CONFIDENTIAL
Version 1.2
Date: 08-08-2018

NCT03010462

Nexstim NBT System

E-FIT TRIAL: ELECTRIC FIELD NAVIGATED 1HZ RTMS FOR POST-STROKE MOTOR RECOVERY TRIAL.

A PROSPECTIVE, MULTI-CENTER, RANDOMIZED, SHAM-CONTROLLED TRIAL TO DETERMINE THE THERAPEUTIC EFFECTS OF NAVIGATION GUIDED 1 HZ RTMS ADMINISTERED TO THE CONTRALESIONAL HEMISPHERE AS ADJUVANT TO TASK-ORIENTED REHABILITATION IN PATIENTS WITH ISCHEMIC STROKE

Study Plan

Statement of Compliance

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

As Principal Investigator, I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol. Modifications to the study are acceptable only with an approved protocol amendment. I agree to obtain approval from the IRB and/or regulatory bodies of competent jurisdiction, for the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrollment in the study, to collect and record data as required by this protocol and case report forms, to prepare adverse event and study reports as required by this protocol and to maintain study documentation for the period of time required.

_____

Signature/Title of Principal Investigator **Date**

CONFIDENTIAL

Revision History

Revision #	Description of Change	Approval Date
1.2	Statistical analysis plan revised according to FDA feedback during pre-submission Q151138-S003	

Caution: Federal (U. S. A.) Law restricts the study device to investigational use only.

Table of Contents

PROTOCOL SUMMARY

Title:	**E-FIT TRIAL: ELECTRIC FIELD NAVIGATED 1HZ RTMS FOR POST-STROKE MOTOR RECOVERY TRIAL.** A PROSPECTIVE, MULTI-CENTER, RANDOMIZED, SHAM-CONTROLLED TRIAL TO DETERMINE THE THERAPEUTIC EFFECTS OF NAVIGATION GUIDED 1 HZ RTMS ADMINISTERED TO THE CONTRALESIONAL HEMISPHERE AS ADJUVANT TO TASK-ORIENTED REHABILITATION IN PATIENTS WITH ISCHEMIC STROKE
Design:	Prospective, double-blinded, randomized, sham-controlled multi-center trial.
Purpose:	To determine whether navigation guided rTMS targeted to the non-lesioned hemisphere in patients with stroke has a beneficial effect on the results of subsequently performed task-oriented motor rehabilitation of the hand.
Study locations:	A total of 5 centers in the USA - Central site : Brain Innovation Center, AbilityLab, Chicago, IL - Other participating centers: Burke Rehabilitation Hospital White Plains, New York University of Cincinnati Cincinnati, OH Rancho Los Amigos National Rehabilitation Center Downey, CA Spaulding Rehabilitation Hospital Boston, MA
Principal Investigator:	Richard L. Harvey, MD Medical Director, Center for Stroke Rehabilitation, The Rehabilitation Institute of Chicago, Northwestern University Feinberg School of Medicine.
Enrollment:	60 patients with sub-acute ischemic stroke
Study duration:	18 months
Subject Population:	Patients with subacute stroke (3-12 months after the insult) aged 18 and over with no other brain abnormalities.

Primary Assessment

Determination of whether 1Hz NBS guided rTMS targeting the motor representation areas of hand muscles on the non-lesioned brain hemisphere has a beneficial effect on the motor recovery of the corresponding stroke-affected muscles when combined with standardized task-oriented motor rehabilitation.

Primary outcome measure: Upper-extremity Fugl-Meyer score.

The beneficial effect of 1Hz NBS guided rTMS will be established if a statistically signicantly greater proportion of patients receiving NBS-rTMS attain clinically important improvement in the primary outcome measure than patients receiving sham-rTMS between baseline and 6 months post-treatment. Minimal clinically important improvement is defined as an increase of 5 points on the upper extremity Fugl-Meyer score [Page SJ, et al. 2012].

Secondary Assessments and Endpoints:

1. Secondary outcome measures for the study are:

Arm-Research Action Test (ARAT)

NIH Stroke Scale (NIHSS)

Quality of life assessment: EQ-5D questionnaire.

The changes on these scales between baseline and 6 months post-treatment will be determined for both therapy groups and the groups compared to each other.

2. Safety endpoint
   To assess safety of study device use, all Serious Adverse Events and Unanticipated Adverse Device Events and Device Related Adverse Events will be recorded and compared between therapy groups..

ABBREVIATIONS

APB	Abductor Pollicis Brevis
CRO	Clinical Research Organization

EDC	Extensor Digitorum Communis
EMG	Electromyography
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
IRB	Institutional Review Board
MEP	Motor Evoked Potential
MRI	Magnetic Resonance Imaging
MT	Motor Threshold
NBS	Navigated Brain Stimulation
NBT	Navigated Brain Therapy
rTMS	Repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Events
SD	Standard Deviation
TMS	Transcranial Magnetic Stimulation

1.0 Introduction

1.1. BACKGROUND AND RATIONALE

Transcranial Magnetic Stimulation (TMS) is a relatively new brain imaging modality. Rather than imaging parts of the brain that are activated when performing certain tasks, TMS non-invasively stimulates an area of the brain, and when evoking a response, establishes a causal relation between brain activation and behaviour.

TMS when given in form of pulse trains (rTMS) can be used modulate cortical activity by either up-regulating or down-regulating cortical excitability depending on rTMS parameters used. The motor cortices in the left and right hemispheres of human brain are strongly interconnected, with each side naturally inhibiting the activity of the other side – and achieving a natural balance. If one side is lesioned as in stroke, however, its activation is decreased and its inhibition to the other side is reduced, leading to increased activation in the non-lesioned side. Additionally, the non-lesioned side still provides inhibitory signals to the lesioned side, even more than in the prior healthy balance situation. This mismatch leads to a condition where the lesioned hemisphere cannot easily deliver action potentials to the lower motor neuron and the corresponding muscles. As result, the ability to participate in motor training which is necessary for recovery of function is severely challenged.

Still, there is ample evidence that rehabilitation therapy focusing on repetitive and skillful task practice (task-oriented therapy) results in long-term functional recovery. Both animal models (Kleim and Jones, 2008) and human clinical trials (Leipert 2000, Wolf 2006) support a use-dependent relationship between task-oriented therapy, neuroplasticity and functional performance. Unfortunately, despite the growing utilization of task-oriented therapy approaches in clinical rehabilitation, functional recovery of arm and hand function is limited to about 50% of persons with stroke and full recovery is achieved in less than 20% (Kwakkel G 2003). Adjuvant treatments that enhance response to task-oriented motor training are needed.

A recent discovery is to use repetitive TMS to modulate regional excitability of the motor cortex (Hummel and Cohen, 2006). Two potential roles have been described for rTMS in stroke recovery: (1) inhibit, i.e., down-regulate, the non-lesioned side (using 1 Hz rTMS), or (2) excite the lesioned side (using 10 Hz rTMS). In the present study 1Hz rTMS will be utilized to down-regulate the non-lesioned hemisphere with the goal of improving response to motor training by reducing interhemispheric inhibition and potentially facilitating activity in the lesioned hemisphere.

Previously at least 27 studies on effects of contralesional 1Hz rTMS targeting the primary motor cortex on motor function utilizing varying rTMS protocols have been performed in 2598 patients with stroke in 2005-2016 [Boggio PS 2006, Mally J and Dinya E,2008, Dafotakis M 2008, Fregni F 2006, Khedr EM 2008, Kirton A 2008, Liepert J 2007, Mansur CG 2005, Nowak DA 2008, Takeuchi N 2005, Takeuchi N 2008(a), Takeuchi N 2008(b), Khedr EM 2009, Emera T, 2010, Kakuda W 2011 (a), Kakuda W 2011 (b), Thielig S 2011, Kakuda W 2011 (c), Kakuda W 2012, Sung W 2013, Abo M 2013, Higgins 2013, Kim, 2014. Rose 2014 Cha H 2015, Zheng C 2015, Kakuda W 2016].

