. Sources of Participants for the Falls Study

Common inclusion criteria among all sources of participant recruitment were men and women age 18 and over who had experienced ischemic or hemorrhagic stroke during the current episode of hospitalization (that is, they had not been discharged to a lesser level of care, such as a skilled nursing unit, prior to inpatient rehabilitation) and were admitted to a UPMC facility for inpatient rehabilitation. Ineligible were stroke patients with an active seizure disorder, as evidenced by a seizure within the past 30 days; a concurrent diagnosis of primary central nervous system disease associated with progressive impairment such as Parkinson's disease, multiple

sclerosis, or history of traumatic brain injury; or severe expressive or receptive language impairment. Determination of severe language impairment was based on scores greater than one standard deviation away from age-corrected norms on the repetition task of the Boston Diagnostic Aphasia Exam or the Token Test (Strauss, Sherman, & Spreen, 2006).

1.5.3.2 Recruitment Procedures.

Research staff visited or telephoned the study units at each site daily to ascertain whether stroke patients had been admitted in the previous 24 hours. Because members of the research team had clinical privileges at UPMC Mercy and UPMC Montefiore, tentatively eligible individuals were directly approached and consented by our team. At the remaining three sites, unit clinical staff invited patients to consider participation in stroke studies. Those who agreed were visited by members of the research team who described the studies for which each patient was eligible and obtained informed consent. Once enrolled, participants underwent a final screening assessment conducted via medical record review to confirm their eligibility.

1.5.3.3 Sample Size.

We anticipated that our recruitment efforts would yield approximately two-thirds of the final participant pool (approximately 150 participants), with the remaining one-third (75 participants) coming from Dr. Whyte's and Dr. Skidmore's studies, for a final projected *N* of 225. We based this sample size estimate on current best evidence from the literature as well as clinical practice at the study sites, to establish assumptions related to event rate and total R^2 for fitting binary logistic regression models.

Although falls have been estimated to occur during inpatient rehabilitation in 20-48% of patients (Suzuki et al., 2005), the observed falls event rate on UPMC Rehabilitation units

fluctuates from month to month. Between July 2009 and May 2011, falls at UPMC Mercy, the largest of the study sites, ranged from 4.44 to 16.05 falls per 1000 patient days. While aggressive fall prevention initiatives periodically implemented throughout the UPMC Health System may temporarily reduce the number of fall events on these units, UPMC RI quality improvement data indicate that these rates have tended to increase again over time, producing little permanent improvement in the occurrence of falls. To be appropriately conservative in sample size estimates, we used a 10% falls rate (i.e., baseline proportion of p_0=0.10) when performing sample size calculations. Many of the studies reviewed for this dissertation noted clinically meaningful effect sizes in terms of odds ratios (OR) between 2.20 and 5.00. Based on power considerations, we conservatively selected a target effect size of OR = 2.25, toward the lower end of the spectrum seen in the literature.

While physical, perceptual, functional, and cognitive impairments are separate constructs, there are relationships among them that must be considered. Literature suggests that in patients with stroke these domains are moderately correlated with each other, with associations ranging from approximately 0.2 to 0.6, depending upon how the construct has been operationalized (Mercier, Audet, Hebert, Rochette, & Dubois, 2001). When calculating sample size, we conservatively used an R^2 of 0.40 to account for the associations among predictors in our study.

Anchored in the aforementioned rationale for an estimated population fall occurrence rate of 0.10, sample size estimation was conducted using PASS for a multiple binary logistic regression model that conservatively assumed moderately correlated predictors (maximum R^2 = 0.40) at alpha = 0.05 (two-tailed), with a desired power level of 0.80 and a clinically meaningful effect size of OR=2.25 (i.e., medium effect size based on behavioral sciences). Based on these calculations, we initially projected that a sample of 225 participants would provide sufficient

power (.80) to test the hypotheses for both Aim 1 and Aim 2. However, because our final falls event rate of 15.5% was higher than projected, we achieved sufficient power to test our hypotheses with 180 participants.

1.5.3.4 Data Collection.

Consented participants underwent initial language screening to confirm their gross eligibility based on possessing the necessary language abilities to complete neuropsychological testing. We ascertained from the medical record basic sociodemographic information, current medications and comorbid conditions, stroke location and type of stroke, and the number and type(s) of fall prevention interventions utilized during inpatient rehabilitation. Participants with sufficient language skills received a baseline assessment of physical functioning, balance, visuoperceptual status (hemineglect), and various measures of general cognitive function and executive and non-executive function. This baseline assessment lasted approximately 2½ hours, and was administered by trained raters who underwent extensive inter-rater reliability testing.

During daily visits or calls to the units, the research staff asked the clinical staff about the occurrence of falls among study participants in the preceding 24 hours. The PI contacted the UPMC Risk Manager weekly to determine whether falls incident reports had been filed for any study participants. When a fall occurred, the research team completed the investigator-developed Falls Occurrence Record, noting the circumstances surrounding the fall and whether the patient incurred any injury during the fall.

1.5.3.5 Measures

Potential predictors and covariates as well as falls were conceptualized and operationalized as follows (see Table 3). Examples of non-standard or investigator-developed instruments are provided in Appendices B-F.

Table 3. Constructs, Instruments, Variables, and Level of Measurement

Construct	Instrument	Variable Name	Level of Measurement, Response Range
		Predictors	
Post-stroke cognition (non-executive function)	Repeatable Battery for Assessment of Neuropsychological Status (RBANS)	a. RBANS Modified Total Index Score	a. Approximately interval scale
Post-stroke cognition (executive function)	Delis-Kaplan Executive Function System (D-KEFS)	a. Color-Word Interference Inhibition Scaled Score b. Letter Fluency Scaled Score c. Category Fluency Scaled Score d. Trail Making Test Number-Letter Switching Contrast Score	a. Approximately interval scale b. Approximately interval scale c. Approximately interval scale d. Approximately interval scale
Balance impairment	Chedoke-McMaster Stroke Assessment Postural Control subscale	a. Postural Control	a. 1-7 approximately interval scale (1 = poor postural control, through 7 = can complete 2 or 3 dynamic standing balance activities)
Visuospatial hemineglect	Line Bisection Test (LBT)	a. Average percent deviation (from true center)	a. 0.00-100.00 ratio scale
ADL performance deficit	Functional Independence Measure (FIM); collected from medical record	a. mFIM (sum of 13 motor FIM items) b. cFIM (sum of 5 cognitive FIM items)	a. each item 0-7 approximately interval scale (higher number = better) b. mFIM 0-91 approximately interval scale (higher number = better) c. cFIM 0-35 approximately interval scale (higher number = better)
		Covariates	
Age	From medical record	a. Age (in years) at enrollment	a. Ratio scale (≥18)
Gender	From medical record		a. Nominal (1=Male; 2=Female)
Education	Study demographic information form	a. Years of education	a. Ratio scale
Co-morbidities	Cumulative Illness Rating Scale modified for geriatric participants (CIRS-G), completed using medical record data	a. Severity of illness burden	a. 0-52 approximately interval scale
Depressive symptoms	Hamilton Rating Scale for Depression (HRSD)	a. Severity of depressive symptoms	a. 0-54 approximately interval scale (0=clinically insignificant depressive symptoms; 54=severe depressive symptoms)

Construct	Instrument	Variable Name	Level of Measurement, Response Range
Stroke etiology	From medical record	a. Stroke etiology	a. Nominal (1=ischemic; 2=hemorrhagic)
Stroke location	From medical record	a. Stroke location (hemisphere)	a. Nominal (Left; Right)
Stroke type	From medical record	a. Stroke type	a. Nominal (1=cortical; 2=subcortical; 3=cortical/subcortical; 4=brainstem or cerebellar)
Stroke Severity	National Institutes of Health Stroke Scale (NIHSS)	a. Severity of stroke-related impairment	a. Ratio scale (0-42; 42=most severe stroke)
Intervention group	Intervention vs. control group randomization in Enhance study	a. Group membership for intervention study	b. Nominal (1=Enhance Group 1, 2=Enhance Group 2, 3=Non-Enhance)
Fall prevention interventions	From medical record	a. Number of interventions used	a. 0-15 ratio scale (lower number = fewer discrete types of interventions used)
		Outcome	
Falls	Fall Occurrence Record	a. Fall	a. Nominal (1=yes; 2=no)

Balance impairment. The Postural Control subscale of the Chedoke-McMaster Stroke Assessment (CMA) assesses balance impairment measured on an approximately interval 7-point ascending scale, where 1 indicates poor postural control and 7 indicates that the participant can complete at least two out of three specific dynamic standing balance tasks. In the stroke population, the Postural Control subscale of the CMA has shown substantial reliability, with intra-class correlation coefficients of 0.96 (95% CI, 0.93-0.98) for intra-rater reliability and 0.92 (95% CI 0.84-0.96) for inter-rater reliability (Gowland et al., 1993). The Postural Control subscale of the CMA has also been compared to the Fugl-Meyer Test, a clinical "gold standard" test designed to measure similar impairments. The correlation between the CMA Postural Control subscale and the balance items on the Fugl-Meyer was 0.84, $p < .01$(Gowland et al., 1993), suggesting that the CMA is valid and appropriate for use in measuring postural control in the post-stroke population.

Visuospatial hemineglect. The Line Bisection Test (LBT) provides a measure of visuospatial inattention, commonly referred to as hemineglect (Schenkenberg et al., 1980). The participant is presented with a paper containing 18 horizontal lines of various lengths and is asked to bisect each stimulus line by drawing a hash mark or slash in the middle of each line. Patients with left sided visuospatial hemineglect tend to bisect the lines to the right of the true center of the stimulus line, while those with right sided neglect tend to bisect the lines to the left of the true center of the stimulus. We utilized an average Percent Deviation Score as a ratio-level variable quantifying visuospatial hemineglect. Test-retest reliability of the LBT ranges between .84 and .93 (Lezak, Howieson, & Loring, 2004). This test has also been shown to reliably distinguish between right hemisphere stroke patients demonstrating visual neglect and inattention on functional tasks in rehabilitation therapies, *phi* = 0.84 (Schenkenberg et al., 1980).

ADL performance deficit. The Functional Independence Measure (FIM) is used to assess functional ability, and this assessment is performed for all patients upon admission to UPMC rehabilitation units. All members of the clinical team are trained in FIM rating, and they are credentialed by the Uniform Data System for Medical Rehabilitation (UDS^{MR}), creator of the FIM instrument, thus assuring the reliability of FIM scores gleaned from the participant's clinical record. The FIM evaluates 18 motor and cognitive activities of daily living (for example, bathing, dressing, toileting, locomotion, and communication function) on an approximately interval 7-point scale. A score of 7 indicates complete independence for that activity (that is, the participant performs 100% of the effort required to complete the task), 3 indicates the participant can perform > 50% of the effort required but less than 75% effort, and 1 indicates complete dependence (participant performs 0% effort to complete the task). Each item score can be used alone. In addition, the total FIM can be summed (tFIM), and motor and cognitive tasks can be summed to a Motor FIM (mFIM) score and a Cognitive FIM (cFIM) score, respectively. Internal consistency of the FIM items in the stroke population is high (Cronbach's alpha = 0.94); construct validity (convergent and discriminant) of each item as well as of the overall FIM scale is also moderately strong (Hobart et al., 2001). The FIM provides a measure of functional ability particularly related to mobility, activities of daily living, and communication/global cognition ability. Moreover, the FIM is widely used in inpatient rehabilitation, as FIM scores must be submitted to the Centers for Medicare and Medicaid Services to determine payment rates for each patient. We used the mFIM as our summary measure of ADL disability.

Post-stroke cognition (non-executive function). The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) is a brief (20-30 minute) measure of non-executive cognitive function that provides approximately interval-level summary scores in five areas of

function: immediate memory, visuospatial/construction, language, attention, and delayed memory. The domain scores can also be combined to obtain an overall score, or Modified Total Index Score, which is the measure we used. The domain and index scores are age-normed for the general population. This instrument has been validated for use in the stroke rehabilitation population; construct validity (both convergent and discriminant) of the RBANS subscales was acceptable in a stroke rehabilitation population, with Pearson's r generally ≥ 0.24, $p < 0.05$ for all subtests except attention (Larson, Kirschner, Bode, Heinemann, & Goodman, 2005) when correlated with other standard neuropsychological tests.

Post-stroke cognition (executive function). The Delis-Kaplan Executive Function System (D-KEFS) is a test of executive function that has been age-normed and found appropriate (valid) for use with people ages 8 through 89 (Homack, Lee, & Riccio, 2005). The test includes versions of several 'gold standard' neuropsychological tests of executive function, including the Stroop Test and the Trail Making Test. The D-KEFS transforms each subtest to a uniform scaled scoring system that is co-normed on the same large sample (Delis, Kaplan, & Kramer, 2001), thus facilitating comparison of scores across domains of executive function. In this study we used only the Color-Word Interference (Stroop) Inhibition Scaled Score; the Verbal Fluency test's Letter Fluency Scaled Score and Category Fluency Scaled Score; and the Trail Making Test Number-Letter Switching Contrast Score of the D-KEFS. Each domain score furnishes an approximately interval-level summary score; we also derived an overall executive cognitive function score by computing the mean of the three age-normed subscale scores. Psychometric properties of the D-KEFS have not been specifically investigated in adult stroke patients; however, the test has been studied in various populations that are likely to include stroke patients (e.g., patients with frontal lobe lesions, prefrontal lesions, subcortical ischemic changes, and

lateralized right hemisphere damage) and found to be acceptable (Delis, Kramer, Kaplan, & Holdnack, 2004). Thus, while the psychometric properties of the D-KEFS specifically in the stroke population should be tested, there is reasonable support for its use in this study, as it is reliable and valid in similar populations that likely include some persons with stroke.

We also considered using the Executive Interview (EXIT) (Royall, Mahurin, & Gray, 1992) or the Quick EXIT (Larson & Heinemann, 2010), a brief subset of items on the EXIT, as an overall executive function score. The EXIT is a 25-item, performance-based test administered by a trained rater; it was developed to be a brief screen for the presence of executive dysfunction. Each item is scored on a three-point, Likert-type scale in which 0 indicates a correct response, 1 indicates either a partially correct response or a correct response after verbal prompting by the examiner, and 2 indicates either an incorrect response or a complete lack of response.

The Quick EXIT is a 14-item subset of the EXIT that was developed to be a less burdensome test, particularly for clinical populations with low tolerance for extended testing sessions (Larson & Heinemann, 2010). Psychometric properties of the EXIT have been established in a variety of clinical populations, including older adult retirement community residents (Royall, et al., 1992), mildly demented older adults (Stokholm, Vogel, Gade, & Waldemar, 2005), and depressed older adults with a recent suicide attempt (Dombrovski et al., 2008). The psychometric acceptability of the Quick EXIT was established in a sample of patients with acquired brain injury from either stroke or traumatic brain injury (Larson & Heinemann, 2010a).

We collected EXIT scores (and derived Quick EXIT scores) for a subset of the participants in our sample. However, in a recent examination of the reliability and validity of both the EXIT and Quick EXIT in a sample of older adults (see Appendix G for Manuscript #2),

we concluded that both the EXIT and Quick EXIT may measure global cognition, with a small executive component, rather than evaluating executive function specifically. We thus elected to use the more 'purely executive' D-KEFS tests for this investigation, to elucidate the distinct contributions of both nonexecutive cognitive function and executive cognitive function to our model.

Selected demographics. Age and education may be related to various predictors, especially cognitive abilities (Garcia, Leahy, Corradi, & Forchette, 2008; Lee, Kawachi, Berkman, & Grodstein, 2003); thus, we controlled for both in all analyses, using age in complete years at last birthday and self-reported years of complete education as continuous ratio-scaled variables. Similarly, gender may be related to falls (Nyberg & Gustafson, 1997) and thus was also controlled for, using a categorical, nominally scaled gender designation.

Comorbidities. We collected data regarding both the number of comorbidities and the cumulative burden of these illnesses using the Cumulative Illness Rating Scale that has been modified for geriatric participants (CIRS-G) (Miller et al., 1992). The number of comorbidities (CIRS-G count) is ratio-scaled based on summed 'yes' responses to 14 illness categories (heart, vascular, hematopoetic, respiratory, eyes/ears/nose/throat/larynx, upper gastrointestinal, lower gastrointestinal, liver, renal, genitourinary, musculoskeletal/integumentary, neurological, endocrine/metabolic/breast, and psychiatric). The cumulative illness rating (CIRS-G burden) is an approximately interval-level composite score representing summed scores on a 4-point, ordinal-item severity score for each of the 14 illness items. Scoring is done by a physician or nurse rater using a standardized scoring manual. In a sample of outpatients from a geriatric medical clinic, the CIRS-G demonstrated good inter-rater reliability (ICC = 0.78 for the severity scale, and ICC = 0.81for the number of comorbidities endorsed). Concurrent validity was

demonstrated through significant positive correlation between severity of comorbidity and amount of self-reported ADL disability, $r = 0.58$, $p < 0.02$. Using a one-way analysis of variance, researchers demonstrated that the CIRS-G could accurately differentiate healthy older adult controls from both older adults with depression and older adult medical clinic patients, $p = .0001$ (Miller et al., 1992). Because the count of comorbid conditions and the burden score were highly correlated, in order to avoid issues of multicollinearity we entered only the CIRS-G burden score, as a measure of the severity of comorbid conditions, as a covariate in the final model.

Depressive symptoms. Since falls may be associated with the presence of depressive symptoms (Rubenstein & Josephson, 2006), we controlled for depression using the Hamilton Rating Scale for Depression, or HRSD (M. Hamilton, 1960), a 17-item, self-report questionnaire administered by a trained interviewer, in which each item is rated on an ordinal severity scale. The item scores are summed to yield an approximately interval-level total depressive symptoms score. Inter-rater reliability correlations for the HRSD are high ($r = .84$ -.90) (Hamilton, 1960), and a factor structure consistent with the primary attributes of depression (for example, depressed mood, loss of interest in activities, insomnia, psychomotor agitation or retardation) has been established (Hamilton, 1967).

Stroke etiology. This is a nominally scaled categorical variable indicating whether the stroke was ischemic or hemorrhagic.

Stroke location. We categorized the laterality of stroke using a nominally scaled variable to indicate whether the stroke location involved the left or right side of the brain.

Stroke type. This is a nominal, 4-level variable coded as cortical, subcortical, cortical/subcortical, and brain stem or cerebellar, according to the region of the brain where the stroke primarily occurred.

Stroke severity. Stroke severity was quantified using the National Institutes of Health Stroke Scale (NIHSS), a 15-item, performance-based measure of motor, cognitive, and language impairments evident in acute stroke. Item scores are summed to obtain a single, approximately interval-scaled score of stroke severity (ranging from 0 to 42), with higher values indicating more severe stroke impairment. The NIHSS has acceptable reliability. One study found inter-rater reliability using Cohen's κ = 0.69, and test-retest reliability was κ = 0.66-0.77. Another study noted high inter-rater reliability (using the intraclass correlation coefficient) of 0.93; test-retest reliability was also high, κ = 0.95 (Kasner, 2006). Construct validity of NIHSS was also acceptable when correlated with lesion size, r = 0.68, and with functional outcomes three months post stroke, r =0.79 (Brott et al., 1989).

Fall prevention interventions. We recorded fall prevention interventions employed during the participant's rehabilitation stay that were documented in the clinical record, including restraints (e.g., rear fastening safety belts and enclosure beds), restraint alternatives (e.g., bed and chair alarms), or other strategies (e.g., lift equipment or special transfer techniques). We quantified the prevention intervention variable using a ratio-scaled count of the number of different intervention types documented in the medical record at any time during rehabilitation.

Falls. This primary outcome variable, based on documentation on the Falls Occurrence Record and defined as any unplanned contact with the floor of any body part, excluding the feet, was dichotomized into participants who experienced at least one fall during the inpatient

rehabilitation stay and those without falls, yielding a nominally scaled binary variable. We also collected the total number of falls incurred for each participant, a ratio scaled count variable.

1.5.3.6 Data Analysis

Descriptive statistics. After determining the number of participants who fell at least once and the total number of falls in the sample during the study, we computed the number of falls per person, the frequency and proportion of participants who experienced any falls versus no falls, and the corresponding 95% confidence interval for this proportion. We characterized the demographic and clinical characteristics of the sample using means and standard deviations, medians, and ranges for the whole cohort and for fallers versus non-fallers. As only three participants had more than one fall, we lacked sufficient range and distribution in the number of falls per participant to explore differences between those participants with one fall versus those with multiple falls. We examined demographic and clinical differences between the outcome groups using t-tests of group means for variables with a reasonably normally distributed distribution, the Mann-Whitney *U* test for medians between groups for non-normally distributed variables, and the chi-square test of independence for comparisons of the groups on nominally scaled variables such as stroke location. Because participants were pooled from five separate studies, and from five separate UPMC inpatient rehabilitation programs, we also examined demographic and clinical characteristics among the studies.

Data screening procedures. Initially we screened for missing data among predictor, covariate, and outcome variables. Because of the process we used to identify falls and because the study sites endorse an aggressive incident reporting philosophy in which staff are accustomed to reporting all potential safety incidents including falls, when we found no falls documentation

we considered it reasonable to assume that no fall had occurred, and the falls data were coded accordingly.

Missing data among neuropsychological, perceptual, depression, and co-morbidity variables were coded based upon reasons for missing values. For participants unable to complete a cognitive test because of severe cognitive impairment, we imputed their test value by taking the worst score among all participants, and adding one more incorrect response, and thus did not consider these values to be missing data. A similar approach is employed by other researchers at the University of Pittsburgh, and is similar to the convention used by the Late Life Mood Disorders data center, the custodian of the database for the present study (Butters, 2008). Literature also supports the use of the worst score in imputation of missing neuropsychiatric variables (Smeding & de Koning, 2000).

