Psychometric Properties of the National Institutes of Health Stroke Scale in Post Acute, Minimally Impaired Stroke Survivors

THESIS

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By

Brittani Ann Basobas

Graduate Program in Allied Medicine

The Ohio State University

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Master's Examination Committee:

Stephen Page, Advisor

Amy Darragh

Andrew Persch
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Abstract

Stroke remains a leading cause of disability in the United States, frequently leaving survivors with impairments that diminish ability to perform daily activities. Rehabilitation clinical trials have traditionally used The Fugl Meyer Assessment (FMA) and the Arm Motor Ability Test (AMAT) to ascertain motor impairment and functional limitation, while the NIHSS has been increasingly used in stroke trials. Data collected from the Everest multi-center, randomized, controlled trial of implanted cortical stimulation for UE movement in chronic stroke was used to determine the sensitivity to change and concurrent validity of the NIHSS when compared with the upper extremity portion of the FMA (UEFM) and the Functional Ability (AMAT-FA) and Quality of Movement Scales (AMAT-QOM) of the AMAT. Sensitivity to change was only found to be statistically significant for the UEFM. NIHSS and UEFM, UEFM and AMAT-FA, UEFM and AMAT-QOM, and AMAT-QOM and AMAT-FA correlations were all statistically significant. Because of its weak correlation with measures of motor impairment and participation in daily activities and its insensitivity to change, the NIHSS should be exclusively used in acute stroke populations and not to predict or assess UE motor changes.
Dedication

This thesis is dedicated to my family, especially my husband, without whose unwavering support, this could not have been done.
Acknowledgments

I wish to express my sincerest gratitude to my committee for their guidance and encouragement in completing this work.

I am especially thankful for Dr. Amy Darragh and Dr. Andrew Persch for their utmost support and direction, both in this project and beyond.

I am forever grateful for my advisor, Dr. Stephen Page, and for his steadfast support of my education, research, and overall well-being.
Vita

December 2012 ..............................................B.A. Psychology, The Ohio State University
2013-2014 ..........................................................Clinical Research Assistant, Department of Neurology, The Ohio State University
Wexner Medical Center
2013-2015 ..........................................................Clinical Research Coordinator, Health and Rehabilitation Science, The Ohio State University Wexner Medical Center
2015 to present.................................................Graduate Research Associate, Health and Rehabilitation Science, The Ohio State University Wexner Medical Center

Publications


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Fields of Study

Major Field: Allied Medicine
# Table of Contents

Abstract ............................................................................................................................... ii

Dedication .......................................................................................................................... iii

Acknowledgments.............................................................................................................. iv

Vita...................................................................................................................................... v

Table of Contents .............................................................................................................. vii

List of Tables ...................................................................................................................... x

List of Figures .................................................................................................................... xi

Chapter 1: Introduction ...................................................................................................... 1

  Purpose of the Study ....................................................................................................... 2

  Research Questions/Hypothesis ...................................................................................... 3

  Definition of Terms ......................................................................................................... 3

Chapter 2: Review of the Literature .................................................................................... 5

  Introduction ..................................................................................................................... 5

  Prevalence, Incidence Rate, and Cost of Stroke .............................................................. 6
What Happens to Stroke Survivors? .............................................................. 7

How is Post Stroke Movement Assessed? .................................................... 8

Fugl Meyer Assessment (FMA) ..................................................................... 9

Arm Motor Ability Test (AMAT) ................................................................. 10

National Institutes of Health Stroke Scale (NIHSS) ................................... 11

NIHSS and Functional Outcomes ............................................................... 13

Conclusions and Needed Directions ........................................................ 14

Chapter 3: Research Design and Methods ................................................ 16

Design ........................................................................................................... 16

Subjects ......................................................................................................... 17

Instrumentation ............................................................................................ 20

Fugl Meyer Assessment (FMA) ................................................................. 20

Arm Motor Ability Test (AMAT) ................................................................. 21

National Institutes of Health Stroke Scale (NIHSS) ................................. 22

Sampling ....................................................................................................... 23

Data Collection and Analysis ...................................................................... 23

Chapter 4: Results ....................................................................................... 25

Aims 1 and 2: Sensitivity to Change ............................................................ 25

Aims 3 and 4: Concurrent Validity .............................................................. 27
Chapter 5: Discussion ....................................................................................................... 28

Discussion ..................................................................................................................... 28

Limitations and Future Directions................................................................................. 32

Conclusions ................................................................................................................... 32

References....................................................................................................................... 34

Appendix A: Post-Stroke Motor Rehabilitation Clinical Trials with NIHSS as Primary or
Secondary Outcome Measure ...................................................................................... 44

Appendix B: Demographics and Descriptive Data ........................................................... 48

Appendix C: NIHSS Items and Scoring ........................................................................... 50
List of Tables

Table 1: Schedule of Outcome Assessments for Everest trial.................................16
Table 2: Kruskal-Wallis H Test...............................................................................26
Table 3: Mann-Whitney U Test Group Comparisons..............................................26
Table 4: Correlation matrix of NIHSS, UEFM, AMAT-FA, and AMAT-QOM scores.......................................................................................................................................27
Table 5: Post-Stroke Motor Rehabilitation Clinical Trials with NIHSS as Primary or Secondary Outcome Measure.................................................................44
List of Figures

Figure 1: Final Subjects Included.................................................................18
Chapter 1: Introduction

Acute treatments for stroke have improved in recent years, yet, in the United States alone, up to 80% of the 5.7 million, chronic, stroke survivors exhibit significant weakness in one upper extremity (UE). This burdensome impairment inhibits performance of daily activities and quality of life.\(^1\) While an increased number of trials is being conducted in stroke rehabilitation, discrepancies exist as to which outcome measures should be used in this population.

The Fugl Meyer Assessment (FMA) and the Arm Motor Ability Test (AMAT) have traditionally been used in rehabilitative trials and clinical settings because of their content validity and interrater reliability for measuring functional UE changes.\(^2,3\) A recent study has, in fact, recommended the FMA’s use in chronic stroke rehabilitative trials.\(^4\) Concurrently, the National Institutes of Health Stroke Scale (NIHSS) is being increasingly used in at least 29 stroke rehabilitation research trials as a primary or secondary outcome measure as of February 4, 2016 (Appendix A), although it was developed as a clinical bedside tool to measure neurological status in acute stroke.\(^15-38, 39, 81, 82\) The NIHSS has been validated in predicting lesion size as a measure of stroke severity,\(^40\) to determine use of recombinant tissue plasminogen activator (rtPA),\(^41\) and is a predictor of three month outcomes in stroke using the Barthel Index.\(^42, 43\) That said, there
is little evidence that the NIHSS is a predictor of functional motor outcomes, especially in the chronic phase in which most rehabilitative trials are being run. Because the NIHSS was designed and validated in measuring acute stroke deficit, it may not be sensitive to change in post-acute stroke patients.