Further, in a recent meta-analysis of 18 randomized controlled trials including a total of 392 patients, rTMS therapy was found to have a positive effect on motor function in patients with stroke (Hsu, 2012). This meta-analysis found a significant effect size of 0.55 for motor outcome (95% CI, 0.37–0.72). Further subgroup analyses demonstrated more prominent effects for subcortical stroke (mean effect size, 0.73; 95% CI, 0.44–1.02) and in studies that applied low-frequency (1Hz) rTMS (mean effect size, 0.69; 95% CI, 0.42–0.95). The meta-analysis concluded that rTMS has a positive effect on motor recovery in patients with stroke, especially for those with subcortical stroke.

However, the studies have not been designed to demonstrate clinically relevant efficacy and only some of them combined rTMS with specific rehabilitation training. Importantly, all previous studies have been performed with investigational TMS devices without the aid of neuronavigation. Thus, therapy delivery has been performed "blindly" relying on observed motor responses. The device operator has not been able to confirm targeting of stimulation to a specific neuroanatomic site corresponding to the motor cortex and, importantly, has not been able to keep the location of therapy delivery constant during the delivery lasting several minutes.

Nexstim has developed a Navigated Brain Stimulation (NBS) system that uses TMS with a software based Navigational System that provide spatial accuracy for targeting stimulation to specific areas in motor cortex. The system integrates individual patient's head MRI pictures with navigation software allowing online targeting of the TMS and the induced electric field to specific cortical areas. An integrated EMG allows online detection of MEPs caused by TMS. As an end-result the motor cortical areas commanding a certain muscle or muscle group can be targeted and the possible presence of a functioning corticospinal tract detected.

The high accuracy of the Nexstim's NBS has been validated in studies comparing NBS to intraoperative direct electrocortical stimulation (DCS) in patients undergoing neurosurgery. The mean distance between NBS and DCS has been 6 mm in 81 patients reported in 6 publications [Takahashi, 2013]. Nexstim's NBS technology is FDA approved for pre-procedural localization of functional motor and language cortex and routinely used by leading Departments of Neurosurgery in the U.S.

Nexstim's NBS system overcomes the problems of targeting and repeatability associated with non-navigated rTMS in post-CNS injury therapy. In healthy subjects and in patients with chronic stroke the effects of 1Hz rTMS were greater when NBS was used to target an optimal cortical location [Bashir 2010a and Bashir 2010b]. Further, in a 30 patient Phase II clinical trial, 84% of patients with sub-acute stroke receiving 1Hz contralesional NBS-guided-rTMS as adjunct to task-oriented rehabilitation attained clinically important improvement of at least 5 points on the upper extremity Fugl-Meyer scale while in the sham-rTMS group 50% did the same [Harvey 2014]. The mean point increase was 13.8 and 7.1 in patients receiving active NBS-rTMS and sham-rTMS, respectively. The results are superior to any other technology previously published. Further, no serious adverse events have occurred with NBS-rTMS.

In addition, in a 199 subject multi-center trial (NICHE trial, NCT02089464) performed with the same NBT trial device as in the present trial, similar trial protocol and in a patient population otherwise identical to that of the present trial protocol, with the exception that NICHE trial enrolled patients with ischemic or hemorrhagic stroke while the present trial is

limited to patients with ischemic stroke only, 66% of subjects (gained clinically important improvement of motor function (>5 points) on UEFM [Harvey, RL et al, manuscript in preparation]. In the NICHE trial there were no statistically significant differences in outcomes between the active NBT-rTMS (67% of all subjects, 72% of subjects with ischemic stroke improved at least 5 points on UEFM) and sham-rTMS (65% improved) trial arms. The mean improvement on UEFM was 8.1 points. The clinical results in both trial arms exceed those expected based on literature and by the NICHE site principal investigators by a factor of 2.

In an analysis of the potential reasons for lack of separation, Nexstim has concluded that the sham coil used in NICHE may well have been active and lead to a situation where in addition to the active rTMS group, the control group has also received active stimulation, albeit through a different mechanism of action than the active group.

The present trial aims to determine whether 1Hz NBT- rTMS targeting the motor representation areas of hand muscles on the non-lesioned hemisphere has a beneficial effect on the motor recovery of the corresponding stroke-affected muscles when combined with standardized task-oriented motor rehabilitation. The study is being conducted with a new and different sham coil design that ensures true sham rTMS delivery to the control group. The present trial is also aimed to enroll patients with ischemic stroke only as they were most likely to improve in the NICHE trial (overall 72% of subjects with ischemic stroke gained at least 5 point on UEFM in NICHE active group).

1.2. DEVICE DESCRIPTION

In the present trial the Nexstim Navigated Brain Therapy (NBT) System is used for rTMS delivery. The NBT system is CE-marked for adjunct therapy for upper extremity rehabilitation in patients with stroke in the European Union.
The Nexstim NBS technology provides navigational accuracy for the NBT system. NBS technology is FDA approved for localization of primary motor cortex [K091457] and language function [K112881].
The Nexstim NBS Technology consists of three subsystems. The NBS technology is integrated into the TMS software.

1) TMS Stimulator
2) NBS Technology
3) EMG

TMS Stimulator:
The TMS stimulator provides non-invasive stimulation of the central nervous system (CNS). The stimulation can be delivered as single pulses, or repetitive TMS (in trains). The stimulator provides precise stimulation as the design of the Coil and electronic components enable focal bipulse delivery. The stimulator is designed to allow the practitioner to have precise control of the stimulus location and strength. It also enables the practitioner to accurately record and review which structures have been stimulated, and the level of stimulation delivered. The Nexstim TMS Stimulator will be used in the study to perform the rTMS-therapy in 1Hz rTMS mode and the diagnostic evaluations using single-pulse TMS paradigms. Both paradigms are considered to have a non-significant risk associated with the use of the device (see section 2.2).

NBS Technology
The Navigated Brain Stimulation (NBS) technology provides navigational accuracy. The software uses structural MRI images to control strength and location of TMS stimuli. The software presents the predicted reactions of various brain areas when stimulated with TMS pulses. NBS technology is non-invasive and poses no risk to the patients.

EMG Technology
Surface EMG has been designed for simultaneous use with TMS equipment. Amplifiers are protected from the magnetic pulse by a dedicated design. The software allows free transport of data between integrated EMG and NBS software.

2.0 Benefits/risks

2.1. BENEFITS

Navigation -guided TMS used in the present study enables accurate targeted delivery of long trains of stimulation and modulation of neuronal activity in the brain. The system also makes possible the stimulation of the exactly same cortical location on different days. The beneficial effects of 1Hz rTMS observed in previous studies are hypothesized to be enhanced by the increased accuracy and repeatability made possible by the NBT system. Combining NBT-rTMS to an established task-oriented rehabilitation therapy treatment may result in improved functional outcomes for the patients. For a summary of previous and supporting investigation, see section 1.0 above.

2.2. RISKS

Single-pulse TMS

Localization of the muscle representation area which will be subsequently the target location for delivering 1Hz rTMS therapy will be performed using the NBT device in a single pulse mode. Single pulse TMS has been studied extensively and been established to be safe in practically all subjects [Bridgers 1991; Bridgers and Delaney 1989]. It was judged by a panel of experts with FDA representation at an NIH Consensus Conference in June 1996 to be a **non-significant risk application** [Hallett et al. 1999; Wassermann 1996]. No serious adverse events related to single-pulse stimulation have been reported to Nexstim by any user of the study device or earlier product generation.

1Hz rTMS

In the report of the NIH Consensus Conference cited above [Wassermann 1996] rTMS was recognized to be associated with potentially more frequent (although still rare) adverse effects than single-pulse TMS. The frequency of adverse effects was noted to increase in parallel with the frequency (Hz) and intensity (% of motor threshold) of the rTMS trains used. The workshop issued safety guidelines where for 1Hz rTMS trains of >1800 pulses given at 100 or 110% of motor threshold were considered safe. These guidelines have been reassessed and updated with no change to the evaluation of safety of the 1Hz rTMS paradigm [Rossi 2009]. In the present study 1Hz trains of 900 pulses at 110% of motor threshold targeting the healthy brain hemisphere will be utilized in patients at least 3 months from stroke. The protocol falls within the safety guidelines.