We had a high rate of missing data for several measures, including the NIH Stroke Scale, the HRSD, and the CMA., We elected to pool data from 5 sources to achieve adequate power, even though we would have missing data for some variables, because the Stroke Education study did not include the NIHSS, CMA, or HRSD. Further, some participants were missing values on key variables because physical impairment prevented completion of some tests. For example, people with strokes affecting their dominant hand and people with visual deficits were sometimes unable to complete the Trail Making Test section of the D-KEFS and the Line Bisection Test. A small proportion of participants refused to complete portions of the test battery. Refusal to complete the test may not reflect random missingness, but may instead reflect important differences from participants who did complete the tests, including cognitive compromise, fatigue, or illness. Table 4 summarizes the amount of missing data originally present for each variable.

Table 4. Amount and Reasons for Missing Data among Predictors and Covariates (N=180)

Variable	Missing, Undetermined Circumstances[a]	Participant Refused to Complete	Unable to Complete due to Physical Impairment	Unable to Complete due to Cognitive Impairment	TOTAL MISSING
NIHSS	56 (31.1%)	1 (0.6%)	0	0	57 (31.7%)
CMA Postural Control	27 (15.0)	1 (0.6)	0	0	28 (15.6)
HRSD	36 (20)	3 (1.7)	1 (0.6)	2 (1.1)	42 (23.4)
CIRS-G Burden Score	37 (19.6)	0	0	0	37 (19.6)
LBT Percent Deviation	8 (4.5)	4 (2.2)	3 (1.7)	6 (3.3)	21 (11.7)
RBANS Modified Total Index Score	10 (5.6)	5 (2.8)	5 (2.8)	3 (1.7)	23 (12.8)
Color Word Interference Inhibition Scaled Score	7 (3.9)	2 (1.1)	6 (3.3)	26 (14.4)	41 (22.8)
Letter Fluency Scaled Score	39 (21.7)	1 (0.6)	0	0	40 (22.2)
Category Fluency Scaled Score	39 (21.7)	1 (0.6)	0	0	40 (22.2)
Trail Making Test Number-Letter Switching Contrast Score	7 (3.9)	9 (5.0)	17 (9.4)	30 (16.7)	63 (35.0)

[a]The NIHSS, CMA, HRSD, and CIRS-G were not included in the original protocol of the Stroke Education study (17% of the sample). Other reasons for missingness in this column include the examiner not completing the test due to lack of good subject effort, or inability to test the subject despite multiple attempts (e.g., subject was medically ill).

We evaluated whether missingness in any of our predictors or covariates was significantly associated with key sociodemographic and clinical characteristics or with key predictors in our proposed model. Missingness was not associated with age, gender, stroke type, hemisphere, or etiology, but it was significantly associated with stroke severity (NIHSS) and many of the cognitive variables. Given these associations, we concluded that data were not

missing completely at random, and thus we employed multiple imputation methods prior to analysis to derive the most probable scores for the missing values, based on relevant predictors, for all missing values except those for cognitive variables in which the participant was too cognitively impaired to complete the test (as described above). During model building for hypothesis testing, we also completed a sensitivity analysis for any imputed variables that were significant in the final model, to identify whether the observed effect was still present with the original, non-imputed version of those variables.

FIM data regarding ADL performance are used by the Centers for Medicare and Medicaid Services (CMS) to determine facility payment for inpatient rehabilitation hospitalization, and they are legally required to be complete. We had no missing data for any of the FIM items. Missing covariate data were minimal, as most of these data (age, gender, stroke type, stroke location, medical history of comorbid conditions, fall prevention interventions) are extant in participant medical records and were located via record review if missing from the study database.

After addressing missing data, we screened the data to assure that assumptions for multiple logistic regression were met. Specifically, to ensure independence of the error terms, we first carefully screened and cross-referenced participants from the five studies comprising our participant pool, to identify and eliminate participants enrolled in multiple studies. We also graphically plotted residuals of predictors and covariates against participant ID to identify patterns indicating potential dependence in the data. No issues were identified related to independence.

Next, we assessed linearity in the logit of the outcome variable, falls, using the Box-Tidwell method. We confirmed linearity in the logit for the probability of a fall for all of the

continuous predictors or covariates, so no variable transformations were required. We then evaluated the degree of multicollinearity among the continuous predictors, each of which is approximately interval-scaled. We examined the squared multiple correlations (SMC) between predictor variables re-expressed as tolerance indices and variance inflation factors. For categorical covariates, we evaluated the tolerance indices and variance inflation factors against the continuous predictors using numerical values for the various categories, comparing against the reference group, which was coded as 1. Not surprisingly, we discovered multicollinearity between the CIRS-G count of comorbid conditions and the CIRS-G burden score, so the burden score was chosen as the variable of interest for modeling. Further, multicollinearity between the cognitive FIM score and the RBANS total score was discovered. Thus, when modeling, we included the RBANS as our sole measure of non-executive cognitive function. No other evidence of multicollinearity was identified.

Finally, we examined the solution for the presence of outliers. Using standardized residuals, we examined leverage statistics to determine whether particular cases exhibited unduly large residuals in either predictors or outcomes, and we examined influence statistics to determine whether particular cases exerted undue influence on the regression coefficient, indicating that they could be outliers to the solution. No univariate outliers were identified. To examine the possibility that certain cases were multivariate outliers, we computed Mahalanobis' distance, in which significant results indicate that residuals are an extreme distance from where the model would predict. We also examined these distances graphically to aid in determining which cases were problematic. No issues involving multivariate outliers were identified.

Analysis for hypothesis testing. Aim 1: To evaluate whether the severity of impairment in post-stroke cognition significantly predicts falls during inpatient rehabilitation among adults with

ischemic or hemorrhagic stroke, we first performed univariate logistic regression analyses between each cognitive predictor (the summed total RBANS score and each D-KEFS scale) and the falls occurrence outcome, to obtain an initial estimation of the strength of prediction between post-stroke cognition and falls. Because we hypothesized (H1a) the existence of a positive linear predictive relationship between post-stroke cognition and occurrence of falls, we expected that the predictive relationships between RBANS and D-KEFS subscale and summed variables would be stronger than the predictive relationships between the other independent variables in these initial regression models (H1b).

We also performed a series of bivariate nonparametric correlations (for continuous variables) or cross-tabulations with chi-square (for categorical variables) between each covariate and predictor of interest and the binary outcome of falls occurrence, to identify candidate covariates and likely predictors to include in complex modeling to control for the effects of potential covariates. The level of statistical significance was considered to be $\alpha = 0.05$ for all hypothesis tests in this analysis. However, when selecting covariates to include in our preliminary model, we employed a generous significance threshold of $p < .30$ for the relationship between covariates or predictors and the falls outcome. We included some covariates regardless of whether they met the inclusion threshold, such as age and sex, because they are typically included in most fall risk analyses found in the literature.

To test H1b, because balance impairment, hemineglect, and ADL performance deficit have been shown in the literature to be related to falls and to be moderately correlated, we entered these variables together in a second block, regardless of the degree of significance of their univariate ability to predict falls in our sample. We then sequentially entered cognitive predictor variables regardless of their initial relationship with the outcome variable, due to

theoretical considerations and our hypothesis. We entered non-executive cognitive function variables first, then executive cognitive function variables. We then repeated the regression analysis, but entered the hypothesized and correlated covariates into the logistic regression model in one block before sequentially entering the other predictors as described for testing H1a. The Hosmer and Lemeshow test of goodness of fit was examined to assess model fit. We obtained a nonsignificant χ^2 statistic for our regression model, indicating that the expected frequencies based on predicted probabilities from the fitted model closely matched observed sample frequencies and suggesting that the computed model fits our sample data.

We also examined the omnibus tests for the set of model coefficients, in which a significant result for each entry step would also indicate that at least one of the regression coefficients is significantly different from the null value of zero. We examined differences in the model coefficients and the change in the pseudo R^2 (Nagelkerke R^2) between the entry blocks to determine whether non-executive cognitive function, then executive cognitive function, added to the prediction of falls provided by balance impairment, hemineglect, and ADL performance. Consistent with H1b, we expected that the severity of executive dysfunction would account for larger changes in the pseudo R^2 in the log probability of falling than would the severity of non-executive dysfunction. Throughout the modeling process, we assessed to identify poorly fit and influential predictors and covariate patterns by computing influence diagnostics and deviance statistics, and by examining studentized residuals using the Pearson χ^2 and the deviance χ^2 to identify particular covariate patterns that appeared to exert undue influence on the model. We graphically examined plots of the residuals and determined that there were no poorly fit or highly influential covariate patterns.

Aim 2: To determine whether executive dysfunction moderates the relationship between physical (impaired balance), perceptual (hemineglect), and functional (ADL performance deficit) abilities and falls during inpatient rehabilitation, we performed a multivariate logistic regression. Covariates significantly related to falls (determined univariately, as noted above) were entered as a block in the first step of the model, followed by sequential entry of each predictor of interest (balance impairment, hemineglect, and ADL performance deficit). Third, we sequentially entered non-executive, then executive cognitive function variables individually. Lastly, interaction terms comprised of each predictor of interest by executive cognitive function variables were entered. We assessed model fit as described above for H1. To test H2, we used the Wald test of the significance of the pooled regression coefficients obtained via multiple imputation. A χ^2 Wald statistic significant at the 0.05 level indicated that at least one of the predictors in the tested model significantly predicted the dependent variable, occurrence of a fall.

Of particular interest were significant interactions involving potential predictors and the outcome of interest. Statistical significance for the interaction between any measure of executive cognitive function and a predictor variable indicates that the probability of experiencing a fall for a participant differs depending upon the level of executive cognitive dysfunction present in the participant for a specific aspect of executive function. We examined the odds ratios of each predictor and each interaction to determine the relative importance of each variable to the predictive ability of the model. We hypothesized (H2) that executive dysfunction would significantly moderate the relationship between balance impairment, hemineglect, ADL performance deficit, and falls. Thus, we expected that the interaction term between executive cognitive function and the block of other predictors of interest would have the greatest likelihood

ratio, indicating that the interaction of executive cognitive function and other known fall risk factors is the most important determinant of falls in this setting and population.

Finally, we examined the significance of the Wald statistic for each parameter in the model to determine which predictors are the most important in the model. This was accomplished by sequentially dropping predictors from the model and examining the change in the log likelihood. Predictors with nonsignificant likelihood ratio chi-square statistics were considered to not add to the model and were dropped, yielding a more parsimonious model.

1.5.4 Research Participant Risk and Protection

Human subject involvement and characteristics. Participants were 180 men and women age 18 and older who had sustained a stroke and were admitted to an inpatient rehabilitation unit in one of five hospitals (Mercy, Montefiore, Passavant, Saint Margaret, and McKeesport) of the University of Pittsburgh Medical Center (UPMC). We recruited 21 subjects directly into the proposed study, with data for the remaining 159 participants drawn from Dr. Whyte's and Dr. Skidmore's studies.

Inclusion and exclusion criteria. Included were men and women age 18 and older who experienced ischemic or hemorrhagic stroke within the current hospital stay (without having been discharged to skilled nursing or to home) and were admitted to inpatient rehabilitation following the stroke. Excluded were stroke patients who met the following criteria:

a. active seizure disorder not controlled by medication (as evidenced by a seizure within the previous 30 days)

b. diagnosis of another central nervous system disease such as Parkinson's disease, multiple sclerosis, or history of traumatic brain injury

c. severe expressive or receptive language impairment, as evidenced by a score greater than 1 standard deviation away from age-corrected norms on the Token Test and the Boston Diagnostic Aphasia Examination verbal repetition task.

In addition to these criteria, participants were required to speak English in order to complete the baseline test battery. There were no study assessments or procedures that would pose any risks to pregnant women or women of childbearing age using contraception.

Sources of materials. Data were obtained for the specific purposes of this study from research participants and their identified informants through interviews and questionnaires as well as review of participants' medical records.

Potential risk. There was minimal risk associated with participation in this study. Participants could experience psychological distress (e.g., emotional discomfort, fatigue, or anxiety) as a result of providing demographic information or participating in data collection pertaining to impaired balance, hemineglect, ADL performance deficit, and cognitive function, or when recalling and describing the circumstances of falls, for those participants experiencing a fall (15.5% of our final sample). Participants were afforded the opportunity to rest during testing, to take a break, or to discontinue tests and other data collection that they deemed burdensome or upsetting, to minimize the chance of distress.

1.5.4.1 Adequacy of Protection Against Risks

Recruitment and informed consent. Participants were recruited from five inpatient rehabilitation units under the auspices of the UPMC Rehabilitation Institute. The 5 co-occurring stroke rehabilitation studies at UPMC were granted a HIPAA waiver by the University of Pittsburgh's

Institutional Review Board (IRB), as their respective PIs have clinical responsibilities on the rehabilitation service at UPMC. The research team met with patients who grossly met eligibility criteria based on clinical presentation to assess their willingness to learn about research participation opportunities.

Patients wishing to consider research participation were provided detailed information regarding the various stroke research projects occurring at UPMC, and they were informed of the screening assessments and study design and procedures (e.g., purpose of study, risk/benefits, nature of questions asked, time commitment) for the investigation(s) for which they were interested and eligible, and all questions were answered. Consistent with regulations of the University of Pittsburgh IRB, stroke patients who, in the opinion of the research staff, did not have the capacity to consent, were asked to assent to study participation, and written informed consent was then sought from the patient's legal representative as proxy.

All study procedures complied with HIPAA regulations. All information was kept strictly confidential: data were stored in locked cabinets with access limited to research staff; computer files were password-protected; and code numbers were used in lieu of identifying information on forms or in databases.

Protection against risk. Grace Campbell, the investigator who completed this dissertation, met weekly with Dr. Ellen Whyte and her research staff, in the context of Dr. Whyte's existing study team meetings, to review issues of participant safety during data collection for falls during inpatient rehabilitation and maintenance of participant confidentiality. All participants enrolled in Dr. Whyte's Enhance study, as well as those enrolled directly into Ms. Campbell's Falls Study, were reviewed in these meetings. Dr. Elizabeth Skidmore was also present at these meetings. In the event of a study participant experiencing a fall, the rehabilitation

unit clinical team managed post-fall diagnostic or treatment needs. This care was provided according to unit and facility policy. In addition, Dr. Judith Matthews met at least monthly with Ms. Campbell to discuss issues related to recruitment, maintenance of confidentiality, protection of participants, and conduct of the study, and she provided immediate telephone and email consultation as questions or concerns arose.

1.5.4.2 Data and Safety Monitoring Plan

The University of Pittsburgh Institutional Review Board (IRB) approved this study (see Appendices H and I for notification of IRB approval and IRB-approved consent forms, respectively). The protocol and consent documents were submitted to the IRB for yearly review and approval. Two unanticipated events were reported to the University of Pittsburgh's Institutional Review Board (IRB), consistent with their guidelines. In the first event, a research assessor inadvertently administered cognitive testing to a rehabilitation patient who had not consented to research participation. The second event involved misplaced, de-identified data collection forms discovered during a file completion audit. No further action was deemed necessary by the IRB. Ms. Campbell attended weekly meetings of the research staff for all stroke rehabilitation studies occurring at UPMC, for review of procedures pertaining to participant safety, maintenance of participant confidentiality, data integrity, and participant recruitment and retention.

1.5.4.3 Inclusion of Women and Minorities

Inclusion of women. Our intent was to recruit a sample whose gender distribution generally corresponded to the distribution of this characteristic in the stroke population at our recruitment sites, where 55% of patients are female. Our final sample was 47.8% female.

Inclusion of minorities. In 2006, the racial and ethnic composition of the population of Allegheny County was 13.3% African American, 1.2% Hispanic or Latino, 2.3% Asian, 0.2% American Indian or Alaskan Native, and 1.1% two or more races. For the City of Pittsburgh, the composition was 27.1% African American, 1.3% Hispanic or Latino, 2.7% Asian, 0.2% American Indian or Alaskan Native, and 1.6% two or more races (year 2000 statistics). We anticipated that at least 15% of the eligible sample for this study would represent a racial or ethnic minority and be predominately African American. No one was excluded from participation in this study based on race or ethnicity. Our final sample included approximately 18% minority participants, of whom all but one (a female of Asian descent) were African American (see Section 2.1 for further information regarding sample characteristics).

1.5.4.4 Inclusion of Children

Stroke is relatively rare in pediatric patients, and the pediatric stroke recovery trajectory is likely to differ significantly from that of adult stroke patients. Including children would have introduced excessive variation into the study. In addition, it is unlikely that sufficient numbers of children could have been recruited to permit meaningful statistical analysis. For these reasons, the age eligibility criterion was 18 years of age and older; no children were included in this investigation.

1.5.4.5 Vertebrate Animals (not applicable)

1.5.4.6 Select Agent Research (not applicable)

2.0 SUMMARY OF STUDY

This study was conducted with a sample recruited from the inpatient rehabilitation units of five UPMC facilities between March 9, 2009, and December 31, 2011. The final sample (N = 180) was pooled from five separate co-occurring studies pertaining to stroke rehabilitation. Achieving the necessary sample size took longer than expected, despite a higher fall event rate than had been anticipated, due to a slower than projected recruitment rate into all of the co-occurring stroke studies.

While the admission rate to the inpatient stroke rehabilitation service at all sites was sufficient, many prospective participants verbalized reluctance to participate in research in general. Reasons for refusal were not specified, but anecdotal information from the study team suggests that persons admitted for inpatient stroke rehabilitation felt ill, fatigued, overwhelmed by their situation, or reluctant to commit to anything that might interfere with their rehabilitative process, despite assurances that study evaluations would be scheduled around their rehabilitative care. Over the course of recruitment, we attempted to increase enrollment by relaxing eligibility criteria for all studies. In consultation with the research team's neuropsychologist, Dr. Meryl Butters, we changed the language ability screening testing to focus more specifically on the language skills needed to complete neuropsychological testing. This decision slightly improved our recruitment rate.

Another problem we encountered was the unanticipated amount of missing data that occurred because of the pooling of samples from 5 separate studies that did not all include every study instrument. To address missing CMA Postural Control scores, Dr. Skidmore and an expert neurological physical therapist from the UPMC Mercy clinical team developed a method to clinically derive the score from information gleaned from the medical record. This approach yielded few additional usable scores, largely because all of the information needed to accurately complete the CMA may be documented in the medical record, but such documentation is not required and was frequently missing.

Some participants refused testing on multiple occasions, citing fatigue or medical illness, which necessitated frequent rescheduling of testing sessions. Testing sessions with participants were difficult to schedule and reschedule due to the extensive amount of time spent in prescribed rehabilitation therapies and Medicare's stringent regulations about the number of hours per day that each patient must be documented as participating in skilled therapy. We worked closely with the clinical team to schedule testing and therapy sessions optimally for each participant, and unit therapists and nurses worked diligently trying to assure that participants were prepared for and adequately rested for testing sessions. Despite these efforts, it was common for participants to be too fatigued to complete the entire battery even in multiple sessions. We worked with the neuropsychologist and the testers to prioritize whenever possible the administration of measures most critical to the study: executive cognitive function, NIHSS, and CMA Postural Control.

Further complicating study assessment scheduling was the fact that our neuropsychology testers could not always accommodate the frequently-changing needs of our participants, so some test batteries could not be completed. These missing data required

extensive imputation, as already described, which may have introduced unintended error in our results.

We had originally intended to interview participants in the event of a fall, to obtain descriptive information regarding circumstances surrounding the fall occurrence. However, identifying falls in a timely fashion was challenging. The study team's plan to inquire daily about participant falls during phone or in-person contact with unit personnel while ascertaining new admissions proved impractical and difficult to implement. With IRB approval, the UPMC Risk Manager agreed to provide weekly reports of falls from each hospital's incident reporting system for participants in Dr. Whyte and Dr. Skidmore's co-occurring studies, but these reports were often unavailable until two weeks or more after the fall. Because post-fall interviews were often conducted a week or more after the fall, if they occurred at all (for example, participants may have been discharged, without our ability to follow up), accurate recall of details of the fall may have diminished appreciably. With our specific aims focused on fall occurrence (a binary yes/no variable) rather than circumstances surrounding the fall as the major outcome of interest, the post-fall interview was of secondary importance, providing other valuable data for future analysis.

In summary, the purposes of this study were to evaluate the extent to which post-stroke cognition predicts falls during inpatient rehabilitation, and to explore the nature of the relationships among impaired balance, visuospatial heminiglect, ADL performance deficit, non-executive and executive cognitive dysfunction, and falls during inpatient rehabilitation after stroke. A brief summary of findings related to each aim appears in Section 2.2 and Section 2.3, and a manuscript detailing these findings appears at the end of this chapter.

2.1 FINDINGS DESCRIBING THE SAMPLE

In the final sample (*N* = 180), 28 participants experienced at least one fall (proportion 0.156, 95% C.I. 0.1099 - 0.2188). Only three participants experienced two falls during inpatient rehabilitation and no participants experienced more than two falls, so all fall analyses were completed using a binary (yes/no) variable for fall occurrence. The median age of the largely white (82.2%) sample was 65.81 years (*IQR* 55.31-76.31years), and it was nearly evenly divided by gender (47.8% female). The sample was also highly educated, with 53.3% having more than 12 years of education.

Participants who fell were slightly less educated than those who did not fall. They also exhibited greater motor and cognitive disability according to their Functional Independence Measure (FIM) scores, and they experienced more severe strokes as indicated by significantly higher NIHSS scores. There was no significant difference between fallers and non-fallers regarding depression, comorbidity burden, and non-executive and executive cognitive function variables. Regarding differences among participants across the five co-occurring studies, there were no significant between-group differences for age, education, NIHSS, sex, race, proportion of falls, stroke type, or depression. Yet there were significant between-group differences for balance scores, the comorbidity burden score, motor FIM, and cognitive FIM. These differences are not unexpected, based on slight variations in the studies' eligibility criteria. There were slight differences across study sites regarding demographic and clinical characteristics which were not unexpected, whereas there were no differences in the occurrence of falls across studies or sites. Please see Table 5 in Manuscript #3 for a complete description of our sample's demographic and clinical characteristics as well as comparisons between fallers and non-fallers for all variables.