A recent study examined the association between the NIHSS and UE impairment and functional measures in the aforementioned post-acute population. These results demonstrated no practical significance between the NIHSS and the Upper Extremity Fugl Meyer (UEFM) and no statistical significance between the NIHSS and the AMAT. Additionally, subjects with equal NIHSS scores exhibited significant variability on the UEFM and AMAT, especially when total NIHSS scores were zero. A subsequent analysis of post-acute subjects determined the NIHSS was not associated with physical domains of the Stroke Impact Scale (SIS), a benchmark measure of health status. This analysis also explored groups of subjects scoring zero versus nonzero on the NIHSS and found no significant difference between the two groups and their median SIS scores. Together, these investigations have developed an argument which demonstrates that NIHSS scores are not accurately associated with function and impairment-based assessments or scales of overall health status.

Purpose of the Study

Prior to its use in clinical and research settings, there is a clear need to determine the NIHSS’s psychometric properties in the post-acute setting. The primary purpose of this study is to determine the sensitivity to change of the NIH Stroke Scale to upper extremity motor impairment as measured by the total UEFM score. Secondary, this study
will also determine the sensitivity of the NIHSS to UE functional limitation as measured by the AMAT Functional Ability and Quality of Movement scores. The tertiary and quaternary aims of this study will be to evaluate the concurrent validity of the NIH Stroke Scale and the total UEFM score and total AMAT score.

Research Hypothesis

1: The NIHSS scores will not show a statistically significant sensitivity to change across the four time points: Baseline, Follow Up Week 4 (FUW4), Follow Up Week 12 (FUW12), and Follow Up Week 24 (FUW24).

2: The Fugl-Meyer – Upper Extremity Assessment and Arm Motor Ability Test Functional Ability and Quality of Movement scores will show a statistically significant sensitivity to change across the four time points: Baseline, Follow Up Week 4 (FUW4), Follow Up Week 12 (FUW12), and Follow Up Week 24 (FUW24).

3: NIHSS scores will be significantly correlated with the Fugl-Meyer – Upper Extremity Assessment scores.

4: NIHSS scores will not be significantly correlated with the Arm Motor Ability Test Functional Ability and Quality of Movement scores.

Definition of Terms

**AMAT-FA**: Arm Motor Ability Test’s functional ability score

**AMAT-QOM**: Arm Motor Ability Test’s quality of movement score

**Hemiparesis**: weakness on one side of the body commonly caused by a neurological disorder
NIH Stroke Scale (NIHSS): 13-item neurological assessment measuring level of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss\textsuperscript{45}

Fugl-Meyer Assessment (FMA): stroke-specific, performance-based, impairment index designed to assess motor functioning, balance, sensation and joint functioning in patients with post-stroke hemiplegia in the paretic arm and leg\textsuperscript{46}

Upper Extremity Fugl-Meyer (UEFM): stroke-specific, performance-based impairment component of the FMA designed to assess motor impairment of the paretic upper extremity in patients with post-stroke hemiplegia\textsuperscript{46}

Arm Motor Ability Test (AMAT): rehabilitation outcome measure used to assess functional limitation in Activities of Daily Living; Coordination; Dexterity; Upper Extremity Function. 19-item measure divided into 4 sub-tests (grasp, grip, pinch, and gross arm movement). Performance on each item is rated on a 4-point ordinal scale\textsuperscript{47}

ADL: Activities of Daily Living

Upper Extremity (UE): upper limb as defined by the shoulder, upper arm (proximal to the elbow), forearm, wrist, thumb, and digits.
Chapter 2: Review of the Literature

Introduction

Stroke remains a leading cause of disability in the United States, frequently leaving survivors with impairments that diminish ability to perform daily activities. Newer interventions effectively target these impairments, yet measures used to determine their efficacy are sometimes not well situated for post acute environments. Specifically, the Fugl Meyer Assessment (FMA) and Arm Motor Ability Test (AMAT) are two of the most widely used assessments in stroke rehabilitation to ascertain motor impairment and functional limitation, respectively. In contrast, the National Institutes of Health Stroke Scale (NIHSS) was developed as an acute measure of neurological status, but is, nonetheless, being used in many post acute and chronic stroke studies of motor function, despite little evidence of its ability to detect or predict functional motor changes or changes in motor impairment.

Recent studies have demonstrated that NIHSS scores are not associated with scores on the Upper Extremity Fugl Meyer (UEFM), as well as the AMAT. Specifically, comparisons between subjects scoring identically on the NIHSS showed considerable variability in UEFM scores. A separate study has shown that the NIHSS was not associated with physical domains of the Stroke Impact Scale (SIS); a post-stroke benchmark measure of health status and participation in valued activities. This latter
study also explored groups of subjects scoring zero versus nonzero on the NIHSS and found no significant difference between the two groups and their median SIS scores. Together, the results of these investigations have developed an argument suggesting that NIHSS scores are not accurately associated with function and impairment-based assessments or scales of overall health status in post-stroke populations. The current study is situated to further test the applicability of the NIHSS to the post acute environment.

In this review – and as a background to the above study - the author discusses the burden of stroke, the importance of outcome measurement in post acute stroke, and contemporary measurement options for post acute stroke.

*Prevalence, Incidence Rate, and Cost of Stroke*

According to the American Heart Association’s 2016 annual statistical update, approximately 6.6 million Americans have experienced a stroke. The National Health and Nutrition Examination Survey data currently suggests an estimated prevalence rate of 2.6% stroke survivors in the United States. Paradoxically, although there has been increased research in stroke prevention and new guidelines for managing acute stroke treatment, the prevalence rate of stroke survivors has not changed appreciably. Because of the high prevalence of stroke survivors, the magnitude with which Americans are suffering from this debilitating neurological disease has created an enormous financial burden on survivors and their caregivers. In 2011 alone, the estimated costs of stroke care, both direct and indirect, totaled $33 billion, with an average per patient cost of $5,478. Patients’ direct medical costs are estimated to rise from $71.55 billion to
$184.13 billion by 2030. A previous study of 1,341 stroke survivors calculated average short-term and lifetime costs associated with stroke. The average patient cost within the first three months of stroke was approximately $13,649. These results also indicated patient impairment levels as a factor, with lesser-impaired survivors estimated to cost $46,000 and more impaired patients incurring estimated costs of $125,000. In short, stroke remains common, crippling, and costly.

**What Happens to Stroke Survivors?**

Approximately 45% of Medicare patients experiencing a stroke are discharged home, while 24% and 31% of patients are discharged to an inpatient rehabilitation facility or skilled nursing facility, respectively. Although nearly half of patients are discharged home, approximately one third receive home health service. Despite acute and rehabilitative interventions, only 14% of stroke patients return to premorbid levels of functional activity. A 2000 study investigated quality of life in 118 stroke survivors at one year post-stroke using a common measure of health status, the Barthel Index (BI). Average BI scores showed 88.5% of patients still suffered mild to moderate disability and 11.1% of patients were still totally or severely disabled. Additional longitudinal studies showed an estimated 26% of patients were disabled at one and three years post-stroke, defined as a BI score of < 15. Analysis of the Framingham Study, a longitudinal study of stroke and cardiovascular disease, revealed up to 50% of older patients (mean age 78.7 years) were left with residual hemiparesis six months post-stroke. A 2011 systematic review and meta-analysis found that in 25 studies analyzing baseline upper extremity impairment, the biggest predictor of long-term recovery was initial severity. From these
varying sources of information, it is evident that, acute care and stroke survival rates are improving, causing an increasing prevalence of stroke survivors in the community. Effective measurement is fundamental to cost effective, appropriate care in this growing stroke survivor population. Below, the author discusses contemporary measurement trends and gaps in post acute stroke.