In the clinical trials investigating the efficacy and safety of rTMS paradigms similar to the one used by the NBT in the patients with stroke, no serious adverse events have been reported in the 27 studies in 2598 patients with stroke in 2005-2016 (Boggio 2006 Mally J and Dinya E,2008, Dafotakis M 2008, Fregni F 2006, Khedr EM 2008, Kirton A 2008, Liepert J 2007, Mansur CG 2005, Nowak DA 2008, Takeuchi N 2005, Takeuchi N 2008(a), Takeuchi N 2008(b), Khedr EM 2009, Emara T, 2010, Kakuda W 2011 (a), Kakuda W 2011 (b), Thielig S 2011, Kakuda W 2011 (c), Kakuda W 2012, Sung W 2013, Abo M 2013, Higgins 2013, Kim, 2014. Rose 2014 Cha H 2015, Zheng C 2015, Kakuda W 2016).

Further, no serious adverse events have occurred in the studies where NBS-guided rTMS has been used (a total of 3813 rTMS sessions in 224 patients with stroke) [Bashir S 2010 (b), Harvey RL,

2013, Harvey RL, manuscript in preparation].This includes the use experience in the NICHE multicentre trial in which no device related SAE occurred in the 3448 therapy sessions performed in 199 patients using the same trial device and protocol as the present trial. In addition, the independent Data and Safety Monitoring Board (DSMB) monitoring the NICHE trial identified no safety related concerns during the trial.

Based on the fact that the rTMS train used in the present clinical trial falls comfortably and with a wide margin (50%) within the consensus safety guidelines and the lack of side-effects in the relatively extensive literature specific to the study population in the present trial the rTMS paradigm of the present study can be considered a non-significant risk application.

Potential adverse effects

There are, however, potential risks of seizures, hearing loss, immunological and neuropathological changes, as described below.

Microvascular Changes

Studies of prolonged exposure to TMS were performed in animal models. Microvascular changes in the cortex were found in rats exposed to over 100 pulses at 2.8 Tesla, but these findings were not evident in rabbits exposed to 100- 200 pulses per day at 2.4 Tesla over 30-42 days [Nishikiori 1996], nor were they seen in rabbits exposed to 1000 pulses at 2.0 Tesla over a period of months [Counter 1993]. Furthermore, rats exposed to 50-60 1.9- Tesla pulses delivered over 15 minutes had no significant changes in blood-brain barrier permeability [Ravnborg et al. 1990].

Seizure Activity

Seizure activity is a theoretical risk of TMS. Although, single pulse TMS has not caused seizure activity in healthy volunteers, seizures have been produced by single-pulse TMS in several patients with large cerebral infarcts or other structural lesions [Fauth et al. 1992; Homberg and Netz 1989; Kandler 1990]. Epilepsy patients without gross lesions may also be at a minor degree of risk from single pulse TMS. For example, in a series of studies by Hufnagel and colleagues, single-pulse TMS was occasionally able to induce seizures or activate epileptic electroencephalography (EEG) foci [Hufnagel et al. 1990a; Hufnagel et al. 1990b; Hufnagel et al. 1990c]. In this study slow frequency trains of stimulation were used. In the current study we propose to use single pulse stimuli with a variable interstimulus interval. However, these results may not apply in patients in whom epilepsy is medically controlled. To wit, Tassinari et al [Tassinari et al. 1990] found that TMS did not incite seizure activity in a cohort of patients receiving anti-epileptic therapy. Subjects with a personal history of epilepsy will be excluded from this study.

rTMS has been reported to cause seizures in at least 7 individuals in whom frequencies of 3Hz or higher have been utilized [Wassermann 1996].

In the clinical trials investigating the efficacy and safety of rTMS paradigms similar to the one used by the NBT in the patients with stroke, no seizures have been reported in the 27 studies in 2598 patients with stroke in 2005-2016 (Boggio 2006 Mally J and Dinya E,2008, Dafotakis M 2008, Fregni F 2006, Khedr EM 2008, Kirton A 2008, Liepert J 2007, Mansur CG 2005, Nowak DA 2008, Takeuchi N 2005, Takeuchi N 2008(a), Takeuchi N 2008(b), Khedr EM 2009, Emara T, 2010, Kakuda W 2011 (a), Kakuda W 2011 (b), Thielig S 2011, Kakuda W

2011 (c), Kakuda W 2012, Sung W 2013, Abo M 2013, Higgins 2013, Kim, 2014. Rose 2014 Cha H 2015, Zheng C 2015, Kakuda W 2016).
Further, no seizures have occurred in the studies where NBS-guided rTMS has been used (a total of 365 rTMS sessions in 25 patients with stroke) [Bashir S 2010 (b), Harvey RL, 2013, Harvey, RL, manuscript in preparation]. Similarly, no seizures occurred in the NICHE multicentre trial in the 3448 therapy sessions performed in 199 patients using the same trial device and protocol as the present trial.

Auditory Changes
During TMS there is a loud clicking sound from the coil (up to 120-130dB). Single-pulse TMS induces permanent increases of the auditory threshold [Counter et al. 1990] in animals and transient increases in humans [Pascual-Leone et al. 1992], but these changes can be prevented with the use of foam earplugs [Pascual-Leone et al. 1993].

Immunological Changes
Single-pulse stimulation may induce changes in T lymphocyte subset [Wassermann 2000]. In general, these changes have been short-lived (<48 hours) and comparable to changes seen with stress, menstruation or circadian cycles [Wassermann 2000].

Psychiatric changes
Treatment-emergent mania has been reported for low and high frequency rTMS in patients with uni- and bipolar depression [Xia 2008, Rossi 2009] after stimulation of the left prefrontal cortex. Mania has not been reported in any patients or subjects in whom motor cortex has been stimulated as in the present study.

Neurocognitive Changes
A number of studies have examined the effect of TMS on cognitive function. In general, both transient and short-term studies of TMS have failed to demonstrate consistent effects on cognitive function following TMS [Pascual-Leone et al. 1993; Little et al 2000; Wassermann et al. 1996]. TMS can produce desired and undesired, usually within the frame of the experimental design but potentially long lasting, changes. Such effects, which generally follow a single application of rTMS, can be produced by random neural noise or brain signal suppression (Harris 2008), are small and, are considered not to raise particular safety issues by published consensus statement on the safety of rTMS (for review see Rossi et al., 2007c and Rossi 2009).

EMG
There may be a small amount of irritation of the skin from the electrode paste (less than 5% chance). There is no known risk involved in recording EMG activity from these sensors and electrodes.

Headaches
Another risk that has been cited is a higher frequency of experiencing mild headaches, which resolve soon after the procedure. It is speculated that the headaches may be a result of maintaining a fixed position of the head and neck for the duration of the procedure.

Risk of cardiovascular responses to restful sitting

Given that many potential subjects have cardiovascular disease and hypertension, there is potential for symptomatic reduction in blood pressure with restful sitting in the study chair during the procedures in those subjects taking antihypertensive medications. In some cases this may be associated with feelings of nausea. Maintaining hydration and repositioning in the chair should resolve these problems.

All efforts will be made to minimize these risks by using only trained personnel who are experienced and skilled in using the devices. Moreover, all TMS sessions will be performed in a medical setting with access to a skilled medical team and life-support equipment.

3.0 study objectiveS

3.1. PRIMARY OBJECTIVES

To determine whether NBS guided 1Hz rTMS targeting the motor representation areas of hand muscles on the healthy brain hemisphere has a beneficial effect on the motor recovery of the corresponding stroke-affected muscles when combined with standardized task-oriented motor rehabilitation.

Primary outcome measure: Upper-extremity Fugl-Meyer score.

The beneficial effect of 1Hz NBS guided rTMS will be established if a statistically signicantly greater proportion of patients receiving NBS-rTMS attain clinically important improvement in the primary outcome measure than patients receiving sham-rTMS between baseline and 6 months post-treatment.

3.2 SECONDARY OBJECTIVES

Secondary outcome measures for the study are:

Absolute change in points on UEFM

Action-Research Arm Test (ARAT)

NIH Stroke Scale (NIHSS)

The changes on these scales between baseline and 6 months post-treatment will be determined for both therapy groups and the groups compared to each other to establish effects of therapy.

Quality of life outcomes:

In addition to the other secondary outcome measures above the patients' quality of life will be assessed using the EQ-5D questionnaire. The change on this scale between baseline and 6 months post-treatment will be determined for both therapy groups and the groups compared to each other to establish effects of therapy on quality of life.