2.2 FINDINGS RELATED TO AIM 1

Aim 1: To evaluate the extent to which post-stroke cognition predicts falls during inpatient rehabilitation.

H1a: The severity of impairment in post-stroke cognition will significantly predict falls during inpatient rehabilitation among adults with either ischemic or hemorrhagic stroke, as indicated by a positive predictive relationship between post-stroke cognition and occurrence of falls in this setting and population.

H1b: Severity of executive dysfunction (difficulty with planning and problem solving, disinhibition, perseveration, and decreased cognitive flexibility) will be a stronger predictor of falls during inpatient rehabilitation than severity of non-executive dysfunction (deficits in attention, immediate memory, delayed memory, language, visuospatial function, and psychomotor processing speed).

Initial models in which non-executive cognitive function and executive cognitive function were univariately regressed on occurrence of falls showed that neither type of cognition directly predicted falls. Specifically, the RBANS Total Index Score (OR .98. 95% CI .95-1.01, p = .23) did not predict falls, nor did any of the executive function variables including the Color-Word Interference Inhibition Scaled Score (OR .95, 95% CI .86-1.06, p =.38), the Letter Fluency Scaled Score (OR .97, 95% CI .85-1.10, p = .62), the Category Fluency Scaled Score (OR .93, 95% CI .82-1.06, p = .27), or the Trail Making Test Number-Letter Switching Contrast Score (OR .93, 95% CI .84-1.03, p = .16). Thus, H1a was not supported.

When additional hypothesized predictors of falls (CMA Postural Control, LBT Percent Deviation, mFIM) and relevant covariates (age, education, sex, NIHSS, HRSD, CIRS-G burden

score, stroke location, stroke type, stroke etiology, and total count of fall prevention interventions) were added to a logistic regression model in which the non-executive cognitive variable RBANS Modified Total Index Score was entered, followed by executive cognitive function variables, we found no support for H1b. That is, in a full model adjusted for age, education, and various types of stroke attributes, executive function was not a stronger fall predictor than non-executive cognitive function (Nagelkerke R^2 increased only slightly, from .489 to .492 when non-executive cognitive function was added to the model, and it increased slightly more to .501 with the addition of executive cognitive functioning to the model). Comprehensive tables of univariate logistic regression results and bivariate correlation coefficients appear in Appendix J. The attached results manuscript reports adjusted and unadjusted odds ratios for all covariates and potential predictors of falls.

2.3 FINDINGS RELATED TO AIM 2

Secondary Aim: To explore the nature of the relationships among impaired balance, heminiglect, ADL performance deficit, executive cognitive dysfunction, and falls during inpatient rehabilitation after stroke.

H2 (exploratory): Executive dysfunction will significantly moderate the relationship between impaired balance, hemineglect, and ADL performance deficit and falls during inpatient rehabilitation.

Our initial regression model to test H2 included the same covariates (age, education, sex, NIHSS, HRSD, CIRS-G burden score, stroke location, stroke type, stroke etiology, and total count of fall prevention interventions) as in the above modeling performed to test H1a and H1b,

entered together in a single block, followed by the hypothesized predictors (CMA Postural Control, LBT Percent Deviation, mFIM, RBANS Modified Total Index Score, D-KEFS Color-Word Interference Inhibition Scaled Score, D-KEFS Letter Fluency Scaled Score, D-KEFS Category Fluency Scaled Score, and D-KEFS Trail Making Number-Letter Switching Contrast Score), each entered sequentially as separate blocks, and the interaction terms with each of the four executive function (D-KEFS) variables as an interaction with the other predictors of interest. None of the interaction terms was significant; thus, our results did not support H2.

The final, most parsimonious model of fall predictors included years of education, NIHSS, stroke hemisphere, total count of fall prevention interventions, and mFIM. The below-attached results manuscript (Manuscript #3) presents the odds ratios, confidence intervals, and *p*-values for the final model, as well as a discussion of our findings in light of current literature.

2.4 LIMITATIONS

This study was subject to several limitations. The first and potentially most serious limitation concerns the lack of representativeness of our sample with respect to the population of stroke survivors admitted to the study sites during recruitment. First, although communication deficits after stroke are common, estimated to occur in approximately 30% of persons with stroke (Engelter et al., 2006), moderate-to-severe communication deficit was grounds for exclusion. Our study assessments required grossly intact language ability; we estimate that one-third or more of potential participants were necessarily excluded from our sample. Second, , we suspected that our participants were less impaired than the larger pool of all stroke patients based on our recruitment patterns and clinical knowledge of the typical patient mix of the stroke

rehabilitation service. To explore this suspicion, we compared our sample to all persons admitted for inpatient stroke rehabilitation during our recruitment period, using age, mFIM, and cFIM from de-identified quality improvement data provided by the UPMC Rehabilitation Institute. While our sample was not significantly different from the population related to age (participant age M = 65.58 years, SD = 14.60; population age M = 69.95 years, SD = 14.64), our sample was significantly less physically impaired (participant mFIM M = 48.12, SD = 15.82; population mFIM M = 36.54, SD = 13.04), and less cognitively impaired (participant cFIM M = 24.91, SD = 5.54; population cFIM M = 20.10, SD = 7.34) than the stroke patient population from that same period, suggesting that these groups are not comparable.

This lack of representativeness of our sample may be secondary to our study design, as we required informed consent for participation because data for our key measures were not available through medical record review and could not be ascertained using de-identified data collection methods. We can only surmise that the older, more medically ill, more functionally impaired individuals admitted for stroke rehabilitation were more likely to decline research participation than their healthier and more able counterparts. Other stroke researchers (Grube et al., 2012) have noted a similar lack of representativeness when informed consent is required for study entry.

Our non-representative sample limits the generalizability of our findings and may also have contributed to our inability to reject the null during hypothesis testing due to the restricted ranges of key variables. Physical and cognitive impairments in our sample reasonably approximated a normal distribution, yet population means may be significantly lower than those of our sample. Indeed, our sample may have been significantly less impaired than the general stroke population, creating a floor effect by artificially obscuring the full range (especially of low

responses) for physical and cognitive tests among stroke rehabilitation patients. Because the entire range of responses seen in the stroke population was attenuated in our sample, associations between key variables may have been obscured. Restriction of range due to sampling bias can falsely deflate correlations between two variables if the range of one or both is attenuated in the sample (Tabachnick & Fidell, 2007), which may explain the lack of relationship found between key cognitive variables and falls. Such restriction of range could also have resulted in our failure to confirm findings by other researchers who have detected associations between balance impairment, hemineglect, and falls, and between relevant covariates (e.g., depression) and falls. Obtaining informed consent, on the other hand, was also a relative strength of this study, which stems from our decision to operationalize key variables using more sensitive and nuanced measures than are used in routine clinical care at our sites. Specifically, a relative strength of this study is that we attempted to use 'gold standard' measures to capture most purely the cognitive domains of interest. For a more detailed discussion of the potential sampling bias in this dissertation study, please see Manuscript #4, section 4.0.

Additional limitations stem from issues related to neuropsychological (cognitive) assessment. First, even though we excluded a substantial proportion (30%) of persons admitted for stroke rehabilitation because of moderate to severe aphasia, language deficits may still have confounded our results. Paper and pencil tests of executive cognitive function such as those used in our study dependent upon intact comprehension and expression abilities (Lezak, Howieson, & Loring, 2004a). Indeed, in our sample all of the D-KEFS variables were significantly correlated with language comprehension and expression FIM scores. While FIM scores have shown acceptable inter-rater reliability, methods of evaluating communication ability to arrive at the FIM score are unstandardized and open to clinician discretion, which may have introduced

subjectivity into the scores. We plan to obtain individual domain scores for the RBANS (currently our data set includes only the Modified Total Index Score) and correlate the language domains of the RBANS against our cognitive variables to investigate whether our cognitive scores are confounded by communication deficits.

Second, an irregularity in the administration and scoring instructions for the D-KEFS Color Word Interference Test, discovered by our consultant neuropsychologist, Dr. Meryl Butters, may have obscured an actual relationship between falls and this measure of impulsivity. Under the published administration and scoring instructions, scores for persons who complete the task quickly but inaccurately are not appropriately penalized, resulting in scores that cause these participants to appear less cognitively impaired than persons who complete the task more slowly but more accurately (Email communication from Meryl A. Butters, March 3, 2013). The test publisher is currently developing a correction factor for scoring the test. We plan to recalculate the Color Word Interference scores when the correction is available, and repeat our analysis.

A further limitation concerns conducting research in a clinical environment where the research team has little influence over standards of clinical practice. Over the course of the study, in response to pressure from the health system, restrictive policies intended to reduce fall rates were implemented on the rehabilitation units. For example, every stroke patient admitted for rehabilitation received a low bed, bed alarm, and chair alarm as part of routine care. These devices were often used for the duration of the patient stay in rehabilitation, rather than phased out as rehabilitation progressed, particularly at the largest two study sites. Patients were therefore not given an opportunity to assimilate new learning related to safety during concomitant removal of the alarms and other fall prevention devices. In addition, there was a shift in attending

physicians for the stroke service. Many of the new physicians were accustomed to practices on traumatic brain injury units, where physical restraints were used on nearly every patient.

Quality improvement data regarding restraint use were obtained from UPMC Mercy, but the available information is inadequate for estimating the true prevalence of restraint use and other fall prevention interventions in the population during our study period. Anecdotal information from the nursing and therapy clinical supervisors indicates that restraint use increased on the Stroke Unit over the course of our study. Low beds, alarms, and restraints may have reduced the occurrence of falls, perhaps contributing to our fall rate of 15.5% —a rate greater than projected but still considerably less than that reported in the literature. In contrast, in 1993 Rapport and colleagues noted that 47% of their stroke rehabilitation participants fell. Although fall prevention is clearly desirable as an overall goal, achieving it through the use of restrictive methods may be at the expense of the overall recovery and rehabilitation of our patients, and it may have contributed to a low event rate with related restriction in range of our outcome variable.

A final limitation of our study was our need to impute a large amount of missing data. Though multiple imputation is considered a valid approach for handling missing data (Tabachnick & Fidell, 2007), it assumes that sample participants with missing values statistically resemble participants with complete data on key variables. It is possible that our participants' imputed values, derived through five separate random samples drawn from participants with complete scores, were not an accurate reflection of their true test values, leading to erroneous conclusions that are not applicable to the population of persons undergoing inpatient stroke rehabilitation. Using sensitivity analysis, we found no difference in effects between original and imputed data, so it is unlikely that our conclusions were affected by errors in estimation for

imputation. Further discussion of the participant-related, clinical and institutional barriers to conducting this dissertation study can be found in Manuscript #4.

2.5 RECOMMENDATIONS

Future research should attempt to overcome the limitations of the present study, and further expand our understanding of the relationships we identified. While a relative strength of our study was the use of 'gold standard' assessments of balance, hemineglect, non-executive cognitive function, and executive cognitive function, participants may have found the additional two to three hours of testing time to be burdensome and tiring. Testing burden may have contributed to missing and unreliable data (please see Manuscript #4 for a discussion of the potential unreliability of our data), especially for cognitive tests, and it may have discouraged the oldest, most frail, and least functionally independent patients from participating.

Future studies could improve upon our methodology by streamlining data collection using standard clinical measures of balance (such as the Berg Balance Test or Chedoke-McMaster Stroke Assessment), hemineglect (such as the Star Cancellation Test or the Catherine Bergegos Scale), and cognitive impairment (such as the Montreal Cognitive Assessment [MOCA]). Further, clinical leaders and researchers could adopt documentation instruments that facilitate both groups' needs simultaneously, such as the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (Saver et al., 2012), which would permit pooling of data across rehabilitation sites for both research and clinical performance benchmarking, and eliminate the need for extra testing sessions that are tiring and difficult to schedule.

Studying falls in any inpatient setting is challenging. Because current hospital reimbursement structures are contingent upon reducing adverse patient outcomes, including injury from falls (Kruse, Polski, Stuart, & Werner, 2012), many hospitals have instituted aggressive fall prevention programs that utilize alarm belts, side rails, enclosure beds, and other restrictive devices. In addition, health care professionals are ethically bound to protect patients from harm and are thus motivated to prevent falls. Though we hesitate to recommend decreasing the use of restrictive fall prevention equipment, further exploration of the strong relationship we found between the use of fall prevention interventions and falls during rehabilitation is needed.

Indeed, our findings appear to challenge the commonly held notion that alarms and other such devices prevent falls. Because of the strong relationship we found between the number of fall prevention strategies used and the occurrence of falls, it is crucial to better understand the role of fall prevention devices in the occurrence of falls during inpatient rehabilitation. The temporal relationship between application of various interventions and the occurrence of falls must be identified. For example, it is unclear whether these devices were applied before any falls occurred, yet did not prevent falls; or, whether the devices were used after a fall occurred, to help prevent future falls. If these devices do not serve their intended purpose by preventing falls, but instead serve as an impediment to the rehabilitative process by blocking crystallization and carryover of skills learned, their clinical utility is questionable and their use should be re-evaluated. Exploring the clinical team's assessment and decision making process surrounding implementation of fall prevention interventions could further illuminate the role these devices play in falls and fall prevention. Identifying and exploring patients' perspectives on falls, their perceptions of fall risk after stroke, and their experiences related to fall prevention interventions

during rehabilitation, could also enrich our understanding of falls and fall prevention during inpatient stroke rehabilitation.

Additional research is needed to further explore the apparently complex relationship between cognitive impairment and falls. While some evidence suggests a relationship between cognitive impairment and falls in the stroke rehabilitation population (Nyberg & Gustafson, 1997; Rabadi et al., 2008; Suzuki et al., 2005; Teasell et al., 2002), our study was unable to replicate a relationship between the RBANS Modified Total Index Score or the D-KEFS (Color-Word Interference, Verbal Fluency, and Trail Making tests) and falls. The disparity between our results and those of others may be due to the previously discussed lack of representativeness of our sample relative to the population in inpatient stroke rehabilitation. The studies that found relationships between cognitive impairment and falls used measures collected as part of routine clinical care, or a brief testing battery, thus were able to include almost all persons admitted for stroke rehabilitation during the study. In contrast, we used a lengthy battery which, as we have discussed, may have contributed to our low recruitment rate and biased sample. Repeating our study using a more representative sample is indicated. Additionally, while we did not specifically measure the time between stroke onset and admission to rehabilitation, the typical interval for stroke onset to rehabilitation admission currently at our health system is approximately one week, while several of the studies listed here report onset to admission of two weeks (Rabadi et al., 2008), three weeks (Teasell et al., 2002), and nearly 8 weeks (Suzuki et al., 2005). Patients are admitted to rehabilitation much sooner after stroke currently than they were several years ago, which may lead to more impaired persons entering rehabilitation,alteration of the nature of associations between cognitive and physical impairments and risk of falls.

Some studies suggest a relationship between cognitive FIM scores (cFIM) and falls during stroke rehabilitation (Suzuki et al., 2005; Teasell et al., 2002). In the present study, we used gold standard cognitive tests to effectively isolate 'pure' measures of non-executive and executive function. Our data should be re-analyzed, substituting cFIM scores for RBANS and D-KEFS scores. Substantiating a relationship between cognitive FIM and falls would suggest that the cFIM, as rated by real-world experienced clinicians, captures aspects of functional cognition that gold standard tests of executive function do not. Further investigation would then be warranted, examining both the role of clinician judgment in cognitive evaluation during rehabilitation and the precise domains of cognitive dysfunction that contribute to 'risky' behavior leading to falls, as operationalized by cFIM scores

Rapport and colleagues (1993) have demonstrated the clearest empirical link between executive dysfunction and falls in stroke rehabilitation. In their study, one aspect of executive function, 'behavioral impulsivity,' isolated using an investigator-developed visual scanning task, was a strong fall predictor. Their results are echoed in a recent study of a newly developed fall risk assessment for stroke, in which 47.5% of persons who fell were rated by clinicians as being impulsive, whereas only 27.5% of persons who did not fall were so rated (Breisinger, Skidmore, Niyonkuru, & Campbell, under review). In contrast, the present study using three D-KEFS scales did not find the same relationship between impulsivity and falls. Our results could be due to our sample's much lower incident fall rate (15.5%, compared to 47% for the Rapport study), impeding our ability to detect small effects. An alternative explanation that should be explored, however, is that by isolating the behavioral manifestation of impulsive thought processes, these researchers may have captured an essential source of fall risk that may not be detected by the paper-and-pencil D-KEFS test.

Executive function is thought to be supramodal, i.e., discernible and consistent across a variety of situations or tasks (Lezak et al., 2004). Traditional tests of executive function are useful for identifying various cognitive deficits, tracking these deficits over time, and aiding in differential diagnosis. Yet, there is growing concern in the neurorehabilitation community that traditional tests of executive function may not fully capture clinically relevant real-world abilities and behaviors that result from impaired executive functioning. Indeed, the 'ecological validity' of numerous gold standard executive function tests, including the Stroop Color Word Interference Test, has recently been questioned (for example, see Dawson et al., 2009; Dimoska-Di Marco, McDonald, Kelly, Tate, & Johnstone, 2011; Mitchell & Miller, 2008; Rand, Rukan, Weiss, & Katz, 2009). In particular, relationships between Stroop scores and behavioral rating scales of impulsivity are not robust (Dimoska-Di Marco et al., 2011). The visual scanning task used by Rapport's group attempts to measure impulsive behavior, but it is a laboratory-based measure requiring sophisticated equipment that would be nearly impossible to implement in a clinical setting. Identifying alternative valid behavioral tests of executive function is paramount to replicating and extending Rapport's findings. One candidate may be the Virtual Multiple Errands Test, or MET (Rand et al., 2009), in which persons complete a series of complex life skills that involve planning, organization, and impulse control in a virtual environment. Additional research examining relationships between executive function and falls using performance-based, behavioral tests like the Virtual MET could shed further light on the complex relationships between cognition, behavior, and falls.

Finally, further exploration of the mechanisms underlying the strong predictive relationship we found between low levels of educational attainment and falls should be undertaken. There are three possible explanations for this relationship. One, it is possible that

more highly educated patients have a better social support network and better access to resources, possibly leading to decreased length of hospital stay and hence, a reduced window of opportunity in which to experience an inpatient fall. Two, more highly educated patients may have a greater cognitive reserve, which protected them from falls. The theoretical construct of 'cognitive reserve' (Stern, 2002; 2003) postulates that premorbid intelligence and education may explain variations in cognitive performance between individuals sustaining similar neurological injuries or diseases. Persons with greater education and/or greater premorbid intelligence (e.g., greater cognitive reserve) may have developed a greater number and complexity of synaptic connections, and/or more sophisticated, experientially-based, cognitive processing methods and problem solving skills pre-morbidly; hence, these high cognitive reserve persons will exhibit higher levels of cognitive function after neurological injury than will people with less 'reserve.' Reserve, often quantified as educational attainment, has been linked to improved long term survival and higher levels of cognitive function and to improved health outcomes after stroke (Ojala-Oksala et al., 2012). Unfortunately, there are no direct measures of cognitive reserve currently available (Jones et al., 2011); educational attainment is typically used as a proxy measure.

Three, educational attainment has been associated with increased disease susceptibility and poorer outcomes in various disease states (Manuck et al., 2005; Matthews, Flory, Muldoon, & Manuck, 2000; Muldoon, Mackey, Williams, Korytkowski, & Manuck, 2004). The relationship between educational attainment and these poor health outcomes has been linked to various neurobiological pathways including the sympathetic-adrenal-medullary (SAM) system, the hypothalamic pituitary adrenal axis (HPA) system, inflammatory and immune markers such as interleukin-6 (Matthews & Gallo, 2011), and the action of serotonin on the cerebral cortex.

(Manuck et al., 2005; Matthews, Flory, Muldoon, & Manuck, 2000; Muldoon, Mackey, Williams, Korytkowski, & Manuck, 2004). Linkages between various biological pathways, education (SES), and negative health outcomes are not well understood and require further research to develop our understanding of these mechanisms (Matthews & Gallo, 2011). In particular, a potential serotonin-falls relationship warrants further investigation, given the association between depression (also related to serotonin pathways) and falls both among persons with chronic stroke (Kerse et al., 2008) and older adults (Rubenstein & Josephson, 2006).

3.0 MANUSCRIPT #3: RESULTS MANUSCRIPT

3.1 ABSTRACT

Purpose: To investigate relationships among post-stroke non-executive and executive cognitive dysfunction, balance impairment, hemispatial neglect, and ADL impairment and the occurrence of falls; and to identify a parsimonious model that predicts the risk of falling during inpatient stroke rehabilitation.

Methods: Prospective observational study of persons admitted for inpatient stroke rehabilitation. Using multivariate logistic regression, we examined associations between cognitive, perceptual, and functional predictors and the occurrence of falls during inpatient stroke rehabilitation. We then adjusted the original model for relevant demographic and clinical characteristics including age, education, sex, stroke characteristics, and comorbidity burden. Using sequential backward elimination of nonsignificant predictors, we determined a final parsimonious model of fall prediction.

Results: Of 180 participants, 28 (15.6%) fell. Fallers were slightly less educated than those without a fall, and they had more severe strokes and were more functionally impaired. In the initial unadjusted model, ADL performance (motor FIM) was the only significant predictor of falls. In the model adjusted for covariates, significant predictors were low education, left

hemisphere stroke, brain stem/cerebellar stroke, and number of fall prevention interventions used during rehabilitation. Neither non-executive nor executive cognitive function predicted falls. The final fall prediction model included education, NIHSS, left hemisphere stroke, number of types of fall prevention interventions, and mFIM.