How is Post-Stroke Movement Assessed?

The enormous burden associated with disability after stroke has prompted rehabilitation researchers to explore new interventions that may alleviate these persistent impairments. In doing so, valid, responsive, and reliable outcome measures must be selected in order to evaluate the intended effects of an intervention. These outcome measures are typically classified by the World Health Organization’s International Classification of Function, Disability, and Health, or ICF classifications. Classification of disability involves one or more improper functions in impairment, activity limitations, or participation. The FMA is classified as a measure of disability, specifically, assessing impairment in the upper extremity. The AMAT is a measure of disability classified as assessing activity limitation through performance of ADLs. The NIHSS, however, does not, and was not developed to measure disability, but physiological function of body systems including consciousness, vision, motor, and speech.

The FMA and AMAT remain two of the most commonly used measures assessing impairment and activity limitation in the upper extremity, respectively, and are necessary to evaluate the efficacy of stroke interventions.
Fugl Meyer Assessment (FMA)

The FMA evaluates motor impairment in post-stroke hemiplegic patients and was developed for rehabilitation professionals to measure functional motor, balance, sensory, and joint impairments. The FMA was developed in accordance with observable stages of motor recovery.\textsuperscript{61} Used in both clinical and research settings, it is one of the most widely used quantitative measures of motor impairment and considered to be the gold standard for measuring motor impairment.\textsuperscript{5-14, 48, 81, 84}

The assessment is comprised of five domains: motor function, sensory function, balance, joint range of motion, and joint pain. The motor domains are scored from 0 to 100 points, with 0 being total hemiplegia and 100 being totally normal function. The upper extremity domain accounts for 66 points, while the lower extremity accounts for 34 points.\textsuperscript{48} Wrist and hand function is additionally scored on the upper extremity portion. These motor domains encompasses reflex activity, movement with and without synergies, coordinator and speed, sensation, and passive joint motion.\textsuperscript{46}

The FMA has been utilized to measures changes in response to interventions, including robotics, mental practice, virtual reality, and neuromuscular stimulation for hemiparesis after stroke.\textsuperscript{12, 13, 14, 62, 63} A 2009 review of the Cochrane Library found 115 trials targeting recovery of arm and hand function after stroke. Of these, the FMA was listed as one of the most common measures of arm functional recovery.\textsuperscript{64} Furthermore, a study assessing six-month outcomes of 104 patients measured ability to perform activities of daily living and motor function using the BI and FMA, respectively. Analysis of FMA motor domain scores revealed that 53.2\% and 86\% of the variance could be explained by the baseline and 30-day FMA motor domain scores, respectively. FMA and BI scores
were strongly associated \[r=0.80 \text{ to } 0.91, (p< 0.001)\] at all visits from five up to 180 days post-stroke. A systematic search of clinicaltrials.gov was made on February 4, 2016 using the keyword “stroke” for condition and “Fugl Meyer” for outcome measures. This search yielded 266 clinical trials at the time of this writing.

**Arm Motor Ability Test (AMAT)**

The AMAT is a 13-part motor outcome measure of functional limitation, assessing both qualitative and quantitative upper extremity movement during performance of activities of daily living. The AMAT was created to be used in conjunction with the Wolf Motor Function Test in order to assess patients for a new rehabilitative technique, Constraint-Induced Movement Therapy. Each ADL activity involves one to three component tasks or movement segments which involve bilateral tasks, use of the distal and proximal musculature of the affected arm, and are not all of the same difficulty. ADLs range from picking up a knife and fork to buttoning a sweater. Tasks are scored according to functional ability (AMAT-FA) and quality of movement (AMAT-QOM). Previous research has demonstrated excellent correlation with the FMA and, as such, the AMAT has been used previously in studies of upper-limb robotics, cortical stimulation, intramuscular electrical stimulation, and constraint induced movement therapy. A systematic search of clinicaltrials.gov was made on February 4, 2016 using the keyword “stroke” for condition and “Arm Motor Ability Test” for outcome measures. This search yielded 21 stroke trials using the AMAT as a primary or secondary outcome measure, indicating that the AMAT is widely used in post acute stroke trials.
National Institutes of Health Stroke Scale (NIHSS)

The NIHSS was developed as an acute measurement to detect the deficits of stroke. This instrument was originally designed as a research tool to measure initial neurological data on patients in acute stroke clinical trials. Now, it is widely used in the clinical setting to evaluate the severity of neurological deficits in stroke patients. The scale tests domains from consciousness to sensory and motor impairments. Level of Consciousness, LOC Questions, LOC Commands, best gaze, limb ataxia, sensory, dysarthria, and extinction and inattention items are all scored on a scale of zero to two. Visual impairment, facial palsy, and best language items are scored from zero to three. Motor arm and motor leg, both left and right sides, are scored from zero to four. For the motor domains, a score of zero indicates the limb being tested holds at 90 degrees for a full 10 seconds. A score of one indicates the limb holds at 90 degrees, but drifts before the full 10 seconds. A score of two indicates the limb cannot hold a 90-degree position for a full 10 seconds, but there is some effort against gravity. A score of three indicates the limb falls with no effort against gravity. A score of four indicates the limb has no movement. The NIHSS reports an overall score across all domains and does not differentiate to which impairment the points are attributed. Based on the total score, stroke severity may be broken down as follows: Very Severe: >25, Severe: 15 – 24, Mild to Moderately Severe: 5 – 14, Mild: 1 – 5.

Because the NIHSS was developed to collect patients’ baseline neurological status, it has been used as a prognostic factor and to attempt to predict patient outcomes. Prognostic factors were measured using a sample of 1,754 patients within 72 hours of admission. Total NIHSS score was deemed a prognostic factor for functional
independence as measured by BI scores after 100 days. Additionally, motor arm scores coupled with modified Rankin Scale (mRS) scores appeared to be prognostic factors for this same time point. The NIHSS was also determined to have predictive value for BI index scores seven days after stroke in a study of 50 acute ischemic stroke patients.

The National Institute of Neurological Disorders and Stroke rtPA Stroke Trial determined the NIHSS to be predictive of mRS scores up to three months post-stroke. Initial NIHSS scores were predictive of 2-hour, 24-hour, and 7-10 day mRS scores. Moreover, baseline NIHSS scores >17 were predictive of worse mRS scores, defined as a score of ≥3, at three months post-stroke.