Assessment of safety:

To assess safety of study device use, all Serious Adverse Events, Unanticipated Adverse Device Events and Device Related Adverse Events will be recorded and compared between therapy groups..

.

4.0 study design

This is a prospective multi-center sham-controlled double-blinded study.

4.1. SELECTION OF SUBJECTS

This trial will include volunteers who meet eligibility criteria and agree to participate in the study. The purpose of the study including risks and benefits will be explained to potential participants who will then be asked to sign an informed consent form. Potential participants will be screened for inclusion and exclusion criteria.

60 patients will be randomized to the study (for rationale see section 6.1 Power analysis). Additional subjects may be recruited to compensate patients lost from follow-up or withdrawn from the study.

4.2. SUBJECT SELECTION CRITERIA

Candidates for this study must meet **ALL** of the following inclusion criteria and **NONE** of the exclusion criteria:

Inclusion Criteria :

- ≥ 18 years of age
- An ischemic stroke suffered 3-12 months prior to the study;
- no other known brain abnormalities by history;
- A one-sided stroke resulting in upper extremity paresis
- A Chedoke–McMaster Stroke Assessment arm stage and hand stage of 3-6 for the affected limb

Exclusion Criteria

- Implanted metallic parts of implanted electronic devices, including pacemakers, defibrillators, or implant medication pump;
- Pregnant or trying to become pregnant; Lack of pregnancy established in females of child-bearing potential by a negative urine pregnancy test at screening.
- Active alcohol abuse, illicit drug use or drug abuse or significant mental illness
- Patients suffering from depression as measured by a score of ≥10 on the Patient Health Questionnaire (PHQ9). For clarity, patients diagnosed with depression which is controlled with stable anti-depressive medication and in whom PHQ9 is <10 are eligible to participate in the trial.

- History of epilepsy, defined as at least two unprovoked seizures occurring greater than 24 hours apart or diagnosis of an epilepsy syndrome, and no seizures within the last 12 months.
- Any condition that would prevent the subject from giving voluntary informed consent;
- An implanted brain stimulator;
- Any metal in head with the exception of dental work or any ferromagnetic metal elsewhere in the body ;
- Enrolled or plans to enroll in an interventional trial during this study;
- Scalp wounds or infections;

- Claustrophobia precluding MRI;
- A fixed contraction deformity in the affected limb that would prevent normal dexterity if patient were neurologically intact;
- Excessive spasticity as indicated by the Modified Ashworth Spasticity (MAS) Scale >2/4 in either elbow flexors, wrist flexors or finger flexors of the affected limb
- previous stroke with residual deficits (TIAs not a reason for exclusion);
- premorbid (retrospective) modified Rankin Scale (mRS) score ≥2 of any aetiology;
- a concurrent progressive neurologic disorder, acute coronary syndrome, severe heart disease (NYHA Classification ≥ 3), or other major medical condition,
- confirmed or suspected lower-limb fracture preventing mobilization,
- patients requiring palliative care
- patients planning to undergo any other occupational therapy during the 6 week active treatment period of the trial (see section 5.2 for study schedule) than what is provided in the study
- A recent injection of botulinium toxin to the affected upper limb in the last 3 months, or the need of an injection of botulinum toxin anytime during the study period and follow up.
- A recent injection of phenol to the affected upper limb in the last 6 months, or the need of an injection of phenol anytime during the study period and follow up.

- Ataxia as measured by a score ≥ 1 on item 7 (limb ataxia) of the NIH stroke scale.
- Severe sensory deficits as measured by a score of 2 on item 8 of the NIH stroke scale.
- Severe aphasia as measured by a score of ≥ 2 on item 9 (best language) of the NIH stroke scale.
- Severe neglect as measured by a score of 2 on item 11 (extinction and inattention) of the NIH stroke scale.
- Patients unable to comprehend or follow verbal commands
- Based on PI's or local physician's assessment patient unable to tolerate the trial procedure due to medical condition
- A Mini mental status exam (MMSE) <25.

4.3. INFORMED CONSENT

All potential subjects will give written informed consent prior to any study related procedures. The background of the proposed study and the benefits and risks of the procedures and study must be explained to the subject. The subject must sign the Institutional Review Board (IRB) approved informed consent document prior to participation. Failure to provide informed consent renders the subject ineligible for the study.

5.0 study procedures

5.1 BLINDING AND SHAM-CONDITION.

5.1.1. Blinding

Blinding is achieved as follows:

Study staff: only the person responsible for randomization and the person(s) administering rTMS at the study site(s) will be aware of whether the patient is receiving NBS-rTMS or sham-rTMS. Neither of these persons is allowed to discuss randomization with the patient or study staff. Neither of these persons will direct or perform task-oriented rehabilitation with the patient nor will they perform any outcome measure testing thus ensuring that these tasks are not influenced by knowledge of randomization.

All other members of the study staff will be unaware of randomization. The reason for the person administering rTMS is unblinded is that since a supra-motor threshold protocol of rTMS is delivered to the patients healthy motor cortex, this will cause muscle activation and visible muscle movement in the patients hand which the person administering rTMS can not avoid to observe. Since sham rTMS condition by definition will not lead to muscle activation the person administering the rTMS would become unblinded by observing the patient undergoing rTMS.

Patients:
Each individual patient will be blinded to randomization by the fact that (s)he has no prior experience of rTMS and therefore can't assess whether an active or sham condition rTMS (through the use of sham coil for rTMS) has been used in her treatment. Further, of the staff that the patient meets only the person administering rTMS will be aware of the randomization. Since that person will be explicitly forbidden to discuss that issue, the patient will be unable to obtain information on randomization. The effectiveness of the blinding will be assessed at the end of the study asking the patient what group they thought they were in.

5.1.2 Sham condition:

Sham condition will be delivered by using the NBT system to navigate and localize a sham TMS coil to the same position on the patients head as the active TMS coil would be located if active NBT-rTMS would be delivered. The sham coil will cause an auditory sensation and a mechanical scalp sensation similar to the active TMS coil but will not induce an intracranial electric field capable inducing neuromodulation. The sham coil will be used to deliver an rTMS train of equal frequency and length as the active coil (900 pulses at 1Hz).

The study will consist of 24 study visits with the possible addition of 5 additional visits as needed to complete outcome assessments.

5.2. VISIT SCHEDULE

The study will be performed over 24 to 29 sessions:

1) Visit 1(Screening visit): Baseline = 3-12 months after the stroke. The purpose of this visit is to obtain informed consent for the study (if not previously obtained) and to screen subjects for inclusion and exclusion criteria.
2) Visit 2: Baseline assessment. The purpose of this visit is to establish the baseline of injury, motor status and NBS parameters (Localization of cortical motor representation area of the target muscle to which therapeutic rTMS will be subsequently delivered, see appendix A). Subjects will also undergo a structural MRI. The subject will then be randomized to either rTMS or to sham treatment. The baseline visit may if necessary take place on 2 separate days.

3) Visits 3-20: During these visits the patient will undergo standardized task-oriented motor rehabilitation of the hand. In addition the patient will receive the rTMS therapy according to the protocol of the group she/he was randomized into during visit 1. The visits will take place during a 6 week period, three visits per week. During each week the visits will take place each on a separate day and a maximum of two visits will take place on consecutive days.
4) Visit 21: End of the task-oriented motor rehabilitation. The purpose of the visit is to establish the extent of recovery that has occurred during the rehabilitation. The visit will take place 5-10 days after the last rTMS/rehabilitation session and includes functional motor testing).1-2 visits may be needed to complete assessment.
5) Visit 22: 1month ($\pm$5 days) after the end of the rehabilitation therapy. The purpose of the visit is to determine whether any changes in motor function have occurred within 1 month of ending therapy. The assessment includes functional motor testing. 1-2 visits may be needed to complete assessment.
6) Visit 23: 3 months ($\pm$5 days) after end of the rehabilitation therapy. The purpose of this visit is to determine whether any changes in motor function or NBS parameters have occurred within 3 month of ending therapy. The assessment includes functional motor testing. In patients experiencing a new stroke, only the data prior to the event will be used in the analysis. 1-2 visits may be needed to complete assessment.
7) Visit 24: 6 months ($\pm$5 days) after end of the rehabilitation therapy. The purpose of this visit is to determine the long-term rehabilitation success. The assessment includes functional motor testing. In patients experiencing a new stroke, only the data prior to the event will be used in the analysis. 1-2 visits may be needed to complete assessment.