Conclusion: Contrary to other published literature, balance impairment, hemineglect, and cognitive impairment did not predict falls. Sampling concerns suggest that these results should be interpreted with caution. Additional research is needed to further elucidate the relationship between post-stroke cognition and falls.

3.2 INTRODUCTION

Falls are among the most commonly occurring complications of stroke (Moroz et al., 2004). Stroke affects 795,000 Americans annually (AHA, 2012) and leads to permanent disability for an estimated 450,000 individuals (Salter et al., 2007). Stroke-related falls occur at especially high rates in the inpatient rehabilitation setting, where incidence ranges from 20% to 48% (Suzuki et al., 2005). Up to one-third of those who fall sustain injuries such as fractures and hematomas (Teasell et al., 2002). Other deleterious consequences include decreased physical activity related to fear of further falls (Suzuki et al., 2005) and a diminished sense of dignity (Rapport, Hanks, Millis, & Deshpande, 1998).

Accurately identifying patients most likely to fall is vital to initiating appropriate, effective preventive interventions. Reasonably convincing evidence links balance impairment, hemineglect, and functional (activities of daily living, or ADL) disability with falls during stroke

rehabilitation. In contrast, altered cognition, which is a widely accepted risk factor for falls among older adults (Buracchio et al., 2011; Chen, Peronto, & Edwards, 2012; Muir, Gopaul, & Odasso, 2102; Rubenstein & Josephson, 2006), has not been adequately investigated for its role in falls during stroke rehabilitation. Specifically, the importance of executive cognitive dysfunction, estimated to affect 20% to 50% of persons with stroke (Jaillard et al., 2009; Pohjasvaara et al., 2002; Zinn et al., 2007) and encompassing higher order skills needed to control, integrate, and organize other cognitive abilities has not been clarified (Campbell & Matthews, 2010).

We undertook this observational investigation with stroke rehabilitation patients to investigate three aims: 1) to evaluate the extent to which cognitive dysfunction predicts falls, including whether executive cognitive dysfunction is a stronger predictor of falls than non-executive cognitive dysfunction; 2) to evaluate whether executive cognitive dysfunction moderates the relationship between other empirically established risk factors (balance impairment, hemispatial neglect, and ADL impairment) and the occurrence of falls; and 3) to identify a parsimonious model that predicts the risk of falling during inpatient stroke rehabilitation.

3.3 METHODS

3.3.1 Setting and Participants

This prospective observational study involved five inpatient stroke rehabilitation units of a large multi-hospital university health system in western Pennsylvania. Our sample (N = 180)

aggregated data from five co-occurring studies on the units between March, 2009, and December, 2011. All studies were approved by the Institutional Review Board of the University of Pittsburgh. All participants provided written informed consent or, in cases of decisional incapacity, proxy consent with participant assent was obtained.

3.3.2 Procedure

Patients were approached about participation shortly after admission to the rehabilitation service. Eligible for inclusion were patients admitted for a new ischemic or hemorrhagic stroke diagnosed based on clinical presentation or confirmed via imaging during the current hospitalization. Exclusion criteria included history of seizure within the previous 30 days or presence of traumatic brain injury or other brain disorders such as multiple sclerosis, Parkinson's disease, or brain malignancies. Participants were required to speak English and to demonstrate receptive and expressive language ability within 1 SD of age-corrected norms on the Token Test (Strauss et al., 2006) or the Boston Diagnostic Aphasia Examination Repetition Task (Strauss et al., 2006). Consented participants with acceptable language scores were administered a battery of physical and cognitive tests and monitored daily for the occurrence of falls during their inpatient stay. Data regarding their sociodemographic and health profile, stroke history, and exposure to fall prevention interventions were retrieved from the medical record. Falls data were gathered from the medical record and the hospital risk management report.

3.3.3 Measures

Covariates. Sociodemographic and clinical covariates included age (years), education (years), gender, stroke hemisphere, stroke etiology (ischemic or hemorrhagic), stroke type (cortical, subcortical, cortical/subcortical, or brain stem/cerebellar), and the number of types of fall prevention interventions implemented.

Predictors. We operationalized balance impairment using the 7-point Chedoke-McMaster Stroke Assessment (CMA) Postural Control subscale (Gowland, et al., 1993), with 1 indicating poor postural control. For the Line Bisection Test (LBT), a measure of visuospatial inattention, or hemineglect (Schenkenberg et al., 1980), participants were presented with a paper containing 18 horizontal lines of various lengths and asked to draw a mark in the middle of each line. The discrepancy between this bisection and the line's true center was recorded. We measured hemineglect using the average percent deviation for the overall LBT. The sum of 13 motor items (mFIM) on the Functional Independence Measure (Hamilton et al., 1987), a 7-point scale (7=complete independence) administered clinically on admission, was our measure of ADL performance deficit.

Post-stroke non-executive cognitive function was assessed using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) measures of immediate memory, visuospatial/construction, language, attention, and delayed memory, with domain scores combined to obtain an age-normed overall Modified Total Index Score (Larson et al., 2005). Executive function was evaluated via the Delis-Kaplan Executive Function System (D-KEFS), an age-normed test of executive functions valid in people ages 8-89 years (Homack et al., 2005) that employs a uniform scaled scoring system across the component subtests, co-normed on the same large sample (Delis et al., 2001), facilitating comparison of scores across domains of

executive function. We used the Color-Word Interference (Stroop) Inhibition Scaled Score (disinhibition), the Verbal Fluency test's Letter Fluency Scaled Score and Category Fluency Scaled Score (verbal fluency), and the Trail Making Test Number-Letter Switching Contrast Score (divided attention and set shifting).

Outcome variable. Falls occurrence was operationalized as a binary: 'no' indicated no falls and 'yes' signified one or more falls. We also ascertained the total number of falls by each participant.

3.3.4 Data Analysis

Because the five co-occurring studies did not include all variables, data for selected variables were missing for approximately 20% of subjects. To assure adequate statistical power, we employed multiple imputation to estimate missing values, based upon associations of variables with missing data with other key demographic, clinical, and study measures that were fully observed. We carefully screened for duplicate subjects across studies, so as not to violate the assumption of independence. We also evaluated our data considering the underlying statistical assumptions of multiple logistic regression. No assumptions, including linearity in the logit of the outcome variable, were violated, so no remediation was required.

We described the sample according to the frequency and proportion of participants with and without falls, and the corresponding 95% confidence intervals for this proportion, and we computed descriptive statistics for all demographic and clinical characteristics. We compared outcome groups (fallers vs. non-fallers) using the Student's *t*-test or Mann-Whitney *U* test, respectively, for continuous variables, and the chi-square test of independence for comparison of

the groups on nominally scaled variables. Rather than transform variables we elected to present both parametric and non-parametric results.

To test the hypotheses for Aim 1, we first investigated the bivariate associations between the binary falls variable and each potential predictor variable or covariate using univariate binary logistic regression analysis. Multivariate logistic regression models were fitted hierarchically, with established predictors (balance impairment, ADL disability, and hemispatial neglect) entered first, and the non-executive cognitive function and executive cognitive function variables entered sequentially in the second block. We then expanded the multivariate logistic regression model using a hierarchical approach to enter covariates correlated at a liberal *p*-value of .30 or less first, followed by non-correlated but theoretically relevant covariates (age, sex, stroke etiology and location, CIRS-G burden score) and subsequent entry of non-executive cognitive dysfunction and each executive cognitive dysfunction variable in separate blocks. We noted changes in the model's Nagelkerke (pseudo) R^2 when adding non-executive, then executive, cognitive function, to determine their relative contributions to the model and thus their strength of prediction.

For Aim 2, we added interaction terms to the adjusted logistic regression model developed in Aim 1, to investigate whether executive cognitive dysfunction significantly moderated the effects of impaired balance, ADL disability, and hemispatial neglect. For Aim 3 we entered all covariates and predictors simultaneously and then sequentially removed variables through backward elimination based on the *p*-value of included predictor variables until only statistically significant predictors remained in the model. Analyses were performed using IBM® SPSS® Statistics version 21.0 (Armonk, NY), with $\alpha = .05$ for two-sided hypothesis testing.

3.3.5 Results

In the final sample (N = 180), 28 participants experienced at least one fall ($\hat{p}$ = 0.156, 95% C.I. 0.1099 - 0.2188). Our sample was largely white (82.2%) and approximately half (47.8%) female, with a median age of 65.81 years (*IQR* 55.31-76.31years); 53.3% had more than 12 years of education. Participants who fell were slightly less educated than those without a fall; they also had higher NIHSS scores, lower mFIM and cFIM scores, and similar depression (HRSD) and comorbidity burden (CIRS-G) scores (see Table 5).

In the initial unadjusted model, mFIM was the only significant predictor of falls. In the second model, possible risk factors for falls significant at $p \leq .30$ entered in the adjusted model were education, NIHSS, stroke hemisphere, stroke etiology, stroke type, HRSD, CIRS-G burden score, number of types of fall prevention interventions, CMA Postural Control, and mFIM. We also included several predictors such as age (*rho* = -0.08, p = .31) and gender ($\chi^2_{(1)}$ = 0.45, p = .50) that did not meet the inclusion threshold but have been linked to falls in the literature. The initial Naglekerke R^2 of the adjusted multivariate model was 0.489. Subsequent sequential entry of the non-executive function and executive function variables resulted in only a slight change in R^2 to 0.492 with addition of the RBANS score, and to 0.501 (final R^2) with the addition of the D-KEFS. The adjusted model included education (OR 0.65, 95% CI 0.49 - 0.87, p = .003), left hemisphere stroke (OR 0.25, 95% CI 0.07 - 0.92, p = .04), brain stem or cerebellar stroke (OR 4.27, 95% CI 1.06 - 17.17, p = .04), and total number of fall prevention interventions used during the rehabilitation stay (OR 1.74, 95% CI 1.14 - 2.63, p = .01)

None of the interaction terms in which executive cognitive function (D-KEFS) variables were modeled were statistically significant. Odds ratios ranged from 0.94 (95% CI 0.79-1.13, p = .51) for the interaction of the D-KEFS Category Fluency Scaled Score with CMA Postural

Control to 1.00 (95% CI 0.99-1.01, p = .97) for the interaction of the D-KEFS Category Fluency Scaled Score and the LBT Percent Deviation Score (see Table 6).

The final parsimonious model to predict falls during inpatient rehabilitation in our sample included education (OR 0.70, 95% CI 0.56 - 0.89, p = .01), NIHSS (OR 1.14, 95% CI 1.01-1.29, p = .04), stroke hemisphere—left (OR 0.28, 95% CI 0.09 - 0.82, p = .02), number of fall prevention interventions used (OR 1.60, 95% CI 1.13-2.25, p = .01), and mFIM (OR .96, 95% CI .92-0.99, p = .04) (see Table 6). Because imputed NIHSS scores were used to achieve this parsimonious model, we also performed a sensitivity analysis using only original NIHSS scores; the significant relationship was unchanged when using original NIHSS scores.

3.4 DISCUSSION

This investigation is the first adequately powered prospective study to specifically examine the influence of both non-executive and executive post-stroke cognition on falls during inpatient stroke rehabilitation. It is also the first to examine the potential moderating effect of executive dysfunction on the relationship between post-stroke balance impairment, hemineglect, and ADL performance deficit and falls. Although our hypotheses were not supported, we developed a predictive model that identified (from strongest to weakest prediction) use of more preventive interventions during the inpatient stay, low educational level, greater stroke severity, having a brain stem or cerebellar stroke, and ADL performance deficit as significant predictors of falls; in this same model, left hemisphere stroke was protective for falls.

3.4.1 Demographic and Clinical Risk Factors

We found that use of more types of fall prevention interventions was associated with a 1.5-fold increase in the risk of falling and was the strongest predictor in our final model. A crucial question involves the timing of providing fall prevention devices to patients. Neither the present study nor the aforementioned QI study ascertained whether patients evaluated by clinicians as being at high fall risk were given these devices and yet still fell (and potentially received more restrictive interventions such as restraints), or whether prevention measures were implemented after a first fall occurred to prevent further falls. Because few of our participants incurred a second fall, the latter interpretation makes sense. However, the former explanation is likewise plausible, given that standard clinical practice on the rehabilitation units included aggressive use of fall prevention devices upon admission for anyone perceived to be at risk, including most patients with stroke. In our sample, only six participants had no documented use of fall prevention interventions during their rehabilitation stay, and none of these individuals fell. All participants who fell received at least one type of fall prevention intervention during inpatient rehabilitation. Additional research is needed to clarify the temporal relationships between institutional fall prevention interventions and fall occurrence.

Particularly intriguing is the link we found between educational level and falls. Education is rarely included in analyses of fall risk in the stroke population. Although Bugdayci et al. (2011) found no difference in education between fallers and non-fallers, both groups' mean educational attainment was only four years, far lower than our more highly educated sample. Various cognitive tests are correlated with education, in particular tests of verbal fluency (Lezak, et al., 2004). We found education to be significantly correlated with RBANS and D-KEFS verbal fluency scores, but not with D-KEFS Color Word Interference Inhibition or D-KEFS Trail

Making Number-Letter Switching. Scaled scores for the D-KEFS are not corrected for education. Adjusting the scores for education might broaden our distribution of executive function scores slightly, as our sample was highly educated, while diminishing the strength of education as a predictor. Further, we did not collect a measure of pre-stroke cognitive functioning or intelligence, and thus we could not control for these factors, which could be highly related to educational level. Future research could include premorbid cognitive function, using a measure such as the Wechsler Test of Adult Reading (WTAR), which could help to explain the apparent role of educational attainment in falls.

Low educational attainment has been associated with overall poor outcomes in stroke (Grube et al., 2012), although the mechanisms underlying this relationship are not clear. Education, often used as a marker for the broader construct of socioeconomic status (SES),may be linked to falls in several ways. One, it is possible that more highly educated patients have a better social support network and better access to resources, possibly leading to decreased length of hospital stay and hence, a reduced window of opportunity in which to experience an inpatient fall. Second, Education and SES may influence health outcomes as an indicator of premorbid synaptic and problem-solving skill development, often called “cognitive reserve” (Ojala-Oksala et al., 2012; Stern, 2002, 2003). Third, neurobiological pathways such as the sympathetic-adrenal-medullary (SAM) system, the hypothalamic pituitary adrenal (HPA axis) (Matthews & Gallo, 2011) or the serotonin pathway which are highly related to SES and correlate strongly with elevated risk for cardiovascular disease and related negative outcomes (Manuck et al., 2005; Muldoon et al., 2004). Particularly intriguing is the possible link between SES, serotonin, and falls, since depression, also closely related to serotonin levels in the brain, has been linked with falls in older adults and in persons with stroke, though not in our sample. Further research is

warranted to investigate the relationship between education, other socioeconomic variables, and falls.

To our knowledge, this is also the first study of fall risk during inpatient rehabilitation to include a measure of stroke severity (NIHSS score). It is not surprising that low scores on the NIHSS are associated with falls, because NIHSS items include ratings of balance, coordination, and motor strength, which could contribute to falls. Findings reported in the literature related to hemisphere and lesion location (stroke type) are conflicting. Several groups have found no association between hemisphere and/or lesion location and falls during inpatient stroke rehabilitation (Bugdayci, Paker, Dere, Ozdemir, & Ince, 2011; Mayo, et al., 1990; Nyberg & Gustafson, 1996, 1997; Rabadi et al., 2008; Teasell et al., 2002) whereas, consistent with our results, others have found that falls were highly associated with right hemisphere strokes (Stapleton et al., 2001).Rapport's (1993) and Webster's (1995) groups included only participants with right hemisphere strokes, because of the high likelihood of falls among these patients. It makes sense clinically that persons with right hemisphere strokes are more prone to falls, both because right parietal lesions are often associated with hemispatial neglect, and because of the quick, impulsive behavioral style that is characteristic of persons with right sided lesions. We are one of the few groups to characterize stroke location according to brain region of lesion (cortical, subcortical, cortical/subcortical, or brain stem/cerebellum). Our finding that falls occur significantly more in persons with brain stem/cerebellar strokes is not surprising, given the cerebellum's function of maintaining balance and coordination.

We found no relationship between age or gender and falls. While advanced age is commonly accepted as a risk factor for falls in the general geriatric population (Rubenstein & Josephson, 2006), the stroke rehabilitation fall literature has largely not found such association

(Bugdayci et al., 2011; Nyberg & Gustafson, 1997; Rabadi et al., 2008; Suzuki et al., 2005; Sze et al., 2001; Teasell et al., 2002), although older age has been associated with repeat falls during stroke rehabilitation (Czernuszenko & Czlonkowska, 2009). Indeed, in our sample fallers were slightly younger than non-fallers (although this relationship was not statistically significant), but there were insufficient numbers of repeat fallers to detect any association with advanced age. Czernuszenko and Czlonkowska's sample from a Polish rehabilitation unit was similar to ours in age; however, these authors caution that their results cannot be generalized to samples in other inpatient rehabilitation facilities because their mean onset to admission (time from stroke to rehabilitation) was over 30 days, and often was as long as 2 or 3 months. In contrast, most inpatient rehabilitation units' onset to admission is much less (Horn, DeJong, Smout, Gassaway, James, & Conroy, 2005), including our own.

Results are mixed regarding the effect of gender on falls during stroke rehabilitation. Two groups' have shown trends toward more falls among males (Nyberg & Gustafson, 1997; Olsson et al., 2005), although their samples had higher mean ages than many other groups, including ours, that have found no such relationship (Bugdayci et al., 2011; Czernuszenko & Czlonkowska, 2009; Rabadi et al., 2008; Suzuki et al., 2005; Sze et al., 2001; Teasell et al., 2002), which may account for this difference.

3.4.2 Previously Established Risk Factors

Similar to other studies, our results suggest a predictive relationship between ADL performance deficit (mFIM) and falls. Yet we did not find predictive relationships between balance impairment or hemineglect and falls. A possible explanation is that our sample may not accurately reflect the population on these key variables. Several of our study instruments were

not used clinically at our study sites (the CMA, LBT, RBANS and D-KEFS). Hence, instead of being able to retrieve these values from de-identified medical record data, we had to obtain informed consent for administration of a lengthy (2-3 hour) assessment battery. This need for informed consent may have negatively affected recruitment, resulting in a non-representative sample of persons with stroke (Grube et al., 2012). This selection bias may also have contributed to an attenuated range of responses on key variables in our sample vis-à-vis the population. Indeed, based on post hoc comparison with de-identified quality improvement (QI) data from all patients admitted for stroke rehabilitation at our study sites during our data collection period, our sample was similar in age (participant age M = 65.58 years, SD = 14.60; population age M = 69.95 years, SD = 14.64), but less physically impaired (participant mFIM M = 48.12, SD = 15.82; population mFIM M = 36.54, SD = 13.04), and less cognitively impaired (participant cFIM M = 24.91, SD = 5.54; population cFIM M = 20.10, SD = 7.34) than the inpatient stroke rehabilitation population.

3.4.3 Post-stroke Cognition

Our findings are largely consistent with those obtained in a recent QI study of a stroke-specific fall risk assessment conducted at the largest rehabilitation site in our study, but they conflict with those of other investigators. The QI study found that two proxies of executive function, clinician ratings of impulsivity and the problem solving FIM, did not predict falls, although fallers and non-fallers were different regarding impulsivity: nearly half of fallers were rated as impulsive on the fall risk assessment, compared with one quarter of non-fallers, a clinically meaningful difference (Breisinger et al., under review). Our study did not find a predictive relationship

between non-executive function or executive function and falls, although fallers had significantly lower cognitive FIM (cFIM) scores than those who did not fall.

Rapport and colleagues (1993) found that behavioral impulsivity was highly correlated with falls in a sample of rehabilitation inpatients with right hemisphere stroke. Behavioral impulsivity explained 55% of the variance in falls, although odds ratios were not reported. Impulsivity was measured with an investigator-developed scanning task where participants were presented with visual stimuli displayed on two video monitors placed 45^{o} off midline, and asked to maintain their gaze at midline until visual stimuli were presented. Deviation of eye gaze prior to stimulus presentation constituted the measure of impulsivity. It is possible that this measure of behavioral impulsivity taps a different construct than our measure of impulsivity, the Color-Word Interference (Stroop) inhibition score. While the task employed by Rapport et al. may be more ecologically valid for determining fall risk, insofar as it measures behavioral effects of altered cognitive processes rather than cognitive processes themselves, their scanning task would be difficult to implement clinically because it requires sophisticated equipment not found in most rehabilitation settings. Their falls incidence (47%) was also much higher than ours (15.6%), making it easier to detect relationships between impulsivity and falls.

Several other studies using measures of general cognition including the cFIM and the Mini-Mental State Exam have found an association between cognitive impairment and falls (Rabadi et al., 2008; Teasell et al., 2002; Zdobysz et al., 2005). However, we have located no other fall risk studies that have measured executive cognitive function using the D-KEFS. In the present analysis, we did not enter cFIM into our regression model because we intended to capture 'pure' elements of executive functioning such as disinhibition (impulsivity), verbal fluency, and the ability to shift set, rather than a global clinical impression of functional

cognition. It is possible that the cFIM captures elements of functional cognition not captured by traditional neuropsychological measures such as the RBANS and the D-KEFS. Future investigations should aim to explicate the specific cognitive domains measured by the cFIM, compared with gold standard tests of executive function, and to further explicate the types of functional cognition that may be more predictive of falls that the 'pure' executive domains tested in our study.