A 2013 study of 2,112 stroke patients developed deficit profiles to determine the predictive value of NIHSS scores as measured by 30- and 90-day mortality, time to death, and a mRS score at discharge of ≤1 or back to baseline. Three profiles were created which included moderate stroke scores with positive motor function scores and mild stroke scores (n=1,532). This analysis demonstrated the NIHSS was significantly associated with 90-day mortality. Additionally, a 1999 study of 1,281 patients determined a strong prediction between the NIHSS and the BI and Glasgow Outcome Scale (GOS) at both seven days and three months post-ictus. Patients from the NINDS tPA Trials 1 and 2 were assessed ninety days after acute ischemic stroke, as this time point was deemed the most suitable endpoint to measure functional disability outcomes. Analysis concluded initial NIHSS scores were significantly associated with mRS scores at 90 days and could be used to predict outcomes during the early stages of stroke recovery. An investigation of 581 patients enrolled in the same NINDS tPA trial
evaluated whether the NIHSS was valid in patients with tPA.\textsuperscript{78} Results showed significant correlations between the NIHSS and BI, mRS, and GOS after three months.

While the above studies seem to suggest that the NIHSS is associated with long-term outcomes on rehabilitative measures (i.e., the BI\textsuperscript{79}), it is yet to be used in combination with functional and impairment based assessments recognized in the rehabilitation literature or commonly used post acutely by rehabilitative clinicians. Indeed, the aforementioned studies have shown a significant association between the BI, mRS, and GOS; however, these do not measure UE impairment or ability.\textsuperscript{77, 80}

Particularly in clinical trials, the NIHSS has been principally used to assess patients’ enrolled during the acute phase of their stroke to predict stroke outcomes. A systematic search of clinicaltrials.gov was made on February 4, 2016 using the keyword “stroke” for condition and “NIHSS” for outcome measures. This search yielded 170 clinical trials.

**NIHSS and Functional Outcomes**

Studies measuring post acute and chronic stroke patients’ NIHSS scores in addition to upper extremity function, in some cases, enroll patients between 7-21 days\textsuperscript{15}, up to 12 months post-stroke,\textsuperscript{81} and six to 60 months\textsuperscript{31} post-stroke. Certain studies may not stipulate time since stroke.\textsuperscript{82} The inconsistency with which these measures were being used lead to three previous studies demonstrating opposing evidence for use of the NIHSS in post acute stroke trials. A 2014 study by Hand, Page, and White demonstrated a high degree of variability among UEFM scores in stroke survivors who scored identically on the NIHSS. For example, the range of scores on the UEFM for patients scoring a one on the NIHSS ranged from 28.5-50.5. This study also demonstrated there
was no significance between the NIHSS total score and the AMAT score. There was also no significance between the UEFM and AMAT and two subsets of NIHSS scores: one group with a score of 0 and the other with any score higher than 0. This is consistent with the report from initial developers of the scale who found that, on eight of the fifteen items assessed, greater than 50% of the patients were scored as normal (score of 0) upon admission.

Another analysis of post acute stroke patients found there was no relationship between the total NIHSS score and the SIS’s physical domain or perception of recovery. Moreover, no association was found between total NIHSS score and the ADL/IADL domain of the SIS measuring perceived recovery.

A study where 459 stroke patients were evaluated within 2 weeks of the enrolling stroke measured NIHSS, BI and FMA scores from baseline assessment to six months post-enrollment. For patients achieving recovery, defined as a BI score of >90, the mean NIHSS score was 1.63 with a range from 0.0-9.0. Total Fugl Meyer scores had a mean 86.30, but a range of 22.0-100.0.

**Conclusions and Needed Directions**

Clinical trials in stroke rehabilitation have preferentially adopted the AMFM and AMAT in order to measure upper extremity impairment and limitation in activities of daily living, respectively. The NIHSS stroke scale has been widely used in acute stroke trials and increasingly used in stroke rehabilitation trials (Appendix A). However, the NIHSS’s psychometric properties must first be determined in the post acute and chronic
settings. The current study aims to determine the sensitivity to change and the concurrent validity of the NIHSS when compared to the UEFM, AMFM-FA and AMFM-QOM.
Chapter 3: Research Design and Methods

Design

The current study was a secondary analysis of data collected from the Everest multi-center, randomized, controlled trial of implanted cortical stimulation for UE movement in chronic stroke. The dependent variable selected for the current analysis was upper extremity motor function as measured by the NIHSS, UEFM, AMAT-FA, and AMAT-QOM. The independent variable of time was measured by four visits: Baseline, Follow Up Week 4 (FUW4), Follow Up Week 12 (FUW12), and Follow Up Week 24 (FUW24). Based on the fact that FUW4 was the primary study endpoint in the Everest trial and that the NIHSS was not completed at FUW1, our independent variable of time of patient visit is limited to those visits where the UEFM and AMAT were also administered. These measures were administered as indicated in Table 1.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Baseline</th>
<th>Baseline Repeat</th>
<th>Pre-Rehabilitation</th>
<th>Follow-Up Week 1 (FUW1)</th>
<th>Follow-Up Week 4 (FUW4)</th>
<th>Follow-Up Week 4 Repeat</th>
<th>Follow-Up Week 12 (FUW12)</th>
<th>Follow-Up Week 24 (FUW24)</th>
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<td>X (x2)</td>
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<tr>
<td>AMAT</td>
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<td>X</td>
<td>X</td>
<td>X (x2)</td>
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</tr>
<tr>
<td>NIHSS</td>
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<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Table 1: Schedule of Outcome Assessments for Everest trial
The primary variables of interest were NIHSS scores as measured by the UEFM, widely used in rehabilitative trials\textsuperscript{7-14} and post acute rehabilitative trials\textsuperscript{84, 81, 5, 6} and time as measured by the UEFM, AMAT and NIHSS scores at Baseline, FUW4, FUW12, and FUW24. Based on the fact that FUW4 was the primary study endpoint in the Everest trial and that the NIHSS was not completed at FUW1, our independent variable of time of patient visit is limited to those visits where the UEFM and AMAT were also administered.

\textit{Subjects}

A total of 373 subjects were enrolled in the Everest trial, 164 of whom met eligibility criteria and were randomized. In order to increase the external validity of the results, only subjects receiving usual and customary treatment were included in the analysis. Usually and customary treatment in this trial was defined as six weeks of rigorous task-oriented functional training of the upper extremity. Subjects randomized to receive the intervention underwent extensive neurological surgery consisting of functional magnetic resonance imaging, general anesthesia, placement of electrodes on the dura matter of the cortex, and placement of a subclavicularly-located neurostimulation system.\textsuperscript{83} Subjects were randomized in a 2:1 ratio, resulting in 60 subjects randomized to the therapy-only cohort. This analysis’ final cohort consisted of the forty-seven of subjects who completed all assessments at all visits (Figure 1).
Subjects were recruited from sites across the United States using print and radio advertisements in markets of enrolling sites and print ads in magazines to which stroke survivors typically subscribe. The inclusion criteria for enrollment were as follows: 1) Image confirmed ischemic stroke above level of brainstem resulting in neurological deficit (index stroke); 2) Enrolling stroke is the most recent; 3) >4 months post-ictus; 4) Medically and neurologically stable; 5) UEFM score 28-50; 6) ≥ 21 years of age; 7) Negative pregnancy test; 8) Willingness to comply with rehabilitation protocol.