5.2.1 Screening and informed consent

Eligibility will be confirmed through a series of steps as follows (see inclusion/exclusion criteria for details).

- Medical history and medications.
- The Modified Rankin Scale (MRS) assessed by interview will used to determine functional ability prior to the stroke.
- The Modified mini mental exam (MMSE) [Teng and Chui 1987] is a series of questions (approximately 5 minutes) to assess orientation (e.g. date, place) and ability to follow commands.
- Spasticity will be measured using the Modified Ashworth Spasticity (MAS) Scale [Bohannon and Smith 1987]. The MAS is a 6-point ordinal rating scale for measuring muscle tone, with ratings from 0 (no increase in tone) to 4 (limb rigid in flexion or extension).
- The National Institutes of Health Stroke Scale (NIHSS) is a measure of neurological functioning, with higher scores reflecting greater deficit (maximum 42).
- Chedoke-McMaster Stroke Assessment (CMSA) [Gowland et al. 2003] includes an impairment inventory and an activity inventory. The Impairment inventory includes staging assessments of shoulder pain, postural control, recovery of arm and hand, and recovery of leg and foot. Only arm and hand impairment will be assessed which stages each between 1 and 7 with higher score indicating better motor performance
- The possible presence and severity of depression will be assessed using the Patient Health Questionnaire (PHQ9) [Graves & Bobardier 2008]. The PHQ9 has nine inquiries about the frequency of symptoms associated with depressed mood over the

previous 2 weeks, each scored between 0 (not at all) to 3 (nearly every day). The maximum score is 27 points. Scores that equal 10 or greater are associated with clinical depression. The PHQ9 has been tested and validated in stroke populations with good sensitivity for detecting depression [de Man-van Ginkel, et al. 2012; Janneke, et al. 2012].

Structural MRI

Unless already existing, an MRI will be acquired using a high resolution (1.5T or more) T1 weighted image of the subject's brain on any standard magnetic resonance system. MRI acquisition parameters and instructions are shown in the NBT System User manual.

The subject's structural MRI sliced images will be loaded into the Nexstim NBT system.

5.2.2 Baseline assessment

The following functional tests will be administered by an experienced researcher. Training and certification of the researchers to perform these tests is described in a separate Outcome Assessment Training and Certification Plan

- The *Fugl Meyer (FM)* will measure functional movement. The FM offers impressive test-retest reliability (total=.98-.99; subtests=.87-1.00), and construct validity [Duncan et al. 1983; DiFabio and Badke 1990]. The upper extremity (UE) FM movement scale is a measure of upper limb function, with higher scores reflecting greater function.

- The *Action Research Arm Test (ARAT) [Lyle 1981]* is used to determine whether fine motor skill changes occurred in the affected hand and fingers. The ARAT is a 19-item test divided into four categories (grasp, grip, pinch, and gross movement), with each item graded on a 4-point ordinal scale (0=can perform no part of the test; 1=performs test partially; 2=completes test but takes abnormally long time or has great difficulty; 3=performs test normally) for a total possible score of 57. The test is hierarchical in that, if the patient is able to perform the most difficult skill in each category, he/she will be able to perform the other items within the category and, thus, they need not be tested. The ARAT has high intrarater (r = .99) and retest (r = .98) reliability and validity [Lyle 1981; Van der Lee et al. 2001]

- *The National Institutes of Health Stroke Scale* (NIHSS) will be repeated at baseline visit.

- *EQ-5D*

  The EQ-5D questionnaire is a standardized, well validated instrument for assessing patients' health and quality of life. The questionnaire will be utilized to establish the overall impact of stroke on the patients' quality of life and used to assess possible changes during the trial period.

Diagnostic NBS-TMS session:

- motor mapping of the healthy hemisphere, and determination of motor threshold and the optimal cortical representation area of the muscle of interest

(m.Extensor Digitorum Communis, m.EDC), The NBS protocol is described in detail in appendix A.

5.2.3 Randomization

Randomization will occur using a random number generator programmed to randomize patients to rTMS vs Sham TMS in a 1:1 ratio such that approximately 30 patients will be randomized to treatment and 30 patients randomized to sham. Randomization will be done separately for each participating site so that the 1:1 ratio for treatment arms will be attained at each participating site. In addition, for each site the randomization will be performed in randomly occurring blocks of 3 to 6 patients. Further, patients who have suffered a stroke 3 to 6 months before the trial will be randomized separately from those who have suffered stroke more than 6 months (maximum 12 months) earlier.

The groups differ only as to the rTMS protocol they receive during the study. The groups are : sham rTMS (900 pulses at 1Hz frequency), and active NBS-rTMS (900 pulses at 110% of motor threshold, 1Hz frequency).

5.2.4 Treatment Visits

The visits will last approximately 3 hours and will consist of the following. (For detailed description see appendix B)

1. Review with subject any new medical problems, medication changes or symptoms occurring since last visit (e.g. headache, changes in hearing, seizure)

2. 20 minutes of pre-functional activities (For detailed description see appendix B)

3. 10 minute rest

4. 1Hz navigation guided rTMS (For detailed description see appendix A)
   For patients randomized to receive rTMS, the stimulation will be delivered in a single pulse train 900 pulses given at 110% of motor threshold. The motor threshold will be determined at each visit. The train will be targeted on the motor representation of the m.EDC on the healthy brain hemisphere determined at the baseline visit (NOTE: the rTMS delivery location will thus be the same at each visit).

   OR

   Sham rTMS
   For patients randomized to receive Sham rTMS, the sham stimulation will be delivered in a single 1Hz pulse train of 900 pulses given using a Sham coil. The train will be targeted on the motor representation of the m.EDC on the healthy brain hemisphere determined at the baseline visit (NOTE: the rTMS delivery location will thus be the same at each visit).

5. 5-15 minute rest

6. 60 minutes of Task-oriented motor rehabilitation of the arm and hand (For detailed description see appendix B).

5.2.5 Outcome Assessments

The visits will take place 5-10 days, 1 month, 3 months and 6 months after the completion of the study treatment visits. The visits will last approximately 3 hours and consist of the following functional tests which will be performed at each and every outcome assessment visit:

- The National Institutes of Health Stroke Scale (NIHSS)
- Fugl Meyer (FM)
    - The Fugl-Meyer test is the primary outcome measure for the trial.
- ARAT
- EQ-5D

5.2.6 Occupational therapy, physiotherapy and home exercise program during the active treatment and follow-up periods of the trial

Occupational therapy:

During the 6 weeks active treatment period of the trial (visits 3-20) the patients are not allowed any other occupational therapy except that provide in the trial. After the active treatment period during the 6 month follow-up period of the trial, patients are allowed occupational therapy. The hours of therapy will be documented. Patients will be queried once every 2 weeks until the final outcome assessment visit at 6 months after end of active trial treatment, either when they visit the study site or they will be called and queried.

Physical therapy:

Patients are allowed participation in physical therapy for the full trial duration including during the active treatment period of the trial (visits 3-20). However, the hours of therapy and time of use of the affected upper extremity in treatment sessions will be documented. Patients will be queried once every 2 weeks until the final outcome assessment visit at 6 months after end of active trial treatment, either when they visit the study site or they will be called and queried.

Home exercise program:

During the 6 weeks active treatment period of the trial (visits 3-20) the patients are not allowed an upper limb home exercise program prescribed by therapists other than the study therapist. The study therapist will provide an upper limb home exercise program for the active treatment period of the trial. The study therapist will also provide an upper limb home exercise program for the post-active treatment period of the trial. However, this home exercise program for the post-active treatment period can be modified by the patient's own therapist based on her/his assessment of the patient's clinical needs. The hours of therapy will be documented. Patients will be queried once every 2 weeks until the final outcome assessment visit at 6 months after end of active trial treatment, either when they visit the study site or they will be called and queried

6.0 ANALYSIS PLAN

The results of functional motor tests at end of rehabilitation (5-10 days post treatment) and at 1, 3 and 6 months after the end of rehabilitation will be compared to the results obtained at baseline to determine the functional recovery if any that has occurred. The results of patients randomized into separate groups will be compared to each other to determine the effect of rTMS.