3.4.4 Study Limitations

Our study has several important limitations. The first and potentially most serious limitation concerns the lack of representativeness of our sample due to exclusion of patients with aphasia who would not have been able to complete the cognitive tests. Communication deficits occur in approximately 30% of persons with stroke (Engelter et al., 2006), many of whom have cognitive deficits in addition to language impairment (Fucetola, Connor, Strube, & Corbetta, 2009). Excluding persons with aphasia may have biased our sample relative to the population of persons with stroke, restricting the range in key cognitive variables, falsely deflating correlations between variables (Tabachnick & Fidell, 2007), and contributing to the lack of relationship found between key variables and falls.

Even though we excluded a substantial proportion (30%) of persons admitted for stroke rehabilitation because of aphasia, language deficits may still have confounded our results. Paper and pencil tests of executive cognitive function such as those used in our study are highly depended upon intact comprehension and expression abilities (Lezak et al., 2004). Indeed, in our sample, all of the D-KEFS variables were significantly correlated with language comprehension and expression FIM scores. We plan to obtain individual domain scores for the RBANS

(currently our data set includes only the Modified Total Index Score) and correlate the language domains of the RBANS against our cognitive variables to investigate whether our cognitive scores are confounded by communication deficits.

A further limitation concerns conducting research in a clinical environment where the research team has little influence over standards of clinical practice. Over the course of the study aggressive policies intended to cut fall rates were implemented on the rehabilitation units. For example, at the largest two study sites, every stroke patient routinely received a low bed, bed alarm, and chair alarm on admission, which were often used during the entire stay rather than phased out as rehabilitation progressed. Such extensive use of fall prevention equipment may minimize the opportunity for patients to assimilate new learning related to safety as devices are removed. These policies may have artificially lowered the fall rate, obscuring relationships between key variables and falls.

Finally, our use of multiple imputation, which is considered a valid approach to handling missing data (Tabachnick & Fidell, 2007), assumes that participants with missing data statistically resembled participants with complete data on key variables. It is unclear whether our sample met this assumption. However, using sensitivity analysis, we found no difference in effects between original and imputed data.

3.5 SUMMARY AND CONCLUSIONS

Our study demonstrated that stroke severity, educational status, use of fall prevention interventions, and functional ability significantly predicted falls, while hypothesized predictors including balance impairment, hemineglect, and executive cognitive impairment did not.

Because our sample was dissimilar to the larger population of stroke rehabilitation inpatients on key variables, these results should be interpreted with caution. Furthermore, some evidence suggests that the use of ecologically based cognitive assessments may be more associated with falls risk than traditional neuropsychological assessment. Additional research is needed to further elucidate the relationship between post-stroke cognition and falls and the best methodology for meaningfully measuring cognition after stroke.

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Table 5. Demographic and Clinical Characteristics of the Sample

Characteristic	Entire Sample (N = 180)	Falls Occurrence: Participants With No Fall (n = 152)	Falls Occurrence: Participants with 1+ Falls (n = 28)	Test statistic (p value)
Age (Years)				
Median (IQR)	65.81 (55.31-76.31)	66.25 (55.75-76.75)	60.93 (48.43-73.43)	U = 1872.00 (p = .312)
Mean (SD)	65.58 (14.60)	66.03 (14.36)	63.12 (15.90)	$t_{(178)}$ = .969 (p = .334)
Gender, n (%) Female	86 (47.8)	71 (46.7)	15 (53.6)	$X^2_{(1)}$ = .446 (p = .50)
Race, n (%) White	148 (82.2)	124 (81.6)	24 (85.7)	$X^2_{(1)}$ = .277 (p = .599)
Education, n (%) >12 years	96 (53.3)	87 (58.0)	9 (32.1)	$X^2_{(1)}$ = 6.35 (p = .012)
Stroke Severity, NIHSS				
Median (IQR)	6.0 (4.0—9.0)	5.0 (2.5–7.5)	10.0 (5.0–15.0)	U = 1063.30 (p < .001)
Mean (SD)	7.11 (4.57)	6.55 (5.96)	10.17 (5.33)	$t_{(44)}$ = -3.358 (p = .002)
Stroke Hemisphere, n (%) Left	67 (37.2)	54 (35.8)	13 (46.4)	$X^2_{(1)}$ = 1.148 (p = .284)
Stroke Etiology, n (%) Ischemic	149 (82.8)	129 (84.9)	20 (71.4)	$X^2_{(1)}$ = 2.996 (p = .083)
Stroke Type, n (%)				
Cortical	54 (30)	49 (32.2)	5 (17.9)	
Subcortical	54 (30)	44 (28.9)	10 (35.7)	$X^2_{(3)}$ = 7.73 (p = .052)
Cortical/Subcortical	35 (19.4)	25 (16.4)	10 (35.7)	
Brainstem/Cerebellum	35 (19.4)	32 (21.1)	3 (10.7)	
Not documented	2 (1.1)	2 (1.3)	0 (0)	
Balance Impairment, CMA				U = 1268.4 (p < .001)
Median (IQR)	3.7 (2.7-4.7)	4 (3.1-4.9)	2 (1.2-2.8)	
Mean (SD)	3.43 (1.39)	3.56 (1.18)	2.71 (1.09)	$t_{(178)}$ = 3.33 (p = .001)
Depression, HRSD				
Median (IQR)	7.0 (3.0-12.0)	7.0 (3.5-10.5)	9.0 (4.5-13.5)	U = 1736.60 (p = .133)
Mean (SD)	7.58 (5.61)	7.36 (7.00)	8.76 (6.95)	$t_{(87)}$ = -1.073 (p = .286)

Number of Comorbid Conditions				
Median (IQR)	5.0 (3.0-7.0)	5.0 (3.0-7.0)	6.0 (4.5-7.5)	U = 1853.60 (p = .317)
Mean (SD)	4.87 (2.38)	4.80 (2.49)	5.26 (2.47)	$t_{(267)}$ = -.867 (p = .387)
CIRS-G Comorbidity Burden Score				
Median (IQR)	10.0 (6.0-13.0)	10.0 (6.5-13.5)	11.0 (7.5-14.5)	U = 1806.00 (p = .238)
Mean (SD)	9.96 (5.08)	9.79 (5.33)	10.92 (4.80)	$t_{(267)}$ = -1.065 (p = .287)
ADL Motor Performance Deficit, mFIM				
Median (IQR)	48.5 (38.5-58.5)	50.5 (41-60)	35 (26-44)	U = 1042.00 (p < .001)
Mean (SD)	48.12 (15.82)	50.25 (15.36)	36.57 (13.28)	$t_{(178)}$ = 4.42 (p < .001)
Functional Cognitive Performance, cFIM				
Median (IQR)	25 (21-29)	26 (21.5-30.5)	22 (17.5-26.5)	U = 1315.00 (p = .001)
Mean (SD)	24.91 (5.54)	25.47 (5.49)	21.89 (4.87)	$t_{(178)}$ = 3.22 (p = .002)
LBT Percent Deviation				U = 1927.20
Median (IQR)	6.59 (2.57-17.89)	6.57 (2.57-16.45)	9.50 (1.96-35.16)	(p = .436)
Mean (SD)	13.99 (17.98)	12.96 (16.76)	19.53 (22.84)	$t_{(145)}$ = -1.64 (p = .104)
RBANS Modified Total Index Score				U = 1784.00 (p = .219)
Median (IQR)	72.00 (60.30-82.70)	72.40 (61.10-80.80)	67.20 (58.25-76.05)	$t_{(94)}$ = 1.22
Mean (SD)	72.11 (15.31)	72.77 (15.32)	68.56 (13.26)	(p = .154)
D-KEFS Color-Word Inhibition Scaled Score				U = 1867.30 (p = .385)
Median (IQR)	4.50 (1.00-9.00)	4.9 (1.00-8.15)	2.2 (0.50-9.00)	$t_{(221)}$ = 0.88
Mean (SD)	5.06 (4.24)	5.19 (4.24)	4.36 (4.40)	(p = .383)
D-KEFS Letter Fluency Scaled Score				U = 1977.50 (p = .563)
Median (IQR)	6.00 (4.00-8.95)	6.20 (4.00-9.00)	6.00 (4.40-7.45)	$t_{(171)}$ = 0.50
Mean (SD)	6.43 (3.52)	6.49 (3.61)	6.09 (2.85)	(p = .616)

Table 6. Odds Ratios for Falls in Unadjusted, Adjusted, and Final Models

	Model 1: Unadjusted OR	95% CI	*p*	Model 2: Full Model Adjusted OR	95% CI	*p*	Model 3: Parsimonious Model Adjusted OR	95% CI	*p*
Age	0.99	0.95-1.03	.69	0.99	0.95-1.03	.69			
Gender (Female)	0.45	0.15-1.37	.16	0.45	0.15-1.37	.16			
Education	0.65	0.49-0.87	.003^	0.65	0.49-0.87	.003^	.702	0.56-0.89	.01^
Stroke Severity (NIHSS)	1.15	0.90 –1.37	.12	1.15	0.90 –1.37	.12	1.14	1.01-1.29	.04+.
Stroke Hemisphere (Left)	0.25	0.07-0.921	.04+	0.25	0.07-0.921	.04+	.28	0.09-0.82	.02+
Stroke Etiology (Ischemic)	0.39	0.09-1.65	.20	0.39	0.09-1.65	.20			
Stroke Type Cortical	*			*					
Subcortical	1.09	0.24-4.87	.91	1.09	0.24-4.87	.91			
Cort/Subcort	2.42	0.62-9.52	.21	2.42	0.62-9.52	.21			
Brain Stem/ Cerebellar	4.27	1.06-17.17	.04+	4.27	1.06-17.17	.04+			
Depression (HRSD)	1.00	0.90-1.11	.99	1.00	0.90-1.11	.99			
CIRS-G Burden Score	1.02	0.91-.1.14	.85	1.02	0.91-.1.14	.85			
Fall Prevention Interventions	1.74	1.14-2.63	.01^	1.74	1.14-2.63	.01^	1.60	1.13-2.25	.01^
CMA Postural Control	0.74	0.44-1.25	.21	0.69	0.38-1.26	.23			
LBT Percent Deviation	0.99	0.97-1.02	.58	0.98	0.95-1.02	.30			
mFIM	0.95	0.91-0.99	.02	0.96	0.91-1.01	.11	0.96	0.92-0.99	.04
RBANS Modified Total Index Score	0.96	0.95-1.04	.84	1.00	0.94-1.06	.88			
Color-Word Interference Inhibition Scaled Score	0.98	0.85-1.13	.75	0.98	0.80-1.21	.88			
Letter Fluency Scaled Score	0.99	0.81-1.23	.99	1.05	0.81-1.35	.73			
Category Fluency Scaled Score	1.01	0.77-1.32	.94	1.03	0.78-1.37	.83			
Trail Making Test Number-Letter Switiching Score	0.93	0.82-1.06	.28	0.96	0.82-1.12	.56			
Color-Word Interference Inhibition * CMA Postural Control				0.96	0.84-.1.10	.57			
Color-Word Interference Inhibition * LBT Percent Deviation				1.00	0.99-1.01	.75			
Color-Word Interference Inhibition * Motor				1.00	0.99-1.01	.70			

	Model 1: Unadjusted OR	95% CI	*p*	Model 2: Full Model Adjusted OR	95% CI	*p*	Model 3: Parsimonious Model Adjusted OR	95% CI	*p*
FIM Letter Fluency * CMA Postural Control				1.00	0.86-1.17	.97			
Letter Fluency * LBT Percent Deviation				1.00	0.99-1.01	.61			
Letter Fluency * Motor FIM				1.00	0.99-1.02	.74			
Category Fluency * CMA Postural Control				0.94	0.79-1.13	.51			
Category Fluency * LBT Percent Deviation				1.00	0.99-1.01	.97			
Category Fluency * Motor FIM				1.00	0.99-1.01	.94			
Trail Making Number-Letter Switching * CMA Postural Control				0.97	0.86-1.09	.62			
Trail Making Number-Letter Switching * LBT Percent Deviation				1.00	0.99-1.01	.92			
Trail Making Set Shifting * Motor FIM				1.00	0.99-1.01	.50			

OR indicates odds ratio; CI, confidence interval

*Reference group

[+]Significant at $p = .05$ level

[^] Significant at $p = .01$ level

4.0 MANUSCRIPT #4

4.1 ABSTRACT

Purpose: This paper describes challenges encountered while forging an academic/clinical rehabilitation partnership. It highlights strategies for overcoming barriers and describes the mutually beneficial effects of collaboration among researchers and clinicians in the inpatient stroke rehabilitation setting.

Setting: Five inpatient stroke rehabilitation units of a large, university-affiliated hospital system in western Pennsylvania.

Barriers and Benefits: Barriers to inpatient stroke rehabilitation research include patient and family/caregiver characteristics (e.g., aphasia, cognitive impairment, and fatigue); clinical staff issues such as busy treatment schedules; and institutional/regulatory constraints (e.g. regulatory requirements surrounding patient eligibility for inpatient rehabilitation, and payor-mandated duration of therapy). Benefits include additional clinical monitoring of participants, sharing of research evidence with clinicians, and buy-in by clinical staff encouraging patients to consider participation.

Conclusion: Conducting research on an inpatient stroke rehabilitation service can be challenging. The potential for mutual benefit to patients, clinicians, and researchers can result in academic/clinical partnerships being advantageous to all.

4.2 INTRODUCTION

Nearly 800,000 Americans experience a new or recurrent stroke annually. Approximately 60% of these individuals survive, many with residual disability (American Heart Association, 2012) that necessitates intensive rehabilitation. Early, intensive inpatient rehabilitation is associated with improved functional outcomes (Teasell, Bitensky, Salter, & Bayona, 2005; Wang, Camicia, Terdiman, Hung, & Sandel, 2011). Yet the science establishing efficacious treatment practices in this setting is limited, and translation of this meager body of evidence into practice has been slow (Bayley et al., 2012; Teasell, 2012).

Conducting clinical research, especially clinical trials, in the rehabilitation setting is difficult (Hart & Bagiella, 2012; Jones, Cifu, Backus, & Sisto, 2013). The relatively scant literature pertaining to rehabilitation interventions in the inpatient setting suggests the complexity of such an endeavor. When the goals and procedures of research and clinical care conflict, protocol fidelity and data integrity may be undermined. Threats to the internal and external validity of the research enterprise may arise due to the medical complexity of patients, patient fatigue, time-consuming treatment schedules, and the regulatory and reimbursement requirements that govern inpatient rehabilitation.

Despite these challenges, successfully integrating clinical research with clinical care can enrich both realms. Benefits that may accrue to the clinical team include the availability of additional monitoring of study participants with complex medical needs and access to the research team's expertise for education and consultation. Researchers benefit when clinical staff encourage patients to consider participating in studies and facilitate obtaining their informed consent or ongoing assent. Patients may also ultimately benefit from translation of evidence-based innovations into clinical rehabilitation practice.

Our group has recently conducted several studies in the inpatient stroke rehabilitation setting as part of an emerging academic/clinical partnership. This paper describes the challenges we have encountered while forging this partnership. It also highlights strategies for overcoming barriers and elaborates on the mutually beneficial effects of collaboration among researchers and clinicians alike.

4.3 SETTING

The studies from which our observations are drawn have been conducted on the inpatient stroke rehabilitation service of a large, university-affiliated hospital system in western Pennsylvania. The UPMC Rehabilitation Institute (RI) is an academic-clinical partnership between schools of the health sciences at the University of Pittsburgh and the post-acute care services of the UPMC Health System, which comprises 10 inpatient rehabilitation units at seven urban, suburban, and rural hospitals, and a network of outpatient rehabilitation clinics. Stroke is the largest diagnostic group among the rehabilitation units. The RI facilitates research performed by its own faculty and staff as well as affiliated researchers, with the goal of translating research into advanced, evidence-based clinical care for persons requiring physical rehabilitation services for a variety of diagnoses, including acquired brain injury and stroke.

4.4 STUDIES

Protocols for the two observational studies and three experimental studies that we conducted are summarized in Table 7 and were approved by the Institutional Review Board of the University of Pittsburgh. All participants provided written informed consent, or assent with written consent by proxy for decisionally impaired individuals. The studies were conducted concurrently and utilized a collaborative recruitment strategy, such that participants were offered the opportunity to participate in the study that most appropriately matched their eligibility and interest. The research teams across all studies shared resources for recruiting and data collection. Only one study, the randomized controlled trial (RCT), remains open to enrollment; all other studies are closed to accrual.

4.5 CHALLENGES

The challenges we encountered while conducting research in the inpatient stroke rehabilitation setting can be broadly categorized as patient and family/caregiver characteristics, clinical staff issues, and institutional/regulatory constraints. These diverse challenges may affect recruitment as well as baseline and follow-up testing, and they may ultimately confound the investigators' ability to draw conclusions from the research findings that are clinically meaningful and applicable.

4.5.1 Patient and Family/Caregiver Characteristics

Persons with recent stroke may have difficulty participating in research due to sequelae that impede physical and cognitive function or contribute to disinterest in research participation. These include aphasia, physical comorbidities, lack of decisional capacity, and fatigue. “Gold standard” cognitive tests used in many stroke studies depend upon intact comprehension and verbal expression for accurate completion (Cumming, Marshall, & Lazar, 2012; Lezak et al., 2004). Yet, at least 30% of persons with stroke exhibit aphasia (Dickey et al., 2010; Engelter et al., 2006), an exclusion criterion for many investigations.

In our studies, patients who were severely aphasic during clinical pre-screening were not approached for study participation. Other participants were subsequently excluded based on performance of 1 SD below age-adjusted norms on the Boston Naming Test (BNT), a measure of naming ability originally chosen to exclude persons with inadequate ability to complete cognitive testing. However, after it was observed that participants who ultimately failed the BNT screening had been able to verbalize understanding of the studies during the consent discussion, the BNT was abandoned in favor of the repetition task of the Boston Diagnostic Aphasia Examination. Even with this more accurate screening of prospective study participants’ language ability, we ultimately excluded approximately 30% of patients from participation based on communication ability.

Persons with stroke typically have serious comorbidities and thus are often excluded from clinical trials (Horn, DeJong, & Deutscher, 2012). Like many stroke rehabilitation RCTs, several of our studies’ eligibility criteria were intentionally narrow, to control for likely confounders. Because of potential adverse reactions to the study medication, our Enhance study (see Table 1) excluded many persons with cardiopulmonary comorbidities. All five studies excluded persons

with pre-existing conditions that affect functional or cognitive status or are associated with falls, including other neurological conditions (e.g., Parkinson's disease, brain tumors), seizure within the past 12 months, psychiatric disorders (e.g., psychotic illness or substance abuse), and intellectual disabilities.

Cognitive impairment is common after stroke (Cavanagh, Hogan, Fairfax, Gordon, & Kopacz, 2002; Pohjasvaara, et al., 2002; Zinn, et al., 2007). Altered cognition combined with the stress of major illness may reduce decisional capacity to consent to research. Accurately screening for decisional incapacity and contacting a proxy, while safeguarding the prospective participant's rights, can be time consuming for research staff (Newberry et al., 2010) and calls into question whether truly 'informed' consent can be granted (Blanton et al., 2006). To determine decisional capacity, we conducted a detailed assessment of general cognition and elicited patients' understanding of study goals and processes. If decisional capacity was questionable, we erred on the side of caution and located the patient's proxy. While our conservative approach safeguarded the right to informed consent, we likely eliminated some patients who were willing to participate, but for whom we could not reach a proxy in a timely fashion.

Physical fatigue after stroke is prevalent and not well understood (Ingles, Eskes, & Phillips, 1999; Lerdal et al., 2009; van Eijsden, van de Port, Visser-Meily, & Kwakkel, 2012). In our experience, fatigue was an oft-cited deterrent to research participation. Patients verbalized extreme fatigue resulting from the demanding daily schedule of physician rounds, nursing care, classes and support groups, and treatment sessions with physical and occupational therapists, speech-language pathologists, psychologists, and social workers that typify inpatient rehabilitation. When we approached patients for study participation, often after a full day of

treatment, many were unable to remain alert and engaged in the discussion. They perceived study participation to be an additional energy demand that would exacerbate their fatigue and compromise their ability to fully participate in rehabilitation.

Fatigue also confounds cognitive testing results, affecting completeness and accuracy of data (Lezak et al., 2004). Like recruitment visits, research testing and interventions by necessity often occur late in the day. Participants may refuse testing or treatment due to fatigue, or they may complete the session with their attention span and processing speed compromised, resulting in unduly poor performance on study assessments. To combat the effects of fatigue, whenever possible we ascertained the participant's daily schedule and preferred research participation times, then worked closely with clinicians to arrange the rehabilitation schedule around research recruitment and testing sessions. When possible, we attempted to schedule recruitment visits early in the day, when prospective participants were well rested. Cognitive testing was administered in shorter sessions when feasible, to maximize research participation.

Emotional fatigue also affects research participation. Stroke is typically emotionally devastating to patients and their significant others. Patients considering our studies expressed feeling "stressed," "overwhelmed," and "worried" about their health, their recovery, and the impact of their illness on their families. Many who declined perceived research participation to be an additional, unwanted obligation. Some acknowledged its importance, but felt unable to "take on one more thing." Others were receptive to enrolling in the RI research registry to learn about future research opportunities, but they were unwilling to commit to research participation during inpatient treatment.

In our studies, families, friends, and significant others exhibited extraordinary protectiveness regarding their loved ones' health and emotional well-being, reinforcing some

patients' reluctance to participate in research and often functioning as gatekeepers for the recruitment process. Consistent with the observations of Newberry and colleagues (2010), families also expressed concern that taking part would be too overwhelming, tiring, or frustrating for the patient and significant others, with little direct benefit to the patient. We attempted to reassure these close associates that research activities could be paced according to their loved ones' needs, but many felt the immediate recovery process demanded undivided attention. One gentleman who was highly motivated toward recovery politely but firmly declined to participate, explaining that his goal was to attend an upcoming family wedding and "if it [research] doesn't help me to walk down that aisle, I can't afford to spend any time on it."