The exclusion criteria for enrollment were as follows: 1) Intracerebral hemorrhage; 2) Additional stroke leading to motor impairment; 3) Medical or neurological conditions that may interfere with upper limb function; 4) History of seizure
(epilepsy, late post-stroke seizure >1 month post-ictus, or any episode of status
epilepticus); 5) Neurological condition compromising the safety of the participant; 6)
Moderate to severe hemispatial neglect and/or anosognosia of the affected limb; 7)
Inability to understand or comply with study procedures; 8). Spasticity (score of 4 on any
muscle of the affected upper limb as measured by the Ashworth); 9) Change in
antispasticity medication within 6 weeks prior to enrollment; 10) Botulinum toxin
injections within 4 months prior to enrollment; 11) Major active psychiatric illness; 12)
Severe depression (≥19 measured by the Beck Depression Inventory; 13) Modified
Rankin Score of ≥4; 14) Substantial cardiopulmonary or metabolic disorder; 15)
Increased risk of cardiac or other complications during anesthesia; 16) Terminal illness
with expected survival <12 months; 17) Inability to discontinue antithrombotic therapy
perioperatively; 18) Initiation of medication affecting CNS within 2 months prior to
enrollment; 19) History of other CNS injury with neurological deficits; 20) Current abuse
of alcohol or other drugs; 21) Contraindications to magnetic resonance imaging; 22)
Nursing, pregnant, or intent to become pregnant during the study period; 23) Participation
in another drug, device, or biological study within 30 days prior to enrollment; 24) Other
conditions that would interfere with study compliance or safety; 25) Medical need for
diathermy over location of device implantation site; 26) Medical need for magnetic
resonance imaging during study when device may be implanted.

Demographic and descriptive data were calculated for the 47 control group
subjects included in the final analysis (Appendix B: Demographics and Descriptive
Data). Of the final cohort, 62% (29) were male and 38% (18) were female.
White/Caucasian subjects made up 89% (42) of the sample, and the remaining 11% (5)
was comprised of Black/African-Americans. Right-handed subjects made up 91% (43) of the sample, while left-handed and ambidextrous subjects made up 9% (4). Affected side was well matched, with 47% (22) left affected and 53% (25) right affected. The average age of the sample was 57.23 years ($SD = 11.44$, $Range = 30-74$ years). The mean months from stroke to enrollment were 49.19 ($SD = 50.72$, $Range = 4-262$ months).

**Instrumentation**

**Fugl Meyer Assessment (FMA)**

The FMA evaluates recovery in post-stroke hemiplegic subjects and was developed for rehabilitation professionals to measure “neuromuscular capacity”\(^{45}\) The FMA is scored using a three-point ordinal scale where 0 equals “cannot perform”, 1 equals “performs partially”, and 2 equals “performs fully”.\(^{46}\) Previous studies have evaluated the validity and reliability of the FMA in measuring motor impairment. Initial validity analyses of the FMA found significant correlations between the subscores and ADL performance greater than 6 months post hospital discharge (0.75).\(^{46}\) Compared to the Barthel Index, a universally used assessment of stroke disability, the upper extremity portion of the FMA also demonstrated significant correlation (0.75).\(^{43}\) The UEFM was used as the primary outcome assessment for the Everest trial, and in this analysis, given its widespread use in stroke rehabilitation trials.\(^{84, 81, 5-11}\)

Further validation of the FMA was accomplished by comparing it to previously validated measures of upper extremity function, the Action Research Arm Test (ARAT)\(^{85}\) and overall motor and cognitive function, the Functional Independence Measure (FIM)\(^{86}\), which measures functional status of subjects throughout rehabilitation.
capturing a range of motor and cognitive outcomes. Validity of the FMA has been shown to be significant when compared to the Action Research Arm Test, with a correlation of $r=0.94$ at 2 months post-stroke. FM validity was also corroborated with the FIM ($r=0.63$), a well-validated disability scale. Intrarater reliability of the FM was most notably studied among 19 subjects assessed by one physical therapist with a robust correlation of 0.995-0.996. The FM demonstrated impressive interrater reliability for both total score (0.96) and the upper extremity score (0.97).

**Arm Motor Ability Test (AMAT)**

In addition to the FMA, the AMAT was also used as a part of the Everest trial to measure upper extremity function. The AMAT is a 13-part, 28-item motor outcome measure of upper extremity function in activities of daily living. Each ADL activity involves one to three tasks or movement portions. Each compound task involves subtasks using the distal and proximal musculature of the affected arm and may not be of uniform difficulty. Nine items involve bilateral tasks (i.e. pick up knife and fork), while the remaining items only test the affected arm. Five tasks allow up to two minutes to reach task completion, while the remainders have a one-minute limit. Each task is scored by functional ability, quality of movement, and time to complete task. The AMAT demonstrated validity and reliability when compared to two common measures of upper extremity function, the Motricity-Index Arm Score and the FMA. Concurrent validity of the total AMAT score with the Motricity-Index Arm Score was also established, especially within the functional ability domain ($r=0.61$). The AMAT has also been highly correlated with the FMA in functional ability (0.94), quality of movement (0.94),
and time of performance (-0.92). Robust interrater reliability was well established (0.97) among 30 subjects.

**National Institutes of Health Stroke Scale (NIHSS)**

The NIHSS was included in the Everest trial in order to monitor neurological status changes. The NIHSS is a 13-item valid and repeatable measure of neurological deficit (Appendix C: NIHSS Items and Scoring). The scale was developed from a combination of three other previously used stroke scales and input from NINDS stroke investigations. The initial analysis correlated baseline NIHSS scores and 7-day scores with infarct volume at 7 days post-stroke. Interrater reliability among four examiners was 0.69 for the overall score. In this analysis, pupillary response (0.95), motor arm (0.85), motor leg (0.82), and level of consciousness questions (0.80) demonstrated high agreement between raters. Test-retest reliability was also robust within the rater, especially the neurologist (0.77). Reliability of the NIHSS was also demonstrated from a group of 20 acute stroke subjects in the inpatient setting. Interrater reliability was calculated from four clinical stroke fellows using κ statistics. Of the 13 items, language (0.79), motor leg (0.78), motor arm (0.77), level of consciousness questions (0.64), and neglect (0.61) all had substantial interrater agreement. Visual fields (0.57), level of consciousness (0.50), sensory (0.50), and level of consciousness commands (0.41) items had moderate interrater reliability. Extraocular movements (0.33) and dysarthria (0.32) items demonstrated fair interrater reliability, while facial palsy (0.22) and limb ataxia (-0.16) showed chance interrater agreement. The NIHSS has also been reported to have a 20% ceiling effect at 6 months evaluations in a study of 97 acute stroke subjects.
Sampling

All data was collected from Everest trial of cortical stimulation in stroke subjects with upper extremity hemiparesis. Sixty subjects were randomized to the control study arm among the 20 sites. Ten subjects did not complete all outcome assessments during follow up, leaving 50 subjects for final analysis. All subjects received six weeks of task-oriented occupational therapy. The first four weeks consisted of treatment five days a week and the subsequent two weeks consisted of three days a week. While superfluous to the aims of the current study, the treatment protocol is described elsewhere in more detail.\textsuperscript{84}

Data Collection and Analysis

The reported scores from the NIHSS and UEFM scores were used in the calculations for this analysis. Means were calculated for Functional Ability and Quality of Movement of the AMAT at each time point based on previous analyses. Time of analysis not included because of noted ceiling and floor effects.\textsuperscript{68}