The primary analysis population will be the intent-to-treat (ITT) population. In addition, a separate analysis will be conducted on the per protocol (PP) population.

Primary outcome measure for the trial is the Upper-extremity Fugl-Meyer score.

The beneficial effect of 1Hz NBS guided rTMS will be established if a statistically significantly greater proportion of patients receiving NBS-rTMS attain clinically important improvement in the primary outcome measure than patients receiving sham-rTMS between baseline and 6 months post-treatment.

The size of the treatment effect will be measured by the odds ratio parameter which is defined as

$$OR = \frac{P_{TRT}/(1-P_{TRT})}{P_{REF}/(1-P_{REF})}$$

where P_{TRT} and P_{REF} denote the proportion of subjects with clinically significant change from baseline in Fugl-Meyer score, in the treatment and reference groups respectively.

The null hypothesis is $H_0 : OR = 1$ and the two-sided alternative hypothesis is $H_1 : OR \neq 1$.

The proportion of responders in each treatment group will be summarized, along with the estimated odds ratio, the 95% confidence interval for OR, and the Wald Chi-square test p-value. The primary analysis will be performed on the ITT, and on the PP population as a sensitivity analysis.

Secondary outcome measures for the trial are ARAT test, , NIHSS, and EQ-5D.

Descriptive statistics will be summarized by treatment and visit. Absolute difference (in points) in improvement will be summarized for both treatment groups between baseline and 5-10 days and 1, 3 and 6 month follow-up visits and the treatment groups compared via a two-way ANOVA.

6.1 POWER ANALYSIS AND BORROWING DATA FROM NICHE-TRIAL ACTIVE TRIAL ARM RESULTS

In a pilot study of 30 patients of whom 20 were randomized to active NBS-rTMS and 10 to sham-rTMS, 84% of the active NBS-rTMS group and 50% of the sham rTMS group attained clinically significant improvement of at least 5 points on the Fugl-Meyer score [Harvey RL 2009, Harvey RL, unpublished].
Similarly, in the completed multi-centre trial (NICHE-trial, NCT02089464) of 199 subjects using the same trial device but different sham coil design, 72% of subjects with ischemic stroke receiving active NBT-rTMS attained clinically significant improvement of at least 5 points on the Fugl-Meyer score [Harvey RL, manuscript in preparation] while the average expectation of NICHE trial site principal investigators of subjects improving was 36%.

Based on this data and sample size calculations utilizing significance level of 0.05 for p, we estimate that enrolling 60 patients need to be recruited to the present study to rule out the null hypothesis that there is no difference between active NBT-rTMS and sham-rTMS with 81% power. This assumption is based on the pilot study finding of 33% difference in responder rate between groups in favour of the NBS-rTMS group and 36% difference in the actual vs expected responder rate in patients with ischemic stroke in NICHE. However, since the active treatment arm of the present trial and the active trial arm of NICHE are treated in a completely identical manner (the same NBT device, same active rTMS protocol, the same standardized occupational therapy protocol as in NICHE, the same number of therapy sessions in the same schedule at the same trial sites, etc) this allows pooling of the data obtained in the NICHE active trial arm to the data obtained in the active trial arm in the present trial. As in NICHE there were 88 subjects with ischemic stroke receiving active NBT-rTMS. Combining their data with that of the present trial will lead into a trial population of approximately 118 subjects receiving active treatment (88 from NICHE + 30 from the present trial) and approximately 30 subjects receiving sham treatment (all from the present trial). The study power in this population is sufficient to rule out the null hypothesis with 96% power.

The statistical analysis of the present trial will be performed in two phases. The Bayesian analysis of the E-FIT data combined with data borrowed from the active trial arm of the previously completed NICHE trial (NCT02089464) will be the primary efficacy analysis. Non-Bayesian analysis of the E-FIT trial data only will be performed to demonstrate robustness of the result. Detailed methodology for the analyses is described in a separate statistical analysis plan (Document NX103391 EFIT Statistical Analysis Plan, version 1.0, dated 06 August 2018).

6.2 ANALYSIS SCHEDULE

No interim analyses will be performed for efficacy. Final analysis including analysis of safety and efficacy will be performed once 60 subjects have completed the trial (completed visit #24).

6.3 ANALYSIS POPULATIONS

Intent-to-Treat (ITT) Population

The ITT population will consist of all randomized subjects. Subjects in the ITT population will be summarized and analyzed in the treatment group to which they were randomized, regardless of the treatment they actually received.

Per Protocol (PP) Population

The PP population will consist of all subjects who were randomized, received study treatment, and had no major protocol violations.

If a subject suffers a new stroke during the trial and the new stroke affects the motor function of the limb being treated in the study, only the outcome assessment data collected prior to the new stroke will be used for PP Population analysis. The sponsor will review the new strokes and determine if it affects the motor function of the limb.

Safety Population

The Safety population will consist of all subjects who received study treatment. Subjects in the safety population will be summarized and analyzed according to the treatment they actually received, regardless of whether or not they were randomized to receive that treatment.

6.4 STRATA AND COVARIATES

The primary efficacy analysis will be stratified by length of time after stroke (3-6 months vs. 6-12 months).

Additional covariate analyses will model the primary endpoint (a binary response of UEFM score improvement) , absolute changes (in points) in the tests of motor function (UEFM, and ARAT) using hours of occupational therapy outside the trial and overall hours of therapy (occupational, physical, and home exercise) as covariates during treatment phase and over the entire 6 months of follow-up.

All covariate analysis will be performed for both ITT and PP population.

6.5 SIGNIFICANCE LEVEL

Unless otherwise noted, all statistical analyses will be conducted with a significance level (α) of 0.05 and utilize two-sided testing.
Since the ARAT test has potential to be used for labelling purposes, a Bonferroni adjustment will be employed. A significance level (α) of 0.025 will be used for this secondary analysis only. All other secondary analyses will use $\alpha = 0.05$ as they are not to be used for any labeling purpose.

6.6 DATA HANDLING METHODS

6.6.1 Missing Data
6.6.1.1 Date Values
In cases of incomplete dates (e.g., AE, concomitant medication, medical history start and/or stop dates), the missing component(s) will be assumed as the most conservative value(s)

possible. For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations (i.e., treatment-emergent status, etc.) unless it is the same month and year (only day missing) or year (day and month missing) as the start date of treatment. In this case, start date of treatment will be used, which assumes treatment emergence. If day is missing for an end date, the last day of the month will be imputed. A similar imputation will be used for missing month dates.

Date imputation will only be used for computational purposes e.g., treatment-emergent status, etc. Actual data values as they appear in the original CRFs will be shown in the data listings.

6.6.1.2 Non-Date Values

Every effort will be made to obtain the protocol-required data for all study assessments that are scheduled for each visit for all enrolled subjects. Missing values for the primary endpoint of Fugl-Meyer scores for post-baseline visits will be imputed using Last Observation Carried Forward (LOCF) for ITT analyses. Subjects with a six-month Fugl-Meyer score but no baseline score will have their six-month Fugl-Meyer score imputed backwards to serve as their missing baseline Fugl-Meyer score. Subjects with no baseline or six-month Fugl-Meyer score will have the mean baseline Fugl-Meyer score for their treatment arm imputed for both their baseline and six-month score.

These same imputation methods will be used for secondary endpoints as well.

6.7 SAFETY ANALYSES

The Safety Population will be used for all analysis, summaries, and listings of safety data.

Adverse Events

All reported terms (investigator descriptions) for AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA v16.0) and summarized with frequencies and percentages by treatment group, system organ classification, and preferred term.

Note that subjects experiencing AEs are counted at most one time per preferred term and at most one time per system organ class, at the highest recorded severity and causality. Events without recorded relationship or causality are summarized as severe or definitely related.

The number and percentage of subjects in the following categories will be summarized by group and overall: subjects with AE, TEAE, SAE, TESAE, UADE, DRAE, TEAE resulting in study discontinuation, and deaths.