4.5.2 Clinical Staff Issues

Facilitating clinical research is integral to the RI mission. While therapists and nurses are encouraged to collaborate with faculty researchers and develop their own funded research projects, they must primarily focus on providing clinical rehabilitation care in an increasingly complex environment. Therapists' schedules are full, with little latitude to shift schedules to provide research testing time for participants. We tried to intrude as little as possible on the workflow of therapists by scheduling our research assessments after participants' daily treatment schedules has been finalized. We only asked therapists and nurses to rearrange the treatment schedule when no practical alternative could be found, such as when we knew late day fatigue would interfere with a participant's ability to complete the assessment. We made sure participants were on time for therapy sessions scheduled after testing, and we encouraged their attendance at therapy. By respecting their demanding patient care schedules, we conveyed to therapists and nurses that we were invested in helping them to meet patients' clinical needs.

4.5.3 Institutional/Regulatory Constraints

Recent federal and third party payor regulations that tighten rehabilitation admission and reimbursement policies pose additional challenges for inpatient stroke rehabilitation researchers. Current admissions guidelines (Centers for Medicare and Medicaid Services, 2009) have narrowed the available pool of potential research subjects by excluding persons at either end of the functional spectrum. That is, severely compromised patients unable to tolerate a "full program" consisting of three or more hours of therapy daily, and persons with minor impairment who fail strict 'medical necessity' criteria embraced by payors, no longer qualify for coverage of inpatient rehabilitation expenses, and thus are not available for research.

Stringent regulations also dictate daily therapy requirements during inpatient rehabilitation such that patients must receive at least 180 minutes of skilled therapy services for five consecutive days out of every seven days during rehabilitation. Insurance claims are denied if a patient's stay does not achieve the required number of therapy minutes. Pressure on clinical staff to meet these regulations intensifies the aforementioned logistical challenges of scheduling research assessments.

Regulatory demands for therapy duration may also underlie the confounding effect of fatigue on cognitive testing. In their authoritative text on neuropsychological testing, Lezak and colleagues (Lezak et al., 2004) note that physical and occupational therapy can be particularly draining for persons in post-acute care settings, and they recommend that testing be scheduled in the morning, when subjects are likely to be well rested, or after a nap. Currently mandated rehabilitation treatment standards make scheduling of research activities early in the day nearly impossible.

Lack of privacy on the inpatient rehabilitation unit also may interfere with accurate completion of research testing. Semi-private patient rooms allow interruption by roommates and staff. Unit lounges are often used for therapy treatments (for example, to practice negotiating furniture in a 'homelike' setting or performing kitchen skills). Transporting research participants off the unit to a quiet conference room wastes testing time, especially when a therapy session is scheduled immediately after testing. We found that blocking test time on the unit schedule board, ensuring that personal care needs were met prior to testing, reminding staff when the testing session commences, and closing the door enabled us to achieve an interruption-free testing environment.

The clinical setting likewise influences the work flow of the research staff, especially during recruitment. Erratic patterns of rehabilitation admissions can make schedule planning difficult, often requiring research staff to be available late in the evening when family members or proxies are present. The demands on research staff to meet recruitment goals, particularly in a high stress clinical environment, can also lead to frequent turnover and short staffing, in turn necessitating continual training and fidelity monitoring which takes additional time away from recruitment efforts (Roberts, Waddy, & Kaufmann, 2012). Our group experienced several turnovers among study coordinators and recruitment staff, resulting in corresponding slowing in recruitment.

Baseline testing had to occur quickly after enrollment, to ensure accurate capture of data and facilitate timely intervention delivery. Because participants had to be tested within one to two days of consenting, conflicts often arose in the testing schedules of assessors from the neuropsychology group that performed cognitive testing for numerous studies. Assessors traveled from a central office to the five hospitals to conduct their testing, and sometimes they

arrived on the unit to find that a participant had developed a medical complication that required testing to be rescheduled. Due to these logistical impediments, we took several steps to minimize missing data. Research staff verified subjects' willingness to complete scheduled testing each day and then notified assessors when patients were too ill, too tired, or unwilling to do so. An additional neuropsychology research group supplemented the available testing services, and some studies' staffs were trained to administer portions of the cognitive testing, thereby minimizing our reliance on neuropsychological assessors. For future studies we are considering using assessment data already collected by the clinical team and entered in the medical record. Even though such measures may not be the gold standard for neuropsychological evaluation, they would eliminate for participants, clinicians, and study staff alike the cost and burden associated with lengthy, incomplete, or extra testing sessions.

4.6 BENEFITS

Despite the considerable challenges we encountered, our partnership with RI clinical staff has been mutually beneficial for all concerned. Though we could not guarantee direct benefit to participants and their families, indirect benefits of participation proved appealing to many patients and their families and significant others. For example, several studies included post-discharge follow-up for up to six months. The additional clinical monitoring of physical and emotional needs afforded by research staff visiting participants' homes reassured some families that participation could be beneficial. In several cases our study team identified acute medical or psychiatric illnesses during research follow-up visits, and they helped participants obtain necessary care to prevent negative outcomes. Because of our position as a large academic

medical center with technologically advanced treatments, we could connect participants to supplementary rehabilitation therapies such as vestibular rehabilitation, driving rehabilitation, and rehabilitation engineering, to which they would not ordinarily have had access.

Benefits to RI clinicians help increase their investment in research. Investigators provided expert clinical consultation around difficult treatment issues such as recognizing and treating post-stroke depression, managing hemineglect, and preventing falls. Investigators provided formal and informal staff education sessions, hosted journal clubs, and served as resources for connecting clinicians with evidence to inform their practice. Researchers regularly presented at RI interdisciplinary continuing education events, which typically attracted an audience of more than 100 clinical staff each month. Our research team also helped to streamline clinical care by collaborating with the RI clinical neuropsychology service regarding cognitive testing. With participants' permission, we shared our neuropsychological testing results with the clinical neuropsychologists for those who were to receive testing as part of their rehabilitation program, thereby avoiding the time, expense, and practice effects of repeat testing.

The research team similarly benefited from our unique partnership. As clinicians' regard for research grew, they began to identify patients who were potential participants; they also increasingly supported participants' efforts to complete study assessments and became engaged in facilitating the process of ongoing informed consent. Moreover, our research team's immersion in the clinical rehabilitation environment enriched our understanding of issues facing people with stroke, especially during the early phases of adjustment and recovery. Such insights will undoubtedly serve to strengthen the design and conduct of future investigations.

4.7 DISCUSSION

The challenges and opportunities encountered while forging an emerging academic-clinical partnership have been mutually beneficial to all parties concerned. We recommend remediation strategies for several issues, but unanswered questions remain concerning optimal recruitment strategies for stroke rehabilitation research, especially regarding the timing of recruitment. While several of the challenges such as the unpredictability of rehabilitation admissions represent minor inconveniences to study staff, other challenges including the potential for bias in the recruitment pool raise questions about the statistical power underlying research conducted with inpatient stroke rehabilitation populations. Even more concerning are the serious methodological ramifications for internal and external validity raised by the problems surrounding exclusion criteria, recruitment concerns, and missing or inaccurate test data.

4.7.1 Power and Recruitment

Recruitment difficulties are widely recognized among researchers in clinical settings; rehabilitation research is no exception. The implications for statistical power and for the cost of conducting research in acute stroke care (Elkins, Khatabi, Fung, Rootenberg, & Johnston, 2006; Pickering, Kunkel, Fitton, Ashburn, & Jenkinson, 2010; Roberts et al., 2012) and in rehabilitation (Blackmer, 2003; Blanton et al., 2006; Horn et al., 2012) are well documented. We have described patient-specific characteristics (e.g. aphasia, cognitive impairment, fatigue) that affect research participation. Reliable, valid alternatives to gold standard cognitive and affective tests typically used in research must be found, to permit inclusion of persons with communication disorders and expansion of the potential pool of subjects. Because recruitment of

cognitively impaired individuals is fraught with ethical concerns (Blackmer, 2003; Newberry et al., 2010), simplifying the informed consent process, or even making it unnecessary, could also improve recruitment. Admittedly, informed consent cannot be eliminated for all rehabilitation research, but rehabilitation sites could adopt commonly used research instruments as their standard of clinical care, permitting de-identified data collection directly from the clinical record (Horn et al., 2012). Using the National Institutes of Neurological Disorders and Stroke's Common Data Elements for this purpose could help to standardize research and clinical care, facilitating large scale studies that were previously impossible.

The timing of recruitment efforts may also influence accrual. Though the optimal time to approach patients for stroke or rehabilitation-related research is unclear, some authors suggest that approaching prospective participants as soon as possible after admission increases recruitment rate for stroke rehabilitation studies (Pickering et al., 2010). Others speculate that waiting until patients and families begin to adjust to life with stroke before broaching research participation yields better results (Blackmer, 2003; Blanton et al., 2006). As noted in our earlier discussion regarding emotional fatigue, our experiences suggest that waiting to approach, when feasible, may result in more effective recruiting. Yet, waiting to approach is not always feasible, especially for RCTs that involve inpatient rehabilitation interventions.

Some researchers advocate offering compensation for time and inconvenience to participants to increase recruitment (for example, see Blanton et al., 2006). Several of our studies offered such compensation, and we can only surmise that, at least in the early post-stroke period, the minor compensations and incentives permitted by current ethical standards were inadequate to overcome participant fatigue and feelings of being overwhelmed. Better understanding of the

issues surrounding research participation is needed. Further research could aim to elucidate patients' perspectives related to enrolling in research, including motivators and barriers.

4.7.2 Threats to Internal Validity

Fatigue, manifested as distractibility and slowed processing, can greatly affect the accuracy of research assessments (Lezak et al., 2004), as does lack of quiet space for cognitive testing on the inpatient unit. Interruptions may affect participants' ability to properly attend to instructions or comprehend a task, especially if the stroke has caused cognitive impairment. Sensory impairments (vision or hearing deficits) can have similar consequences, affecting the accuracy of the data and casting uncertainty on conclusions drawn.

We experienced a higher rate of missing data than might occur in other research settings, due in part to the burdensome (2.5 hour) baseline test battery could not always be completed. Data were not missing at random; participants with missing data tended to be older and more functionally impaired that those with complete data. Though participants with missing data can be dropped from analysis, the resulting implications for small sample sizes and statistical power make this an unattractive option, particularly in settings where recruitment is difficult and time consuming. To preserve sample size, the most acceptable method of handling missing data is multiple imputation (Tabachnick & Fidell, 2007), whereby missing values are imputed based upon probability estimates of their values using regression modeling with other variables as predictors. Multiple imputation relies on random draws from complete sets of predictor variables to determine a regression model for estimating missing values (Tabachnick & Fidell, 2007).

When many variables have missing data, as was the case with our studies, the accuracy of predicting missing values may be decreased.

4.7.3 Threats to External Validity

A major threat to external validity stemmed from our decision to exclude patients with aphasia and other communication disorders, and from potential selection bias related to the need for informed consent. Indeed, the generalizability of many rehabilitation studies, especially RCTs, has been questioned (Horn et al., 2012), in part because the rigorously controlled milieu required by most RCTs excludes many 'typical' persons with stroke, thereby skewing the sample. Self-selection bias further compromises external validity. Patients who refuse research participation may differ from those who enroll in research in important ways (Horn et al., 2012; Rothwell, 2005). We suspected that our sample was younger and less impaired than the overall population of patients admitted for inpatient stroke rehabilitation. Using de-identified RI quality improvement data, we calculated mean age, mean motor Functional Independence Measure (FIM) score, and mean cognitive FIM scores for all persons admitted for stroke rehabilitation between March 2009 and December 31, 2011. Comparison of patient population's values to those of participants enrolled during the same period revealed that participants were no different with respect to age, but they were significantly more functionally independent (Table 8), substantiating our suspicion of selection bias. Such a bias may have result in statistical restriction of range, causing falsely low associations among key variables (Tabachnick & Fidell, 2007) and obscuring true relationships, leading to Type II errors.

4.8 CONCLUSION

Conducting research on an inpatient stroke rehabilitation service can be challenging, and interpretation of research should be tempered by the distinct possibility that data may be obtained from a non-representative sample. Characteristics of patients and the clinical setting raise additional logistical and methodological concerns. Nevertheless, there is potential for mutual benefit for participants, clinicians, and researchers, making academic/clinical partnerships advantageous.

Table 7. UPMC Rehabilitation Institute Stroke Studies

Title, Source of Support, PI	Design and Goals	Description
Enhancing Rehabilitation After Stroke (Enhance) **R01 HD055525** PI: E. Whyte	Double-blinded RCT Examines the effect of donepezil on post-stroke therapy participation, and on cognitive, affective, and functional outcomes	Participants randomized to a medication group or placebo group Baseline functional, cognitive, and affective testing completed prior to starting medication Participants followed for 6 months, receiving regular follow up testing throughout
Web-Based Stroke Education (Stroke Education) **R44 NS052948** **Grant PI: D. Fox** **Site PI: E. Whyte**	Non-randomized effectiveness study Compares novel internet-based secondary prevention education program with 'standard of care' education (classes, informational brochures)	Participants assessed upon admission to inpatient rehabilitation regarding stroke knowledge and secondary prevention self-management practices Control group receives standard clinical education program; intervention group receives the web-based educational program Both groups' stroke knowledge and risk-related behavior (e.g., smoking) re-assessed 2 and 6 weeks post-discharge
Neurobehavior and Activity Interactions After Stroke,' or Neuro ADL **K12 HD055931** **PI: E. Skidmore**	Prospective observational study Explores interactions among motor, cognitive and affective impairments after stroke, and the influences of these interactions on ADL disability	Consenting participants assessed upon admission Re-assessed 6 months post-stroke
Co-operative Training for Stroke Rehabilitation (CO-Op) **K12 HD055931 and the UPMC Rehabilitation Institute Pilot Grant Program** **PI: E. Skidmore**	Single group experimental study Examines effect of intensive cognitive strategy training on cognitive, affective, functional outcomes	Participants receive baseline cognitive, affective, functional testing Daily, one-hour structured problem solving intervention using therapist-guided self-instructional cognitive strategy training protocol supplements usual care inpatient therapy program Participants followed for 6 months

Standing Tall After Stroke: Post-Stroke Cognition as a Fall Predictor during Inpatient Stroke Rehabilitation (Falls Study) **F31 NR01156, John A. Hartford Foundation, and Pittsburgh Pepper Center Pilot Grant Program** **PI: G. Campbell**	Prospective observational study Explores associations between functional, perceptual, and cognitive risk factors and the accidental falls during inpatient rehabilitation	Consented participants receive functional, perceptual, cognitive testing upon admission to inpatient rehabilitation Participants followed during inpatient rehabilitation for occurrence of accidental falls Fall circumstances collected via medical record review and participant interview when possible

Table 8. Comparison of Stroke Studies' Sample vs. Inpatient Stroke Rehabilitation Population

	Sample Mean (*SD*) *N* = 180	Population Mean (*SD*) *N* = 2436	Test Statistic, *p* value
Age	65.58 (14.60)	69.95 (14.64)	$t_{(2614)} = 3.86$, $p = .97$
Motor FIM	48.12 (15.82)	36.54 (13.04)	$t_{(2614)} = -11.32$, $p = .01$
Cognitive FIM	24.91 (5.54)	20.10 (7.34)	$t_{(2614)} = -8.61$, $p < .001$

APPENDIX A

PERMISSION TO REPRINT PUBLISHED ARTICLE, AND

MANUSCRIPT #1 : AN INTEGRATIVE REVIEW OF FACTORS ASSOCIATED

WITH FALLS DURING POST-STROKE REHABILITATION

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Grace B. Campbell, PhD (c), MSW, CRRN

Kirchstein NRSA Pre-doctoral Fellow

John A. Hartford Foundation Pre-doctoral Scholar

University of Pittsburgh School of Nursing

412-417-8804

gbc3@pitt.edu

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APPENDIX B

CHEDOKE MCMASTER STROKE ASSESSMENT

Chedoke McMaster Assessment: Impairment Inventory: Postural Control

Start at Stage 4. Starting position is indicated beside the item or underlined. No support is permitted. The score is the highest stage in which the client has at least 2 Xs.

POSTURAL CONTROL

1	☐	not yet Stage 2
2	☐ Supine	☐ facilitated log role to side lying
	☐ Side L	☐ resistance to trunk rotation
	☐ Sit	☐ static righting with facilitation
3	☐ Supine	☐ log roll to side lying
	☐ Sit	☐ move forward and backward
	☐ Stand	☐ remain upright for 5 seconds
4	☐ Supine	☐ segmental rolling to side lying
	☐ Sit	☐ static righting
	☐	☐ sit to stand
5	☐ Sit	☐ dynamic righting side to side, feet on floor
	☐	☐ stand with equal weight bearing
	☐ Stand	☐ step forward onto weak foot, transfer weight
6	☐ Sit	☐ dynamic righting backward and sideways with displacement, feet off floor
	☐ Stand	☐ on weak leg, 5 seconds
	☐	☐ sideways braiding 2 meters
7	☐	☐ <u>on weak leg</u>: abduction of strong leg
	☐	☐ tandem walking 2 meters in 5 seconds
	☐	☐ walk on toes 2 meters

STAGE OF POSTURAL CONTROL ____

APPENDIX C

LINE BISECTION TEST

ID# _____ Date _____ Data Collector_____

Line Bisection Test—Form A
Administration Instructions

1. Present the test form to the patient. Have the patient take the pencil in his/her dominant hand. If the patient cannot use the dominant hand due to weakness from the stroke or for any other reason, s/he should use the other hand.

2. Instruct the patient to **"Cut each line in half by placing a small pencil mark through each line as close to its center as possible. Do not mark the top line and the bottom line on this page."**

3. Ask the patient to **"Put your other hand in your lap, and try to keep it off the table,"** while pointing to the non-drawing hand.

4. Instruct the patient to **"Make only one mark on a line, without skipping any lines."**

Line Bisection Test
Scoring Instructions

Place the scoring key transparency over the completed test. Each line is numbered, and also labeled L, C, or R.

Score 1: Count the **number of unmarked lines** labeled L and enter in the L column; enter number of unmarked lines labeled C in the C column, and number of unmarked lines labeled R in the R column.

L	C	R

Score 2: Measured Left Half of each line. **Measure the distance from the start of each line to the subject's bisection,** to the nearest millimeter. Enter the number of millimeters in the box below corresponding to the line number. Indicate omitted lines with an X.

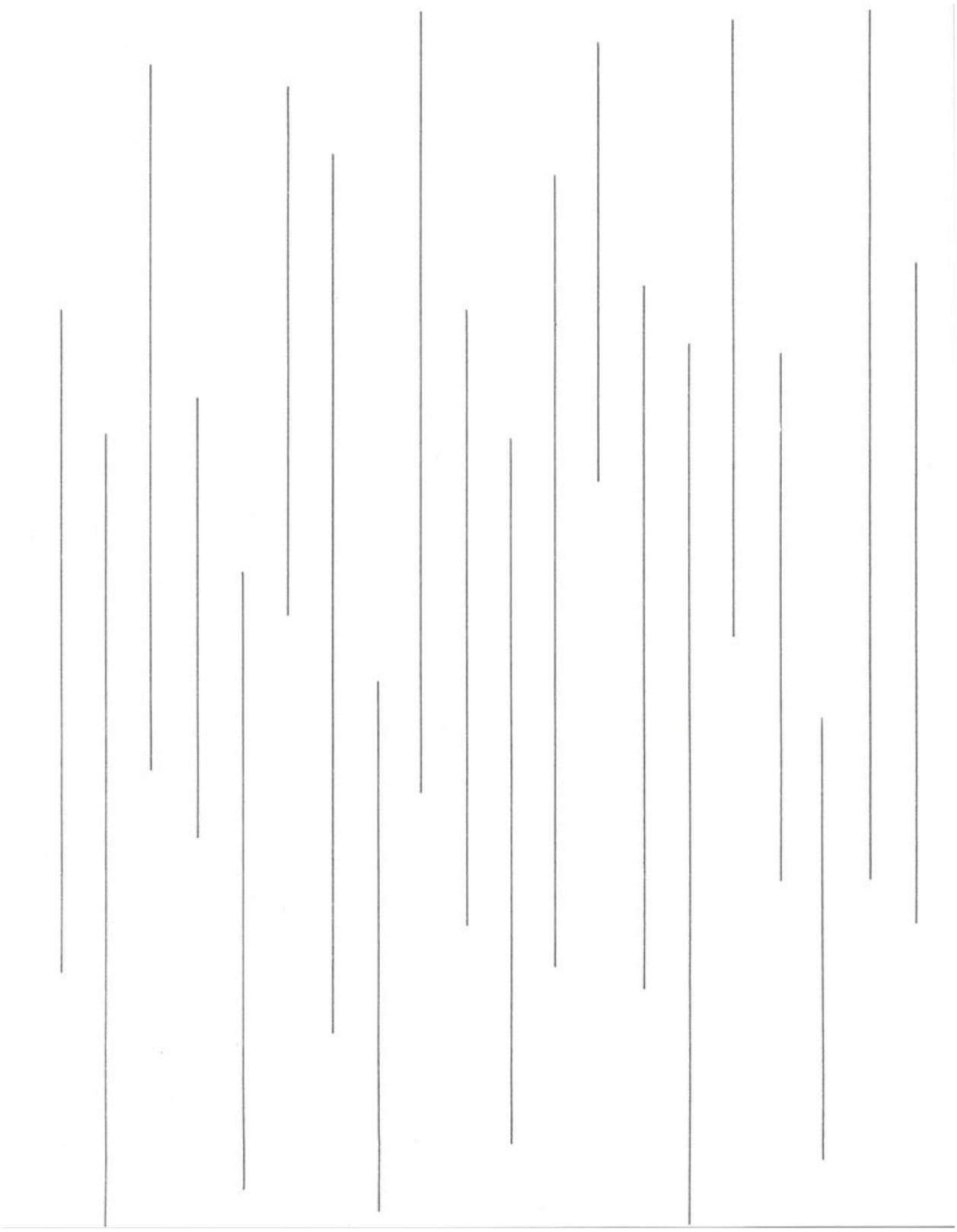
1		2		3	
4		5		6	
7		8		9	
10		11		12	
13		14		15	
16		17		18	

COMMENTS: If needed, please indicate reasons for non-completion or other comments below.