The NIHSS, UEFM, and AMAT employ ordinal-level scales to assess their respective impairments (i.e., motor, sensory), thus a Kruskal-Wallis H test was used. The Kruskal-Wallis H test was used to determine statistically significant differences between the four scales (dependent variables) over Baseline, Follow Up Week 4, Follow Up Week 12, and Follow Up Week 24 (independent variable).
The concurrent validity of the NIHSS will be measured using Spearman’s rho correlation for concurrent validity in order to measure the strength and direction of the associations between the four scales.
Chapter 4: Results

Aims 1 and 2: Sensitivity to Change

First, the four outcome measures (NIHSS, UEFM, AMAT-FA, AMAT-QOM) from the final cohort were analyzed using a one-way analysis of variance (ANOVA). Although the NIHSS, AMAT-FA, and AMAT-QOM employ ordinal level data, they were treated as continuous along with the UEFM in order to compare the means of the four independent groups. However, upon further consideration, the researchers determined a parametric test would be unsuitable given there was no assumption the ordinal measures were normally distributed or contained homogeneity of variances. Therefore, a nonparametric test, the Kruskal-Wallis H test, was used to avoid these assumptions. A Kruskal-Wallis H test was then conducted to compare the effect of NIHSS, UEFM, AMAT-FA, and AMAT-QOM scores on time of visit. A Kruskal-Wallis H test showed that there was a statistically significant difference in UEFM scores over time of visit, $\chi^2(3) = 10.783, p = 0.013$. NIHSS scores ($\chi^2(3) = 1.250, p = 0.741$), AMAT-FA scores ($\chi^2(3) = 3.953, p = 0.267$), and AMAT scores ($\chi^2(3) = 4.199, p = 0.241$) did not show a statistically significant difference over time of visit.
Table 2: Kruskal-Wallis H Test

<table>
<thead>
<tr>
<th></th>
<th>NIHSS</th>
<th>UEFM</th>
<th>AMAT-FA</th>
<th>AMAT-QOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-Square</td>
<td>1.250</td>
<td>10.783</td>
<td>3.953</td>
<td>4.199</td>
</tr>
<tr>
<td>Df</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Asymp. Sig.</td>
<td>.741</td>
<td>.013*</td>
<td>.267</td>
<td>.241</td>
</tr>
</tbody>
</table>

Because the sensitivity to change for the four time times was statistically significant for the UEFM, the researchers then conducted additional analyses to correct for the multiple comparisons between time of visit and to investigate the possibility of a false discovery, or Type I error. A Mann-Whitney U test was conducted for between time point comparisons to correct for multiple comparisons (Table 3). Sensitivity to change was statistically significant between Baseline and FUW4 ($U = 740.500, p = .006$), FUW12 ($U = 769.000, p = .011$), and FUW24 ($U = 745.000, p = .006$). No other pairwise comparison yielded a statistical significance.

Table 3: Mann-Whitney U Test Group Comparisons

<table>
<thead>
<tr>
<th>Asymp. Sig. (2-tailed)</th>
<th>Baseline</th>
<th>FUW4</th>
<th>FUW12</th>
<th>FUW24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FUW4</td>
<td>FUW12</td>
<td>FUW24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>.006*</td>
<td>.011*</td>
<td>.006*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>.949</td>
<td>.964</td>
<td>.898</td>
<td></td>
</tr>
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</table>
Aims 3 and 4: Concurrent Validity

A Spearman's rank-order correlation was run to determine the relationship between subjects’ scores on the NIHSS, UEFM, AMAT-FA, AMAT-QOM (Table 3). There was a moderate, positive correlation between UEFM and AMAT-FA scores, which was statistically significant ($r_s(47) = .494, p = .001$). There was a moderate, positive correlation between UEFM and AMAT-QOM scores, which was statistically significant ($r_s(47) = .490, p = .001$). There was a very strong, positive correlation between AMAT-FA and AMAT-QOM scores ($r_s(47) = .934, p = .000$). There was a weak negative correlation between the NIHSS and AMAT-FA and AMAT-QOM, respectively ($r_s(47) = -.051, p = .740; r_s(47) = -.103, p = .489$), but were not statistically significant. There was a statistically significant weak, negative correlation between the NIHSS and UEFM ($r_s(47) = -.325, p = .026$).

<table>
<thead>
<tr>
<th>TABLE 4: Correlation matrix of NIHSS, UEFM, AMAT-FA, and AMAT-QOM scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>NIHSS</td>
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<tr>
<td>Spearman’s rho</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>UEFM</td>
</tr>
<tr>
<td>Spearman’s rho</td>
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<tr>
<td>Sig. (2-tailed)</td>
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<tr>
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</tr>
<tr>
<td>AMAT-FA</td>
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<tr>
<td>Spearman’s rho</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>AMAT-QOM</td>
</tr>
<tr>
<td>Spearman’s rho</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
</tr>
<tr>
<td>N</td>
</tr>
</tbody>
</table>

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
A post hoc power analysis was conducted to determine the probability of a Type II error. The effect size of the contrast between Baseline and Follow Up Week for was 0.28, a small effect. The observed power achieved was 0.276.
Chapter 5: Discussion

Discussion

Approximately 2.6% of the United States population has experienced a stroke and while there is a surge in the number of clinical trials testing new interventions, up to 80% stroke survivors still exhibit significant weakness in one UE. The number of clinical trials, specifically in stroke rehabilitation, has drastically increased, yet the assessments, which measure their efficacy, are still discrepant. The UEFM and the AMAT have established content validity and interrater reliability for measuring impairment and participation in activities of daily living. While the NIHSS is being increasingly used in stroke rehabilitation research trials as a primary or secondary outcome measure, its psychometric properties are yet to be determined. The groundwork for this research was laid by Hand and Peters, whose work demonstrated poor associations between the UEFM, AMAT, and SIS.

In the above analysis, sensitivity to change only resulted in statistical significance for the UEFM, while the NIHSS, AMAT-FA, and AMAT-QOM did not show statistically significant changes. The current results also supported the hypothesis that the NIHSS would not be sensitive to change. This outcome is consistent with the fact that the NIHSS measures a variety of neurological dysfunctions, but is limited in its evaluation of upper extremity function. Notwithstanding, if the NIHS was sensitive to change, it would
be impossible to know if this change was attributed to the motor arm scores based on the scale’s mechanism of reporting a single score.

The present results confirm the hypothesis that the UEFM would be sensitive to change and bolster the argument for its continued use in post acute rehabilitation trials. It is evident that, even in a cohort of subjects receiving usual and customary care, the UEFM is highly capable of detecting changes in upper extremity impairment. Additionally, pairwise comparisons were able to show the UEFM was sensitive to change from Baseline evaluations through all follow up visits. This is consistent with the construct that subjects’ scores changes after rehabilitation but remain stable thereafter.

Usual and customary rehabilitation for minimally-impaired stroke survivors typically consists of intense task-oriented functional training focusing on activities maximizing proximal and distal use of the upper extremity and was utilized in the Everest study design. The UEFM was able to capture changes in subjects’ impairment because it measures the same objectives the functional training set forth.