Patient Refused _____ Unable to complete—physical reasons _____

Unable to complete—cognitive or emotional reasons (agitation, confusion) _____

Other comments_____



APPENDIX D

THE EXECUTIVE INTERVIEW (EXIT)

APPENDIX E

CUMULATIVE ILLNESS RATING SCALE FOR GERIATRICS (CIRS-G)

APPENDIX F

FALLS OCCURRENCE RECORD

Fall Occurrence Record

Subject ID # _____ Location: _____Inpatient _____Home

Assessment (circle): Wk 1 Wk 2 Wk 3 Wk 4 Wk 6 Wk 8 Wk 12 Wk 18 Wk 24

1. **Occurrence of a fall** (NOTE: a fall is defined as any unplanned contact of the patient with the floor (controlled or uncontrolled) by body parts other than the soles of the feet. This includes assisting or lowering patients to the floor in order to prevent an unassisted fall).

   1a. **Hospital inpatient**: Fall Occurrence Date:_____

   1b. For **post discharge follow up**, ask the patient or caregiver, "**Have you fallen within the past week/2 weeks/4 weeks/6 weeks (since we last spoke with you)?**

   ____Yes, **If so, how many times?**(go to #2) _____ No **(STOP)**

   Number of falls in evaluation period _____

2. **Where did the fall occur?**

   _____ In hospital (go to #2a) _____ At home or in the community (go to #2b)

   2a. For falls occurring in hospital, mark the single ***best*** response for the exact location of the fall. If the exact location is not listed below, choose the response that most closely matches the fall location.

   _____ Patient room/bedroom _____ Bathroom

   _____Shower room _____ Public area (e.g. hall, lounge, lobby)

   _____Therapy gym _____ Outdoors

   _____Unknown

   2b. For falls occurring at home/in the community, mark the single ***best*** response for the exact location of the fall. If the exact location is not listed below, choose the response that most closely matches the fall location.

_____Bedroom _____Bathroom

_____Kitchen _____Other room of home

_____Steps _____Outdoors

_____Public place (mall, church, etc.) _____Unknown

3. Was the fall assisted or unassisted?

_____Assisted _____Unassisted

4. **What was the patient doing during or just prior to the fall (inpatient or home/community)?** (Choose the one ***best*** response).

_____Attempting to transfer into bed

_____Attempting to transfer out of bed

_____Attempting to walk to or from the bathroom

_____Attempting to walk (general)

_____Reaching for an item (e.g. urinal, call bell)

_____Lying in bed

_____Sitting in chair

_____Unknown

5. Did the fall appear to result from an unanticipated medical problem (e.g. syncopal episode, seizure, hypotension) ?

_____Yes _____No _____Unknown

6. Was any injury sustained as a result of the fall?

____None ____Minor (bruise, minor cuts) ____Major (fracture, hemorrhage) ____Death

Patient Interview:

1. Hello, Mr/Mrs/Miss _____. My name is _____, and I am one of the study nurses in the research project about stroke care that you are participating in. May I speak with you for a moment? I'd like to audiotape your comments, if I may, to help me remember what you said later. (see next page)

I understand that you fell yesterday. Is that correct?

_____Yes (go to 10c) _____ No (go to 10b) _____Unknown or unable to specify (go to 10b).

2. The nurses had mentioned to me that you had fallen. Can you think why they might have that impression? Did you lose your balance, or trip? (If unable to provide details or unable to remember a fall, STOP).

3. It is not uncommon for patients with stroke to fall. Falls can lead to serious injuries, so we would like to learn to prevent injuries related to falls. If we can learn about falls from the viewpoint of people who experience them, this may help us to understand how to keep people with strokes safe from injury.

Can you tell me about the fall you had?

4. What do you think caused you to fall?

5. What do you think might have prevented this fall?

6. Have you had any "near miss" falls within the last _____ ? For example, at any time did you lose your balance but catch yourself before you fell? Or, did your legs give out and a staff person or family member kept you from falling? If so, can you tell me about that?

Mr/Mrs/Miss _____, thank you for talking with me. Your comments will be very helpful as we try to understand falls and prevent injuries in people with stroke.

APPENDIX G

MANUSCRIPT #2: RELIABILITY AND VALIDITY OF THE EXECUTIVE INTERVIEW (EXIT) AND QUICK EXIT AMONG COMMUNITY DWELLING OLDER ADULTS

Reliability and Validity of the Executive Interview (EXIT) and Quick EXIT among Community Dwelling Older Adults

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[1]University of Pittsburgh School of Nursing Department of Acute/Tertiary Care; [2]University of Pittsburgh School of Medicine, Department of Psychiatry; [3]University of Pittsburgh School of Medicine, Department of Physical Medicine and Rehabilitation; [4]University of Pittsburgh School of Nursing Department of Health and Community Systems; [5]University of Pittsburgh Graduate School of Public Health, Department of Biostatistics; [6]University of Pittsburgh Graduate School of Public Health, Department of Epidemiology; [7]University of Pittsburgh Department of Psychology

The authors would like to thank Michelle Zmuda, Program Coordinator, and the staff of the Geriatric Neuropsychology Research Program for assessing all of the participants in this study.

Abstract

Objectives: To investigate the psychometric properties of the EXIT and Quick EXIT in community dwelling older adults.

Design: Secondary analysis of cognitive data obtained as part of a longitudinal study of cognitive function in late life depression.

Setting: An academic hospital.

Participants: Community dwelling adults (*n*=422), aged 59 years and older, with current or recent history of non-psychotic unipolar major depression, and never-depressed control subjects.

Measurements: The EXIT and other measures of executive functions (ECF), non-executive cognitive domains and global cognitive function. We calculated Quick EXIT scores from the EXIT.

Results: The EXIT demonstrated strong inter-rater reliability (Intraclass correlation coefficient = .978, $p < .001$), while both the EXIT and Quick EXIT demonstrated moderate internal consistency ($\alpha = 0.66$ and $\alpha = 0.68$, respectively). Both tests also demonstrated acceptable convergent validity against several standard tests of ECF (Spearman's *rho* -.399 to .322, except for the Trail Making Test B, where *rho* was .057 to .063) as well as against measures of global cognition (*rho* -.432 to .491). However, both tests demonstrated inconsistent discriminant validity against a variety of standard non-ECF tests (*rho* -.013 to .376).

Conclusions: Both the EXIT and the Quick EXIT have adequate reliability and appear to be tapping ECF impairment in this population. However, both the EXIT and the Quick EXIT also reflect non-ECF domains. The EXIT and Quick EXIT should be considered to be measures of global cognitive function rather than a pure ECF measure. Given similar reliability and validity,

the Quick EXIT would be preferred clinically as it is briefer and less burdensome than the full EXIT.

Impairments in executive control functions (ECFs), sometimes simply called "executive functions," are common and clinically significant in older adults (Fisk & Sharp, 2004; Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998; Nielson, Langenecker, & Garavan, 2002; Turner & Spreng, 2012). Impairment in ECF is associated with poor performance of important tasks necessary for independent, community-based living, such as dressing, grooming, managing finances, and performing other home- and job-related tasks. Indeed, impairment in ECF has been shown to predict the level of care required by older adults.(Lavery et al., 2005; Mitchell & Miller, 2008; Royall, Chiodo, & Polk, 2005; Royall, Mahurin, & Gray, 1992) Furthermore, deficits in ECF are associated with impaired balance and mobility (Liu-Ambrose et al., 2007) and decreased gait speed (Atkinson et al., 2007; Watson et al., 2010) in older adults, suggesting that intact ECF is integral to both basic and complex functional skills.

ECF is an umbrella term encompassing numerous individual constructs, and there is no consensus on specific components (Rabbit, 1997). Often-studied components of ECF include cognitive fluency (rapidly generating many solutions to a task); set shifting or mental flexibility (ability to switch back and forth between types of stimuli or responses); abstract reasoning; response inhibition (ability to suppress an overlearned or nearly automatic response in favor of producing a more effortful response); and task planning and sequencing (the ability to initiate and follow complex behavior patterns). Some researchers also include working memory (the ability to hold information in one's mind while performing mental manipulations), various behavioral attributes (such as apathy or agitation), and primitive reflexes such as grasp and snout reflexes (Kramer & Quitania, 2007). The components of ECF are complex and interrelated; hence, evaluating ECF requires a lengthy battery of neuropsychological tests which can be a significant burden for patients or research subjects.

Royall and colleagues (1992) developed a single assessment tool, the Executive Interview (EXIT), as an alternative to a traditional ECF battery. The EXIT may be used in any clinical setting, can be administered and scored by trained personnel of any discipline, and requires only 15 minutes to complete, (Stokholm et al., 2005), making it a practical, 'bedside' alternative to traditional ECF tests. During initial validation testing with 40 residents of a retirement community representing a continuum of care from independent living through intermediate care and dementia care, Royall et al. (1992) reported that the EXIT showed high internal consistency (Cronbach's alpha = 0.87) and high inter-rater reliability (Pearson's $r = 0.90$).

However, despite its strengths, the EXIT may have limited utility in some clinical populations. For example, while an administration time of 15 minutes is an improvement over lengthy neuropsychological batteries, even 15 minutes may be burdensome for acutely ill or easily fatigued patients. In addition, the behavioral requirements of certain items could perplex some individuals, leading to scores that may be confounded by either social desirability response bias or a misunderstanding of the examiner's expectations, rather than indicating actual ECF impairment. The Quick EXIT (Larson & Heinemann, 2010) is a short form of the EXIT developed to be less burdensome and perplexing to subjects and to have improved face validity and content validity. In a sample of 147 subjects with acquired brain injury, internal consistency and construct validity were similar to that of the original EXIT.

Initial work establishing the EXIT's reliability and validity was conducted in the small sample of 40 older adults described above (Royall et al., 1992). Neither the EXIT nor the Quick EXIT have been fully validated in a large population of older adults, and against a wide range of neuropsychological tests of both ECF and other, non-ECF domains of cognitive function.

Therefore, we conducted a secondary analysis involving a large sample of community dwelling older adults in order to examine the psychometric properties of the EXIT and the Quick EXIT.

Methods

Participants. Subjects for the analyses were participants in a federally funded longitudinal study of cognitive function in late-life depression [PHS R01 MH080240] (Bhalla et al., 2006; Butters et al., 2000) conducted within the Advanced Center for Intervention and Services Research Center for the Study of Late-Life Mood Disorders at the University of Pittsburgh School of Medicine between 1996 and 2009. The protocol was approved by the Institutional Review Board of the University of Pittsburgh, and all subjects provided written informed consent. Recruitment and eligibility criteria have been described in detail elsewhere. (Butters et al., 2000; Butters et al., 2004) For this study, we analyzed data from 422 community dwelling adults, aged 59 years and older, both with current and recent history of non-psychotic unipolar major depression and never depressed comparison subjects, using data from their baseline assessment. Participants with medical conditions that could directly affect cognitive abilities, such as traumatic brain injury, multiple sclerosis, or dementia, were excluded (Butters, et al., 2004).

Measures.

EXIT. The EXIT (Royall et al., 1992) is a 25-item screening tool that yields a single score reflecting a broad array of executive functions. Each item's possible score ranges from 0 to a maximum of 2 points; total scores range from 0 to 50, with a high score indicating greater ECF impairment. The items test number/letter sequencing; word and design fluency; sentence-

repetition; thematic perception; memory, with distraction; interference inhibition; grasp and snout reflexes; social habits; motor perseveration; finger-nose repetition; echopraxia; complex hand sequences; complex commands; counting and serial-order reversal; and automatic, utilization, and imitation behavior.

Quick EXIT. The Quick EXIT (Larson & Heinemann, 2010) is an abridged, 14-item version of the original EXIT. It was developed by omitting 11 EXIT items that fit the scale poorly, based on a Rasch analysis of item difficulty and fit. Items omitted include those testing primitive reflexes, social habit, and automatic, utilization, and imitation behaviors. It is scored identically to the EXIT, with a range of 0 to 28, with higher scores also indicating greater ECF impairment. For this analysis, we derived the Quick EXIT score from the subjects' original EXIT item scores.

Convergent Validity Measures. We examined the following commonly used tests of ECF, all of which have strong, established psychometric properties in older adults: the Stroop Color-Word Interference Test (Lezak et al., 2004), the Trail Making Test (Lezak et al., 2004) the Wisconsin Card Sorting Test perseverative errors score (Lezak et al., 2004), the Initiation/Perseveration (I/P) subscale of the Dementia Rating Scale (Marson, Dymek, Duke, & Harrell, 1997), and the Clock Drawing Task (Rouleau & Salmon, 1992). See Table 1 for a description of these instruments, and for the median and range of these tests in our sample.

Discriminant Validity Measures. We included tests of other types of cognitive ability, purportedly without a significant ECF component, as well as several tests of global cognitive function, in order to evaluate discriminant validity. These tests included the Trail Making Test Part A (attention and processing speed) (Lezak et al., 2004), the Boston Naming Test (language)

(Lezak et al., 2004), the Speed and Capacity of Language Processing Spot the Word task (vocabulary)(Strauss et al., 2006), the Finger Tapping Test (fine motor speed),(Lezak et al., 2004) the Attention subscale of the DRS (visual construction ability)(Marson et al., 1997), the California Verbal Learning Test discriminability index (verbal recognition memory) (Lezak et al., 2004), and the Simple Drawings Test (visuospatial ability) (Goodglass & Kaplan, 1983). The tests of global cognitive function included the Mini Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975) and the Digit Symbol Subtest of the WAIS-IV (Lezak et al., 2004). All of these tests have demonstrated reliability and validity in older adults. See Table 1.

Procedure. Participants were administered either a full neuropsychological test battery or smaller subset of this battery (depending on when they were enrolled), that is standard for all participants in the Center's studies. Component tests of this battery are described below (see Measures). Five neuropsychological examiners, under the supervision of a qualified, experienced neuropsychologist (MAB), administered all tests, including the EXIT.

After completing the neuropsychological test battery, an 8-subject subset of the sample participated in an EXIT inter-rater reliability study. One of the five examiners administered the EXIT to each of the 8 subjects while being videotaped. The remaining 4 examiners independently viewed the videotaped sessions and computed EXIT raw scores for each subject.

Data Analysis. SPSS software version 21.0 (IBM, Released 2012) was used for all analyses. We analyzed descriptive data for the entire sample on key demographic and clinical characteristics using proportions for categorical variables, and medians with interquartile ranges (IQRs) for continuous variables.

We examined reliability and validity using nonparametric statistics due to the skewed distribution of neuropsychological test scores in our sample, which was expected given our focus on a sample of community dwelling older adults. We computed internal consistency and inter-rater reliability for both the EXIT and Quick EXIT. Because Cronbach's alpha may underestimate the internal consistency of ordinal scales with fewer than 5 levels of response, we used a nonparametric alternative by calculating the mean Spearman's rank order correlations (Zumbo, Gadermann, & Zeisser, 2007) between the EXIT items, then using those nonparametric correlations to calculate Cronbach's alpha. Inter-rater reliability was analyzed using the intraclass correlation coefficient, ICC, calculated to determine consistency among raters using a two-way random effects model, to allow generalization to all possible subjects and all possible raters.

We assessed convergent and discriminant validity by estimating the Spearman's correlation coefficients between the criterion measures described in Table 1, and both EXIT and Quick EXIT total scores. We used the 95% confidence interval to determine statistical significance of validity coeffiecients.

Results

The median age of participants was 73 years (IQR = 68-78); the sample was nearly 70% female, with a median 13 years of education (IQR = 12-16) and with a median Hamilton Rating Scale for Depression score of 5 at the time of assessment (IQR 3-8). The largely Caucasian sample (89%) reflects the demographic characteristics of western Pennsylvania, the geographical area from which the sample was drawn. A convenience sample of 8 participants willing to have their assessed video-recorded were utilized for the inter-rater reliability analysis.

Internal consistency for both the EXIT and Quick EXIT was moderate, $\alpha = 0.66$ and $\alpha = 0.68$, respectively. Inter-rater reliability of the EXIT among 4 raters was robust; the ICC was .978, $p < .001$.

Convergent and discriminant validity coefficients are presented in Table 2. The EXIT was moderately and significantly correlated with most tests of ECF, including the Wisconsin Card Sorting Test, the Stroop Color-Word Test, the Dementia Rating Scale Initiation/Perseveration Subscale, and the Clock Drawing Test, but was not correlated with the Trail Making Test-B. Discriminant validity tests showed the expected weak (non-significant) correlation between EXIT total scores and some of the non-ECF measures (Boston Naming Test, Trailmaking Test-A), but unexpectedly demonstrated a moderate, significant correlation between the EXIT and other non-ECF measures, including the Simple Drawings test, the California Verbal Learning Test discriminability measure, the Dementia Rating Scale Attention Subscale, Spot the Word Errors, and the Finger Tapping Task. Regarding tests of global cognitive functioning, the EXIT was moderately correlated with both the Digit Symbol Subtest and the MMSE.

The Quick EXIT demonstrated similar convergent validity as the EXIT. In terms of discriminant validity, the Quick EXIT demonstrated the same pattern of correlations as seen between the EXIT and tests of non-ECF domains and global cognitive function.

Conclusions

In our sample of community dwelling older adults, the EXIT demonstrated strong inter-rater reliability, while both the EXIT and Quick EXIT demonstrated moderate internal consistency. Both tests also demonstrated acceptable convergent validity against standard tests of

ECF. However, both tests demonstrated relatively poor discriminant validity, as both tests demonstrated moderately high correlations with some measures that tap non-ECF domains.

We demonstrated moderate internal consistency of the EXIT ($\alpha = 0.66$) in our large sample of community dwelling older adults. The EXIT purports to test a variety of the component domains of ECF; hence, our results are not unexpected, and may accurately reflect the multi-dimensional nature of ECF. However, our results for the EXIT differ from those obtained by other researchers, including Royall's and Larson's groups ($\alpha = 0.87$ and $\alpha = 0.86$, respectively). Similarly, our finding regarding internal consistency of the Quick EXIT ($\alpha = 0.68$) also differs from that reported by Larson's group ($\alpha = 0.88$). These differences may reflect differences in the sample characteristics. Our sample excluded persons with clinically definable brain pathology and therefore, demonstrated a more restricted range of cognitive function, and lack of diversity of types of cognitive impairment relative to the participants in the other studies. Royall's sample was selected to have a broad range of cognitive impairment (no impairment to severely impaired) and Larson's sample included persons with acquired brain injury. Nevertheless, the internal consistency demonstrated by the EXIT and QUICK EXIT in our sample is acceptable (Ferketich, 1990; Streiner, 2003). We demonstrated robust inter-rater reliability of the EXIT although our result was slightly lower than reported by Royall. Again, differences in the sample characteristics, with its resultant restriction of range of scores in our sample of community-dwelling older adults, may have affected our results.

Our analysis suggests that both the EXIT and the QUICK EXIT are acceptable measures of ECF, based on their significant correlations with a variety of other accepted tests of ECF and global cognitive function as well as similar internal consistency. Our results regarding the EXIT are consistent with Royall's group regarding convergent validity in that they found that the EXIT

correlated strongly with similar tests of ECF. However, the ability of the EXIT and the QUICK EXIT to distinguish ECF impairment from impairment in other cognitive domains in our target population is variable, at best. Discriminant validity tests showed the expected weak (non-significant) correlation between EXIT total scores and some of the non-ECF measures, but unexpectedly demonstrated a moderate, significant correlation between the EXIT and other non-ECF measures. This finding is consistent with other studies (Larson & Heinemann, 2010; Royall et al., 1992). Royall reported that EXIT scores correlated with ECF tests (Trail Making Test-B, Wisconsin Card Sorting Test) and tests that we considered to be non-ECF tests (Trail Making Test-A, sustained attention/tracking). Similarly, Larson reported that the EXIT and Quick EXIT correlated with ECF tests (Trail Making Test-B) and tests that we considered to be non-ECF tests (Trail Making Test-A, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) subscales including attention, language, visuo-construction, immediate memory and delayed memory).

The association of the EXIT with the 'non-ECF' tests may reflect the innate dependence on executive functions of non-ECF tasks. For example, the Larson study found that the EXIT correlated with the RBANS immediate and delayed memory index. As pointed out by the authors, this is not wholly surprising as these memory indices rely on retrieval ability (an executive function). However, in our study, we selected measures for our examination of discriminant validity that are minimally reliant on ECFs. We used a recognition memory task that tests the person's ability to retain (a pure memory function) but not retrieve information. However, even when using relatively 'pure' non-ECF tasks, we still found correlations with the EXIT. Furthermore, non-ECF skills are needed to complete ECF tasks. For example, as pointed out by Larson et al, the EXIT requires strong expressive language skills and hence a correlation

of the EXIT with language tests is not completely unexpected. We believe that this relationship explains our finding of a correlation between the EXIT, a measure of a higher order cognitive function (executive functions) and tests of motor speed and attention, which measure very basic cognitive functions. Further, our results echo those of Koltai et al. (1997), who found similar correlations between EXIT and a variety of ECF and non-ECF cognitive tests. They suggest that poor scores on the EXIT indicate presence of a cognitive deficit with an executive component, but that the EXIT is not likely to be a specific, reliable measure of ECF alone.

Our study has several limitations. First, as noted above, we focused on a community sample initially chosen to reflect a range of cognitive functioning. However, a ceiling effect can be seen in our sample's global cognitive function (MMSE) scores, suggesting that in our sample, the abilities and skills needed to live in the community may have effectively excluded subjects exhibiting a broad range of cognitive impairment. This ceiling effect may have lowered the level of internal consistency we observed and may have reduced the true sizes of correlations with tests of other domains. We must also consider that our participants in our sample likely have ECF impairments due to subcortical brain dysfunction as seen in subclinical cerebrovascular disease (e.g., small vessel ischemic brain changes which are long term consequences of common disease such as hypertension and diabetes) and/or late-life major depression. As such, it is possible that the types of cognitive impairment seen in our sample were restricted primarily to those deficits in domains associated with subcortical structures, namely ECF, attention, and speed. A relative strength of this study is that for the discriminant validity analysis we chose tasks most likely to be independent of ECF. However, we acknowledge that there are no 'pure' cognitive tests; that is, performance on any given test depends on performance ability in other domains. Another strength is that we only used data

from each subject's initial testing session; hence avoiding practice effects confounding the test scores.

Our analysis suggests that both the EXIT and the Quick EXIT tests are able to detect ECF impairment in this population. However, both the EXIT and the Quick EXIT correlated with tests of non-ECF, suggesting that they have limited utility in distinguishing ECF impairment from other types of cognitive impairment. Practically, this may have two implications. First, it may not be possible to capture 'pure' ECF especially using bedside measures due to the interdependency of cognitive domains. Second, the EXIT and QUICK EXIT could be considered to be measures of global cognitive function with an ECF component, than pure ECF measures. Given the similar reliability and validity between the two tests, the shorter, less burdensome Quick EXIT appears to be the preferred bedside measure of executive cognitive function in clinical populations.

Table 1. Tests Used to Analyze Convergent and Discriminant Validity

	Instrument	Domain Measured	*N*	Median (IQR)
	EXIT		422	8.0 (5.0-11.0)
	Quick EXIT		422	4.0 (2.0-6.0)
Executive Functions	**Wisconsin Card Sort Test (WCST)** (Perseverative Errors)	Set Maintenance and Set Shifting	325	10 (5.5-14.5)
	Trail Making Test-B (TMT-B) (Ratio of TMT-B time/connection to TMT-A time/connection)	Divided Attention	319	2.5 (1.9-3.1)
	Stroop Color-Word Test (Ratio of Color-Word Score to Color Naming Score)	Response Inhibition	311	2.7 (2.2-3.2)
	Clock Drawing Test	Planning and Sequencing	346	9 (8.5-9.5)
	Dementia Rating Scale I/P Subscale	Initiation and Perseveration	422	37 (36.5-37.5)
Non-Executive Function	**Speed and Capacity of Language Processing Spot-the-Word Errors (SCOLP)**	Verbal Memory (Recognition)	318	9 (5.4-12.6)
	Boston Naming Test	Language (Visual Naming Ability)	341	56 (53-59)
	Trailmaking Test A (TMT-A) (Time/connection)	Psychomotor Speed	316	1.6 (1.2-2.0)
	Simple Drawings	Visuospatial Impairment	400	16 (14.5-17.5)
	California Verbal Learning Test (CVLT) Discrimination Task	Verbal Memory-recognition	359	93 (88.5-97.5)
	Dementia Rating Scale Attention Subscale	Complex Attention	422	36 (35-37)
	Finger Tapping Task	Motor Speed	297	38.6 (32.1-45.1)

Global Cognition	**Digit Symbol Subtest (DSST)**	Emphasis on Attention, Visual Scanning, Memory	343	40.8 (33.1-48.6)
	Mini Mental State Exam (MMSE)	Emphasis on Attention, Memory, Language	422	29 (28-30)

Table 2. Validity Coefficients for EXIT and Quick EXIT vs. Criterion Neuropsychological Tests

	Test	EXIT Rho (95% C.I.)	Quick EXIT Rho (95% C.I.)
Executive Functions (Convergent Validity)	**Wisconsin Card Sort Test (WCST)**	.343 (.244, .435)	.351 (.252, .442)
	Trail Making Test B (TMT-B)	.057 (-.053, .165)	.063 (-.047, .171)
	Stroop Color-Word Test	.322 (.219, .419)	.338 (.236, .432)
	Clock Drawing Test	-.389 (-.474, -.296)	-.375 (-.462, -.281)
	Dementia Rating Scale I/P Subscale	-.377 (-.456, -.293)	-.399 (-.476, -.316)
Non-Executive Functions (Discriminant Validity)	**Speed and Capacity of Language Processing Spot-the-Word Errors (SCOLP)**	.326 (.225, .420)	.376 (.278, .493)
	Boston Naming Test	.081 (-.025, .185)	.044 (-.062, .149)
	Trail Making Test A (TMT-A)	-.013 (-.096, .122)	.037 (-.072, .145)
	Simple Drawings	-.142 (-.236, -.045)	-.143 (-.237, -.046)
	California Verbal Learning Test (CVLT) Discriminability Index	-.357 (-.444, -.264)	-.369 (-.455, -.277)
	Dementia Rating Scale Attention Subscale	-.347 (-.428, -.261)	-.365 (-.444, -.280)
	Finger Tapping Task	-.337 (-.434, -.233)	-.338 (-.435, -.234)
Global Cognition (Convergent Validity)	**Digit Symbol Subtest (DSST)**	-.432 (-.514, -.342)	-.491 (-.564, -.407)
	Mini Mental State Exam (MMSE)	-.440 (-.513, -.360)	-.465 (-.536, -.387)

APPENDIX H

INSTITUTIONAL REVIEW BOARD APPROVAL LETTERS

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Grace Campbell

From: Christopher Ryan , Vice Chair

Date: 8/11/2010

IRB#: PRO10010401

Subject: Post-Stroke Cognition as a Fall Predictor During Inpatient Rehabilitation

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110. Your research study was approved under:

45 CFR 46.110.(4)
45 CFR 46.110.(5)
45 CFR 46.110.(6)
45 CFR 46.110.(7)

This study is supported by the following federal grant application(s):
NIH (NINR) 1F31NR011561-01 Post-Stroke Cognition as a Fall Predictor During Inpatient Rehabilitation

The IRB has approved a waiver of HIPAA authorization requirement for the sharing of contact information.

Approval Date: 8/10/2010

Expiration Date: 8/9/2011

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.
Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.
The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).
Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

University of Pittsburgh
Institutional Review Board

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Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Grace Campbell BSN MSW RN

From: Christopher Ryan PHD, Vice Chair

Date: 6/24/2011

IRB#: REN11060101 / PRO10010401

Subject: Standing Tall After Stroke: Post-Stroke Cognition as a Fall Predictor During Inpatient Rehabilitation

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:
45 CFR 46.110.(4)
45 CFR 46.110.(5)
45 CFR 46.110.(6)
45 CFR 46.110.(7)

Please note the following information:

Approval Date: 6/24/2011
Expiration Date: 6/23/2012

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

University of Pittsburgh
Institutional Review Board

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Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Grace Campbell BSN MSW RN

From: Christopher Ryan , Vice Chair

Date: 4/25/2012

IRB#: REN12040145 / PRO10010401

Subject: Standing Tall After Stroke: Post-Stroke Cognition as a Fall Predictor During Inpatient Rehabilitation

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:

45 CFR 46.110.(4)
45 CFR 46.110.(5)
45 CFR 46.110.(6)
45 CFR 46.110.(7)

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

University of Pittsburgh
Institutional Review Board

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Pittsburgh, PA 15213
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Memorandum

To: Grace Campbell BSN MSW RN

From: Christopher Ryan PHD, Vice Chair

Date: 2/14/2013

IRB#: REN13020134 / PRO10010401

Subject: Standing Tall After Stroke: Post-Stroke Cognition as a Fall Predictor During Inpatient Rehabilitation

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:

45 CFR 46.110.(4)
45 CFR 46.110.(5)
45 CFR 46.110.(6)
45 CFR 46.110.(7)

Please note the following information:

Approval Date: 2/14/2013

Expiration Date: 2/13/2014

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX I

INSTITUTIONAL REVIEW BOARD

APPROVED CONSENT FORM

University of Pittsburgh

School of Nursing

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: Standing Tall After Stroke: Post-Stroke Cognition as a Fall Predictor During Inpatient Rehabilitation

PRINCIPAL INVESTIGATOR:
Grace Campbell, BSN, MSW, RN
Doctoral Student, School of Nursing
440 Victoria Building
3500 Victoria Street
Pittsburgh, PA 15261
412-624-4722 or 412-417-8804

CO-INVESTIGATORS:

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Elizabeth Skidmore, PhD
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(412) 383-6617

Patrick Sleeth
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(412) 246-6012

Ellen M. Whyte, MD
Assistant Professor,
Departments of Psychiatry and Physical Medicine and Rehabilitation
(412) 246-6006

SOURCE OF SUPPORT: National Institute of Nursing Research; John A. Hartford Foundation

Why is this research being done?
We are currently conducting a research study to explore whether physical function, visual perception, and cognition (thinking) are related to accidental falls in persons who have recently had a stroke.

At this time, you are being asked to participate in this study. If you agree to participate, we will assess your physical health and function, emotional well-being, and cognitive function. We will also interview you to determine whether you currently have symptoms of depression.

Who is being asked to take part in this study? You are being invited to participate in this research study because you are age 18 or older, have recently experienced a stroke, and are currently a patient at one of the inpatient rehabilitation units of the University of Pittsburgh Medical Center (UPMC).

Two hundred twenty five (225) patients of both sexes and all races are being asked take part in this study.

What procedures will be performed for research purposes?

SCREENING PROCEDURES

First we will determine whether you are eligible to participate in this study by asking you to complete a simple thinking and speaking task, which will take approximately 15 minutes. We will also review your medical history (in your medical chart) for conditions that would interfere with your eligibility for the study, such as a recent seizure or a progressive neurological disorder (e.g. MS, Parkinson's disease).

EXPERIMENTAL PROCEDURES

If you meet the eligibility criteria for the study, we will conduct a detailed assessment of your physical function, your thinking abilities (such as memory and attention), your emotional wellbeing, and your physical health. These assessments will take approximately 2 ½ hrs. The assessment can be broken up into several sessions and will not interfere with your rehabilitation activities.

- We will ask you to demonstrate to us simple tasks (such as speaking, performing a hand grasp or lifting an arm or leg off the surface of the bed,). You will also undergo a neurological examination (similar to the exam done by medical doctors) which will include assessing for numbness and testing your muscle strength, coordination, and vision.

- We will ask you to complete pen-and-paper tests that will assess your memory and concentration, your language skills, and your ability to solve problems. We will also ask you to complete some tests that will assess your memory, concentration and language skills.

- We will ask you questions about your mood, motivation and level of interest and enjoyment in activities.

MONITORING/FOLLOW-UP PROCEDURES:

While you are a patient on the rehabilitation unit, we will speak with the clinical staff at least once a week to determine whether you have experienced a fall.

- ✓ If you have experienced a fall, we will interview you briefly about the circumstances of the fall and whether it caused injury. This interview will take about 15-20 minutes. We will also look in your medical chart to gather clinical information about the circumstances surrounding the fall.

- ✓ We will ask you if we can make an audio recording of this interview. You may decline to have this interview recorded, but still participate in the post-fall assessment.

- ✓ We will also interview anyone who witnessed the fall, including the rehabilitation unit staff as well as any family or friends who were visiting when you fell. We will ask for your specific permission before contacting any family members or friends who witnessed the fall.

What are the possible risks, side effects, and discomforts of this research study? There may be some emotional discomfort or you may become tired while answering some of the questions. We can take breaks during the assessments as needed.

Risks of breach of confidentiality of research data: There is a possibility that if your study research data were to become generally known, this knowledge of your research data could potentially impact your future insurability, employability, or reproduction plans: or have a negative impact on family relationships; and/or result in shame or embarrassment.

If you should fall, we will, with your permission, audio record our interview following the fall with you. If your name is inadvertently be recorded, that portion of the audio tape will be deleted and your name will not appear in any transcripts of the audio tape. There is also a risk that someone hearing that tape may recognize your voice and your research data therefore may become generally known. We will keep all of your research data (including any recordings) in locked file cabinets in locked offices or in password protected, encrypted electronic databases with access only to research staff to minimize this risk.

What are the possible benefits from taking part in this research study? There may not be any direct benefit to you. However, during the assessment of your health and mood, we may discover previously unrecognized medical or emotional problems. If this happens, you will be referred for appropriate treatment based on your needs and desires. This research may benefit society by increasing our understanding of fall risk among persons who have experienced a stroke. By increasing this understanding, we may minimize the occurrence of falls among patients undergoing post-stroke rehabilitation in the future.

What treatments or procedures are available if I decide not to take part in this research study? If you decide not to take part in this research study, you will receive the standard assessment provided through the inpatient rehabilitation program.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study? You will be promptly notified if any new information develops during the conduct of this research study which may cause you to change your mind about participating.

Will I or my insurance provider be charged for the costs of any procedures performed as part of this research study? You or your insurance provider will not be billed for assessments conducted for the purpose of this research study. The study or study sponsor will pay for these research services. You and your insurer will be billed for routine care, including the rehabilitation care being provided during inpatient rehabilitation. Costs of routine care not covered by insurance are your responsibility, including any applicable copays, coinsurances and deductibles.

Will I be paid if I take part in this research study? You will not be paid for participation in this research study.

Who will pay if I am injured as a result of taking part in this research study? University of Pittsburgh investigators and their associates who provide services at the UPMC recognize the importance of your voluntary participation to their research studies. These individuals and their staffs will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. Risk of injury as a result of participating in this study is extremely low.

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation.

Who will know about my participation in this research study? Any information about you obtained from this research will be kept as confidential (private) as possible. All data obtained from this research will be kept in a locked file cabinet and secured in a password-protected database. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by name in any publication of research results unless you sign a separate form giving your permission (release).

Will this research study involve the use or disclosure of my identifiable medical information? This research study will involve the recording of current identifiable medical

information from your hospital and/or other (e.g., physician or psychologist office, pharmacy) records. The information that will be recorded will be limited to information concerning your demographics (such as your age, gender, education, race, marital status), and your name. We will also record information about your mental health that we are unable to obtain during your interviews, such as the symptoms of depression. In addition, we will record information about your physical health such as the Functional Independence Measure (FIM), current medications, history of falls since admission to inpatient rehabilitation, information about certain rehabilitation interventions such as types of therapy and nursing interventions used during the rehabilitation stay, history of falls since admission to the inpatient rehabilitation unit, stroke location and volume (using findings from a brain MRI, if you received an MRI prior to rehabilitation admission), and results from physical exams and lab testing (such as cognitive testing).

This research study will result in identifiable information that will be placed into your medical records held at UPMC. The nature of the identifiable information resulting from your participation in this research study that will be recorded in your medical record includes a copy of your signed consent form, and progress notes about your study participation. In addition, if we discover a previously undiagnosed medical or psychiatric condition, we will inform you and (with you permission) your treatment team here at the inpatient rehabilitation unit and your primary care physician.

Who will have access to identifiable information related to my participation in this research study? In addition to the investigators listed on the first page of this consent form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study:

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives of the sponsors of this research study, the National Institute of Nursing Research (NINR) and the John A. Hartford Foundation, may review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data. While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical information, the UPMC and University of Pittsburgh

cannot guarantee the confidentiality of this information after it has been obtained by the study sponsor.

Authorized representatives of the UPMC hospitals or other affiliated health care providers (such as physical, occupational, and speech therapy staff, neuropsychological staff) may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purposes of (1) providing clinical care and (2) for internal hospital operations (i.e., quality assurance).

There may be future analyses of the research data conducted by the study investigators, as yet unplanned, dealing with other aspects of post-stroke rehabilitation and recovery. In addition, your research data (which may include identifiable medical information) may be provided to secondary investigators for the purpose of conducting additional analyses about stroke.

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study? The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research for at least 10 years. The University of Pittsburgh requires that all research records be kept for at least five years after the study ends.

May I have access to my medical information that results from my participation in this research study? In accordance with the UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in the research study) contained within your medical records filed with your health care provider.

Is my participation in this research study voluntary? Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

May I withdraw, at a future date, my consent for participation in this research study? You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes

described above. If you decide to end your study participation, or if the study investigators decide to end your study participation, your audio recordings will continue to remain the property of the investigators and will continue to be stored with a linkage code to your name.

To formally withdraw your consent for participation in this research study you can inform your hospital treatment team or the research team verbally; or, if your desire to do so, you can provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.
Your doctor may be an investigator in this research study, and as an investigator, is interested in both your medical care and in the conduct of this research. Before entering this study or at any time during the research, you may discuss your care with another doctor who is in no way associated with this research project. You are not under any obligation to participate in any research study offered by your doctor.

If I agree to participate in this research study, can I be removed from the study without my consent? We do not anticipate any circumstances that could lead to you being removed from this study.

****

VOLUNTARY CONSENT: The above information has been explained to me and all of my current questions have been answered. Any future questions I have about this research study will be answered by one of the investigators listed on the first page of this consent document at the telephone numbers given. I understand that I may always request that my questions be answered by a listed physician investigator involved in the conduct of this research study. Any questions I have about my rights as a research participant, will be answered by the Human Subjects Protection Advocate of the University of Pittsburgh IRB Office 1-866-212-2668.

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____ _____

Participant's Signature Date

PROXY CONSENT:

_____
Participant's Name (print)

The above named individual is unable to provide direct consent for study participation because of _____

_____

Therefore, by signing this form, I give my consent for his/her participation in this research study.

_____ _____
Representative's Name (Print) Representative's Relationship to Participant

_____ _____
Representative's Signature Date

_____ _____
Witness Date

****

CERTIFICATION OF INFORMED CONSENT:
I certify that I have explained the nature and purpose of this research study to the above-named individual, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual had about this study have been answered, and we will always be available to address future questions as they arise.

_____ _____
Printed Name of Person Obtaining Consent Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date

CONSENT FOR CONTINUED RESEARCH PARTICIPATION: I understand that I am currently participating in a research study. I further understand that consent for my participation in this research study was initially obtained from my authorized representative as a result of my inability to provide direct consent at the time that this initial consent was requested. I have now recovered to the point where it is felt that I am able to provide direct consent for continued participation in this research study.

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during

the continuation of this study and that such future questions will be answered by the researchers listed on the first page of this form. I also understand that any questions I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668).

By signing below, I agree to continue participation in this research study. A copy of this consent form will be given to me.

_____ _____

Date Participant's Signature

CERTIFICATION OF INFORMED CONSENT:

I certify that I have explained the nature and purpose of this research study to the above-named individual, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual had about this study have been answered, and we will always be available to address future questions as they arise.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date

APPENDIX J

BIVARIATE CORRELATIONS AND UNIVARIATE CRUDE ODDS RATIOS

BETWEEN COVARIATES OR PREDICTORS AND FALLS

Bivariate Correlations, Univariate Crude Odds Ratios Between Covariates or Predictors and Falls

	Test Statistic	***p***	**Crude OR**	**95% CI**	***p***
Age	*rho* = -.08	.31	.99	.96-1.01	.33
Gender (Female)	$X^2_{(1)} = .45$	.50	.76	.34-1.71	.51
Race (White)	$X^2_{(1)} = .277$	.60	.74	.24-2.30	.60
Education	ρ = -.21	.004ˆ	.78	.65-.93	.007ˆ
Intervention Group (RCT subjects)	$X^2_{(2)} = .47$	.79	1.54	.42-5.62	.52
Hospital and Unit	$X^2_{(4)} = 1.16$	.89	.89	.33-2.39	.81
Stroke Severity (NIHSS)	*rho* = .32	.001#	1.19	1.06-1.32	.003ˆ
Stroke Hemisphere (Left)	$X^2_{(1)}$ = 1.148	.28	.64	.29-1.15	.29
Stroke Etiology (Ischemic)	$X^2_{(1)}$ = 2.996	.08	2.24	.88-5.70	.09
Stroke Type					
Cortical	$X^2_{(4)}$ = 9.363	.05+	*		
Subcortical			1.09	.24-4.87	.91
Cortical/ Subcortical			2.42	.62-9.52	.21
Brain Stem/ Cerebellar			4.27	1.06-17.17	.04+
Depression (HRSD)	*rho* = .12	.14	1.06	.99-1.14	.09
CIRS-G Burden Score	*rho* = .10	.26	1.047	.96-1.15	.32
Fall Prevention Interventions Count	*rho* = .28	.001#	1.56	1.20-2.03	.001#

CMA Postural Control	*rho* = -.26	.001[#]	.54	.35-.81	.003ˆ
LBT Percent Deviation	*rho* = .05	.54	1.01	.99-1.03	.43
mFIM	*rho* = -.32	.001[#]	.94	.91-.97	.001[#]
RBANS Modified Total Index Score	*rho* = -.10	.25	.98	.95-1.01	.23
Color-Word Interference Inhibition Scaled Score	*rho* = -.08	.34	.95	.86-1.06	.38
Letter Fluency Scaled Score	*rho* = -.05	.57	.97	.85-1.10	.62
Category Fluency Scaled Score	*rho* = -.09	.28	.93	.82-1.06	.27
Trail Making Test Number-Letter Switiching Score	*rho* = -.12	.15	.93	.84-1.03	.16

Test statistic: Spearman's *rho* for continuous data; X^2 for categorical data
OR indicates odds ratio; CI, confidence interval
*Reference group
[+]Significant at $p = .05$
ˆSignificant at $p = .01$
[#]Significant at $p = .001$

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