The present findings do not support the hypothesis that the AMAT is sensitive to change over time. Despite not being statistically sensitive to change, the results may be explained by the nature of the functional ability scale. The cohort’s mean AMAT-FA at Baseline was 3.06, meaning the movement was performed slowly, with effort, or influenced by synergy. A score of 4 is defined as having normal movement with complete elimination of all synergistic movement patterns. This one-point increase in score, statistically significant or not, would be nearly impossible for chronic stroke survivors. The aforementioned results confirmed previously reported moderate to strong correlations between the UEFM, AMAT-FA, and AMAT-QOM. These results showed a
statistically significant, although weak, negative correlation between the NIHSS and UEFM. This result is logical in that several items on the NIHSS measure upper extremity deficits. The correlation’s negative value is explained in that improvements in scores are measured by an increase on UEFM score and decreases in NIHSS score. The current results validate the discrepancy between the content of the NIHSS and AMAT, as NIHSS scores were not significantly correlated with AMAT-FA or AMAT-QOM. While the NIHSS solely measures proximal shoulder flexion, the AMAT measures performance of multi-step ADLs.

It is apparent that outcome measures in clinical trials must quantify changes in participant scores, regardless of measure, in order to determine the efficacy of the intervention. The current results suggest the UEFM can measure these changes in the aforementioned population, and the NIHSS cannot. Although the NIHSS contains elements measuring motor impairment and related sensory impairments, it is fruitless to include such a measure, which is not sensitive to changes over time, even if subjects’ impairments change. Additionally, NIHSS scores are reported as a single score and are not deconstructed to show to which items the points belong.

Altogether, these results suggests that the NIHSS may not have the capacity to detect changes over time and may not be appropriate for classifying subjects’ impairment or participation in activities of daily living. Even in the small range of impairments tested in this analysis, the NIHSS was not sensitive to change, while the UEFM was able to capture changes in UE impairment. These results indicate that in a sample of stable stroke survivors, the NIHSS is poorly equipped to represent changes in subjects’ upper extremity levels, while the UEFM accurately captures these changes.
Limitations and Future Directions

The current analysis included only the sample of subjects receiving six weeks of usual and customary care in order to improve external validity and generalizability of the results. Similar to the majority of multi-center, randomized trials, the enrolled cohort was homogenous due to strict inclusion and exclusion criteria. Although the inherent homogeneity may reduce the generalizability of the results to the larger, more heterogeneous stroke population, internal validity was augmented through precise control of study variables. Nonetheless, this limitation is intrinsic to the majority of multi-center, randomized trials of stroke rehabilitation.

Another possible limitation was the small sample included in these analyses. Although only 47 patients in the cohort receiving usual and customary care completed all assessments at all follow-ups, each of the four outcomes consisted of 188 data points across the four time points. Together, this resulted in 752 data points used in the analysis.

Conclusions

It is of formidable concern that the NIHSS is being used in stroke rehabilitation trials with interventions targeting motor function, given its unresponsiveness to change in a sample of subjects who received six weeks of rehabilitation therapy and were assessed six months after its completion. Alternatively, the UEFM was able to capture the changes in subjects’ impairment from Baseline to 24 weeks after rehabilitation. Ultimately, the NIHSS does not provide additional practical information regarding subjects’ impairment or level of participation in activities of daily living that are not already accounted for by
other measures. It is concerning that the NIHSS is being used to evaluate the efficacy of interventions may be influencing available stroke rehabilitation therapies. Because of its weak correlation with measures of motor impairment and participation in daily activities, the NIHSS should be exclusively used in acute stroke populations and not to predict or assess UE motor changes.
References


the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the american heart Association/American stroke association. *Stroke; a Journal of Cerebral Circulation, 44*(3), 870-947. doi:10.1161/STR.0b013e318284056a [doi]


Appendix A: Post-Stroke Motor Rehabilitation Clinical Trials with NIHSS as Primary or Secondary Endpoints
<table>
<thead>
<tr>
<th>Study Title</th>
<th>Sponsor</th>
<th>Intervention</th>
<th>Fugl Meyer Performed?</th>
<th>Inclusion Post-Stroke</th>
<th>Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study of Purified Umbilical Cord Blood CD34+ Stem Cell on Chronic Ischemic Stroke</td>
<td>China Medical University Hospital</td>
<td>Intercerebral implantation of allogenic CD34+ stem cell</td>
<td>X</td>
<td>6 to 60 months</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Autologous Bone Marrow Mesenchymal Stem Cell Transplantation for Chronic Stroke</td>
<td>Wenzhou Medical University</td>
<td>Intracerebral transplantation of autologous bone marrow mesenchymal stem cell</td>
<td>X</td>
<td>3 to 60 months</td>
<td>1 year</td>
</tr>
<tr>
<td>Efficacy Study of CD34 Stem Cell in Chronic Stroke Patients</td>
<td>China Medical University Hospital</td>
<td>Intercerebral implantation of Autologous Stem Cells</td>
<td>X</td>
<td>6 to 60 months</td>
<td>1 year</td>
</tr>
<tr>
<td>Intravenous Autologous Mesenchymal Stem Cells Transplantation to Treat Middle Cerebral Artery Infarct</td>
<td>National University of Malaysia</td>
<td>autologous bone marrow-derived mesenchymal stem cells</td>
<td>X</td>
<td>2 weeks to 2 months</td>
<td>1 year</td>
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<tr>
<td>The Efficacy of Acupuncture on Patients With First Acute Ischemic Stroke, With Signs of Hemiplegia and Hemiparesis</td>
<td>Rambam Health Care Campus</td>
<td>Acupuncture</td>
<td>X</td>
<td>&lt; 3 weeks</td>
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<tr>
<th>Study Description</th>
<th>Institution(s)</th>
<th>Treatment/Intervention</th>
<th>Days to Months</th>
<th>Years</th>
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<tbody>
<tr>
<td>Combining Armodafinil With Neuro-rehabilitation to Improve Neurological Recovery and Reduce Disability Post-Stroke&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Burke Rehabilitation Hospital&lt;br&gt;Rehabilitation Institute of Chicago&lt;br&gt;MedStar National Rehabilitation Network&lt;br&gt;University of Southern California&lt;br&gt;Nexstim Ltd&lt;br&gt;Hadassah Medical Organization&lt;br&gt;IRCCS San Camillo, Venezia, Italy</td>
<td>Armodafinil&lt;br&gt;rTMS to contralesional hemisphere with task-oriented motor rehabilitation&lt;br&gt;Intensive upper extremity motor training&lt;br&gt;1Hz rTMS with task oriented rehabilitation&lt;br&gt;Deep TMS (Transcranial magnetic stimulation)&lt;br&gt;Folrex cream&lt;br&gt;Reinforced Feedback in Virtual Environment (RFVE)</td>
<td>7 to 21 days&lt;br&gt;3 to 9 months&lt;br&gt;28 days of admission to inpatient rehabilitation&lt;br&gt;14 to 32 months&lt;br&gt;3 to 12 months&lt;br&gt;3 months to 2 years&lt;br&gt;&lt; 24 hours&lt;br&gt;&lt; 1 year</td>
<td>100 days&lt;br&gt;6 months&lt;br&gt;1 year&lt;br&gt;1 year&lt;br&gt;6 months&lt;br&gt;2 years&lt;br&gt;4 weeks&lt;br&gt;4 weeks</td>
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continued
Table 5 continued

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<tr>
<th>Study Description</th>
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<th>Treatment Details</th>
<th>Treatment Duration</th>
<th>Follow-up Duration</th>
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<tr>
<td>Autologous Endothelial Progenitor Cells Transplantation for Chronic Ischemic Stroke&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Southern Medical University, China</td>
<td>Intravenous transplantation of autologous endothelial progenitor cells</td>
<td>✓</td>
<td>6 to 60 months</td>
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<td>Autologous Bone Marrow Mesenchymal Stem Cell Transplantation for Chronic Ischemic Stroke&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Southern Medical University, China</td>
<td>Intravenous transplantation of autologous bone marrow mesenchymal stem cell</td>
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<td>6 to 60 months</td>
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<td>Predictors of Treatment Response of Motor Sequels After a Stroke&lt;sup&gt;27&lt;/sup&gt;</td>
<td>University of Sao Paulo General Hospital</td>
<td>Observational</td>
<td>✓</td>
<td>&gt; 1 month</td>
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<td>New Technology for Individualised, Intensive Training of Gait After Stroke (HAL-RCT-I)&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Danderyd Hospital</td>
<td>Hybrid Assistive Limb (HAL) exoskeleton system</td>
<td>✓</td>
<td>4 to 7 weeks</td>
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<tr>
<td>New Technology for Individualised, Intensive Training of Gait After Stroke- Study II (HAL-RCT-II)&lt;sup&gt;29&lt;/sup&gt;</td>
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<td>Hybrid Assistive Limb (HAL) exoskeleton system</td>
<td>✓</td>
<td>1 to 10 years</td>
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<td>Robotic Therapy and Transcranial Direct Current Stimulation in Patients With Stroke (ROTS)&lt;sup&gt;30&lt;/sup&gt;</td>
<td>University of Sao Paulo General Hospital</td>
<td>Robotic Therapy with transcranial direct current stimulation</td>
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<td>3 to 9 weeks</td>
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<tr>
<td>Amphetamine-Enhanced Stroke Recovery&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Duke University</td>
<td>10 mg of d-amphetamine</td>
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<td>10 to 30 days</td>
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<td>Safety of Transcranial Direct Current Stimulation in the Subacute Phase After Stroke (NEUROSTIM)&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Hospital Israelita Albert Einstein</td>
<td>Active tDCS</td>
<td>✓</td>
<td>72 hours to 6 weeks</td>
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<tr>
<td>Life After STroke - the LAST Study (LAST)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Norwegian University of Science and Technology</td>
<td>Observational</td>
<td>X</td>
<td>2.5 to 4 months</td>
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<td>Umbilical Cord Derived Mesenchymal Stem Cells Treatment in Ischemic Stroke&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Affiliated Hospital to Academy of Military Medical Science</td>
<td>Human umbilical cord mesenchymal stem cells</td>
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<tr>
<th>Study Description</th>
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<tr>
<td>Efficacy and Safety Study of rTMS for Upper Extremity Motor Function Recovery in Ischemic Stroke Patients (TAMAS)(^3)</td>
<td>Seoul National University Bundang Hospital</td>
<td>Low frequency rTMS</td>
<td>✓</td>
<td>&lt; 90 days</td>
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<tr>
<td>The Influence of the Sleep Apnea on the Neurological and Functional Recovery (SAS-AVC)(^3)</td>
<td>Assistance Publique - Hôpitaux de Paris</td>
<td>Observational</td>
<td>✓</td>
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Appendix B: Demographics and Descriptive Data
### Demographics and Descriptive Data

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<tr>
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<tr>
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<th>Mean</th>
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<tr>
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<td><strong>UEFM Total Score</strong></td>
<td>37.23</td>
<td>41.49</td>
<td>41.77</td>
<td>41.74</td>
</tr>
<tr>
<td><strong>AMAT-FA Total</strong></td>
<td>3.06</td>
<td>3.32</td>
<td>3.33</td>
<td>3.25</td>
</tr>
<tr>
<td><strong>AMAT-QOM Total</strong></td>
<td>3.02</td>
<td>3.31</td>
<td>3.27</td>
<td>3.19</td>
</tr>
<tr>
<td><strong>NIHSS Total Score</strong></td>
<td>2.30</td>
<td>2.04</td>
<td>2.05</td>
<td>2.19</td>
</tr>
</tbody>
</table>
Appendix C: NIHSS Items and Scoring
### NIHSS Items and Scoring

<table>
<thead>
<tr>
<th>Item</th>
<th>Scoring</th>
</tr>
</thead>
</table>
| **1a. Level of Consciousness:** | 0 = Alert; keenly responsive.  
1 = Not alert; but arousable by minor stimulation to obey, answer, or respond.  
2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).  
3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic. |
| **1b. LOC Questions:**     | 0 = Answers both questions correctly.  
1 = Answers one question correctly.  
2 = Answers neither question correctly. |
| **1c. LOC Commands:**      | 0 = Performs both tasks correctly.  
1 = Performs one task correctly.  
2 = Performs neither task correctly. |
| **2. Best Gaze:**          | 0 = Normal.  
1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation and total gaze paresis is not present.  
2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver. |
| **3. Visual:**             | 0 = No visual loss.  
1 = Partial hemianopia.  
2 = Complete hemianopia.  
3 = Bilateral hemianopia (blind including cortical blindness). |
| **4. Facial Palsy**        | 0 = Normal symmetrical movements.  
1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling).  
2 = Partial paralysis (total or near-total paralysis of lower face).  
3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face). |
Appendix C: NIHSS Items and Scoring

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5. Motor Arm:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5a. Left Arm</strong></td>
<td>0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement.</td>
<td></td>
</tr>
<tr>
<td><strong>5b. Right Arm</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6. Motor Leg:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6a. Left Leg</strong></td>
<td>0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement.</td>
<td></td>
</tr>
<tr>
<td><strong>6b. Right Leg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>7. Limb Ataxia</strong></td>
<td>0 = Absent. 1 = Present in one limb. 2 = Present in two limbs.</td>
<td></td>
</tr>
<tr>
<td><strong>8. Sensory</strong></td>
<td>0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.</td>
<td></td>
</tr>
<tr>
<td><strong>9. Best Language</strong></td>
<td>0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient’s response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.</td>
<td></td>
</tr>
</tbody>
</table>
### 10. Dysarthria

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal.</td>
</tr>
<tr>
<td>1</td>
<td>Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty.</td>
</tr>
<tr>
<td>2</td>
<td>Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.</td>
</tr>
</tbody>
</table>

### 11. Extinction and Inattention

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No abnormality.</td>
</tr>
<tr>
<td>1</td>
<td>Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.</td>
</tr>
<tr>
<td>2</td>
<td>Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.</td>
</tr>
</tbody>
</table>