The following tables will also be presented:

- All TEAEs
- SAEs and TESAEs
- TEAEs by severity
- TEAEs leading to premature discontinuation of study treatment.

Separate data listings will be presented for all AEs and SAEs.

Unanticipated Adverse Device Events (UADE)

A UADE is defined as any AE that is definitely related to the study device. All UADEs will be summarized by System Organ Class and Preferred Term. A listing of UADEs will also be provided.

Device-Related Adverse Events (DRAE)

A DRAE is defined as any AE that is possibly, probably, or definitely related to the study device. All DRAEs will be summarized by System Organ Class and Preferred Term. A listing of DRAEs will also be provided.

6.7.1 Primary Safety Analysis

The use of study treatment will be considered safe if the proportion of SAEs in the active rTMS group is not statistically significantly higher than that in the sham group. Number of subjects with SAEs and TESAEs will be summarized by group and compared using a Chi Square test.

6.7.2 Use of Safety results in future labeling

A summary of SAE, UADE and DRAE will be included in future labelling of the NBT device.

6.8 ASSESSMENT OF BLINDING SUCCESS

Subject blinding Success

The patients will be asked at the end of the baseline visit (Visit 2), at the end of the first treatment visit (Visit 3), at the end of the last treatment visit (Visit 20 and at the 6 month follow-up visit (Visit 24) whether they think they were in the active group or in the sham group. The data will be summarized with frequency and percentage by actual treatment received. Chi-square test will be used for this assessment of subject blinding success.

Outcome Assessment Therapist Blinding Success

Outcome assessment therapists will be asked at the first follow-up visit (Visit 21) and at the 6 month outcome assessment visit (Visit 24) whether they think the subject was in the active rTMS group or in the sham rTMS group or they didn't know. The data will summarized with frequency and percentage by treatment group received. Chi-square test will used for assessment of outcome assessment therapist blinding success.

In addition, the therapists will be asked if the study staff revealed group randomization and if the subject told them what group they believed they were in. The data will be summarized for those therapists who don't know which group the subject was in and those who think the subject was in either the active or sham rTMS group separately. The data will used for background information to explain the results of assessment of therapist blinding success.

7.0 Monitoring and quality assurance

INDEPENDENT MONITORING OF SOURCE DATA AND SAFETY

The data will be collected by staff members (PI, co-investigators and study staff) familiar with the protocol and the TMS technology. The care, safety, and comfort of the subjects will be under the supervision of a physician and therapist at each trial site).

Clinical monitoring

The study sponsor will be responsible for Clinical Monitoring of the study. The Clinical Monitor's responsibilities include maintaining regular contact with the clinical site through telephone contact and on-site visits, to ensure that:

- the trial is conducted according to protocol;
- the Investigational Plan is followed;
- study staff is trained and capable of performing the tasks required from them in a uniform manner at each trial site. The central site (Rehabilitation Institute of Chicago) will provide training for all assessors and therapists. At the beginning of the study and every 6 months during the study all assessors will be trained, certified and/or re-certified for their role. Additional training will be provided to study staff who do not pass the review. Staff members will only be permitted to perform study duties if they have successfully passed their most recent evaluation.
- complete, timely, and accurate data are recorded and submitted;
- problems with inconsistent or incomplete data are addressed;
- complications and unanticipated adverse effects are reported to the IRB and Sponsor;
- the site facilities continue to be adequate to meet the requirements of the study.

The Clinical Monitor will initiate the Study during an on-site visit and will continue to perform on-site monitoring visits as frequently as deemed necessary. The first monitoring visit will usually be made as soon as possible after enrollment has been initiated. At this visit and all monitoring visits, the Clinical Monitor will compare the data entered onto the CRF's with the hospital or clinic records (source documentation). At a minimum, source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of AEs. Findings from the review of CRFs and source documents during a monitoring visit will be discussed with the PI. Completed pages of the CRFs will be collected for evaluation at each visit. The dates of the monitoring visit will be recorded in a Log to be kept at the clinical site. During monitoring visits, the Sponsor expects that the study coordinator and the PI will be available (as needed), the source documentation will be available, and a suitable environment will be provided for review of Study related documents.

Independent Data and Safety Monitoring Board

The study will be performed under the supervision of an Independent Data Monitoring Board (DSMB) that will consist of clinician who are not Investigator(s) in the study, and one independent statistician.

Details of the DSMB composition and operational activities will be described in detail in a separate DSMB charter.

Briefly, the DSMB responsibilities are to:

- evaluate the progress of the trial, including assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
- protect the safety of the study participants;
- report on the safety and progress of the trial;
- make recommendations to the Sponsor, the PI, and, if required, to the Food and Drug Administration (FDA) and the Institutional Review Board (IRB) concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
-
- ensure the confidentiality of the trial data and the results of monitoring; and,
- assist Sponsor by commenting on any problems with study conduct, enrollment, and sample size and/or data collection.

All subjects will be monitored by a member of study staff during the study visits. All cases performed during a calendar month will be reviewed at the end of that month to monitor for any potential adverse effects from the subjects' participation in the study.

ADVERSE EVENT REPORTING GUIDELINE

Serious adverse events will be reported to the IRB and the sponsor verbally within 24 hours, followed by a full written report within 10 working days. All other adverse events will be summarized in the progress report at Continuing Review by IRB and evaluated by DSMB. All adverse events will be assessed for their relationship to the study device or procedure by DSMB.

Throughout the study, adverse events and concomitant medications will be monitored and recorded. All Serious Adverse Events will be captured and assessed. All Serious Adverse Events will be reported as event and patient based count.

ADVERSE EVENT

An adverse event (AE) is any undesirable clinical experience (any sign, symptom, illness, abnormal laboratory value or other medical event) that occurs in a subject (or an event that worsens during the course of the study) and that could possibly be associated with the investigational product, procedure or medications required by this protocol. An adverse event may result from a device failure if an undesirable clinical event occurs. In this study, subjects should be encouraged to report AEs spontaneously.

Adverse event information will be collected throughout the study. Data collection will include event type, date of onset severity relationship to the procedure and investigational device, and event resolution, if any, at the conclusion of the study. All events will be followed for the duration of the study until they are resolved or their status at study conclusion is explained.

Serious Adverse Event

Each study investigator must decide whether an adverse event meets the definition of a "serious" adverse event. The regulatory definition of a serious adverse event (SAE) is an event that is fatal or life-threatening, results in persistent or significant disability, requires intervention to prevent permanent impairment, results in hospitalization (or prolongation of a hospitalization) or results in congenital anomaly or malignancy.

Any serious adverse event or subject death occurring during the study follow-up period must be reported within one working day after the investigator learns of the event.

Device Failure, Malfunctions and Near Incidents

Investigators are instructed to report all possible device failures, malfunctions or near incidents observed during the course of the trial. These incidents will be documented in the case report form provided as follows:

Device Failure: A device failure has occurred when the device is used in compliance with the study protocol, but does not perform as described in device manual and also negatively impacts treatment of the study subject.

Device Malfunction: A device malfunction occurs when an unexpected change to the device that is contradictory to the device manual is observed, which may or may not affect device performance.

Device Misuse: Any use of the investigational device by an investigator that is contradictory to the application described in the study protocol will be categorized as device misuse.

8.0 References (alphabetical order)

Abo M, et al. Randomized, multicenter, comparative study of NEURO versus CIMT in poststroke patients with upper limb hemiparesis: the NEURO-VERIFY Study. Int J Stroke. 2013 Sep 9. doi: 10.1111/ijs.12100. [Epub ahead of print]

Barreca S, Gowland CK, Stratford P, Huijbregts M, Griffiths J, Torresin W, Dunkley M, Miller P, Masters L. Development of the Chedoke Arm and Hand Activity Inventory: Theoretical constructs, item generation, and selection. Top Stroke Rehabil. 2004; 11: 31-42.

Bilney B, Morris M, Webster, K. Concurrent Related Validity of the ® Walkway System for Quantification of the Spatial and Temporal Parameters of Gait. Gait and Posture 2003; 17: 68-74.

Boggio PS, et al..Hand function improvement with low-frequency repetitive transcranial magnetic stimulation of the unaffected hemisphere in a severe case of stroke. Am J Phys Med Rehabil. 2006;85(11):927-30.

Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987;67:206-207.

Bridgers, S.L., The safety of transcranial magnetic stimulation reconsidered: evidence regarding cognitive and other cerebral effects. Electroencephalogr Clin Neurophysiol Suppl, 1991. 43: p. 170-9.

Bridgers, S.L. and R.C. Delaney, Transcranial magnetic stimulation: an assessment of cognitive and other cerebral effects. Neurology, 1989. 39(3): p. 417-9.

Bütefisch CM, et al. Relationship between interhemispheric inhibition and motor cortex excitability in subacute stroke patients. Neurorehabil Neural Repair. 2008;22(1):4-21

Chumney, D., et al. Ability of Functional Independence Measure to accurately predict functional outcome of stroke-specific population: Systematic review. *J Rehab Res Dev* 2010; 47 (1): 17–30.

Counter, S.A., et al., Hearing loss from the acoustic artifact of the coil used in extracranial magnetic stimulation. Neurology, 1990. 40(8): p. 1159-62.

Counter, S.A., Neurobiological effects of extensive transcranial electromagnetic stimulation in an animal model. Electroencephalogr Clin Neurophysiol, 1993. 89(5): p. 341-8.

Cutlip, RG, Mancinelli C, Huber F, DiPasquale J. Evaluation of an Instrumented Walkway for Measurement of the Kinematic Parameters of Gait. Gait and Posture 2000; 12: 134-38.

Dafotakis M, et al. Effects of rTMS on grip force control following subcortical stroke. Exp Neurol. 2008;211(2):407-12.

Danner N, Julkunen P, Könönen M, Säisänen L, Nurkkala J, Karhu J. Navigated transcranial magnetic stimulation and computed electric field strength reduce stimulator-dependent differences in the motor threshold. J Neurosci Methods. 2008 Sep 15;174(1):116-22. Epub 2008 Jul 11.

de Man-van Ginkel J M, Gooskens F, et al. Screening for poststroke depression using the patient health questionnaire. Nurs Res. 2012, 61(5): 333-341.

Di Lazzaro V. et al., The physiological basis of transcranial motor cortex stimulation in conscious humans. Clin Neurophys 2004;115:255-266.

DiFabio RP, Badke RB. Relationship of sensory organization to balance function in patients with hemiplegia. Phys Ther 1990;70 (9):542-8.

Duzel, E., et al., Verbal working memory components can be selectively influenced by transcranial magnetic stimulation in patients with left temporal lobe epilepsy. Neuropsychologia, 1996. 34(8): p. 775-83.

Duncan PW, Propst M, Nelson SG. Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. Phys Ther 1983;63:1606-10.

Duncan PW, Lai SM, Bode RK, Perera S, DeRosa J. Stroke Impact Scale-16: a brief assessment of physical function. Neurology. 2003; 60: 291-296.

Duncan PW, Bode RK, Lai SM, Perera S. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. Arch Phys Med Rehabil. 2003; 84: 950-63.

Emara TH, et al. Repetitive transcranial magnetic stimulation at 1 Hz and 5 Hz produces sustained improvement in motor function and disability after ischaemic stroke. Eur J Neurol. 2010;17:1203–1209.

Fauth, C., et al., Seizure induction and magnetic brain stimulation after stroke. Lancet, 1992. 339(8789): p. 362.

Fregni F, et al. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke. 2006; 37(8):2115-22.

Flansbjer UB, Holmback AM, Downham D, Patten C, Lexell J. Reliability of gait performance tests in men and women with hemiparesis after stroke. J Rehabil Med 2005;37(2):75-82.

Graves D, Bombardier C H. Improving the efficiency of screening for major depression in people with spinal cord injury. J Spinal Cord Med. 2008, 31(2): 177-184.

Hallett M, Wassermann EM, Pascual-Leone A. Repetitive transcranial magnetic stimulation. In, Deuschl G., Eisen A. (eds.) Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Neurophysiology Elsevier Science, B.V. 1999.

Harris, J., Clifford, C., Miniussi, C. The Functional Effect of Transcranial Magnetic Stimulation: Signal Suppression or Neural Noise Generation? J. Cogn. Sci., 2008; 20: 734-40

Harvey RL, Winstein CJ. Design for the Everest randomized trial of cortical stimulation and rehabilitation for arm function following stroke. Neurorehab Neural Repair. 2009; 23: 32-44.

Harvey RL et al. Abstract presented at International Stroke Conference 2014

Hendricks HT, et al. Motor recovery after stroke: a systematic review of the literature. Arch Phys Med Rehabil, 2002. 83 (p.1629-1637).

Homberg, V. and J. Netz, Generalised seizures induced by transcranial magnetic stimulation of motor cortex. Lancet, 1989. 2(8673): p. 1223.

Hufnagel, A., et al., Activation of epileptic foci by transcranial magnetic stimulation: effects on secretion of prolactin and luteinizing hormone. J Neurol, 1990a. 237(4): p. 242-6.

Hufnagel, A., et al., Magnetic motor-evoked potentials in epilepsy: effects of the disease and of anticonvulsant medication. Ann Neurol, 1990b. 28(5): p. 680-6.

Hufnagel, A., M. Jaeger, and C.E. Elger, Transcranial magnetic stimulation: specific and non-specific facilitation of magnetic motor evoked potentials. J Neurol, 1990c. 237(7): p. 416-9.

Hummel FC, Cohen FG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurology. 2006; 5: 708-712.

Hsu W-Y, et al. Effects of Repetitive Transcranial Magnetic Stimulation on Motor Functions in Patients With Stroke – a Meta-Analysis. Stroke 2012;43:1849-1857

Janneke M, Hafsteinsdóttir T, et al. An Efficient Way to Detect Poststroke Depression by Subsequent Administration of a 9-Item and a 2-Item Patient Health Questionnaire. Stroke. 2012 43(3): 854-856.

Kandler, R., Safety of transcranial magnetic stimulation. Lancet, 1990. 335(8687): p. 469-70.

Kakuda W., et al., Combination treatment of low-frequency rTMS and occupational therapy with levodopa administration: an intensive neurorehabilitative approach for upper limb hemiparesis after stroke. Int J Neurosci. 2011a. 121(7):373-8

Kakuda W., et al., Anti-spastic effect of low-frequency rTMS applied with occupational therapy in post-stroke patients with upper limb hemiparesis. Brain Inj. 2011b.25(5):496-502

Kakuda W., et al., Baseline severity of upper limb hemiparesis influences the outcome of low-frequency rTMS combined with intensive occupational therapy in patients who have had a stroke. PM R. 2011c.3(6):516-22

Kakuda W, et al. A multi-center study on low-frequency rTMS combined with intensive occupational therapy for upper limb hemiparesis in post-stroke patients. J NeuroEng Rehab 2012, 9:4

Khedr EM, et al.. Dysphagia and hemispheric stroke: A transcranial magnetic study. Neurophysiol Clin. 2008;38(4):235-42

Khedr EM, et al., Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke. Eur J Neurol. 2009;16(12):1323-30

Kirton A, et al. Contralesional repetitive transcranial magnetic stimulation for chronic hemiparesis in subcortical paediatric stroke: a randomised trial.. Lancet Neurol. 2008;7(6):507-13.

Kleim JA, Jones TA. The principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. J Speech Lang Hearing Res. 2008; 51: S225-S239.Lai SM, Perera S, Duncan PW, Bode R. Physical and social functioning after stroke: comparison of the Stroke Impact Scale and Short Form-36. Stroke. 2003; 34: 488-93.

Liepert J, Bouder H, Wolfgang HR, et al. Treatment-induced cortical reorganization after stroke in humans. Stroke. 2000; 31: 1210-1216.

Liepert J, Zittel S, Weiller C. Improvement of dexterity by single session low-frequency repetitive transcranial magnetic stimulation over the contralesional motor cortex in acute stroke: a double-blind placebo-controlled crossover trial. Restor Neurol Neurosci. 2007;25(5-6):461-5.

Little, J., et al., Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation in depression: preliminary report. Neuropsychiatry Neuropsychol Behav Neurol, 2000. 13: p. 119-124.

Lord SE, McPherson K, McNaughton HK, Rochester L, Weatherall M. Community ambulation after stroke: how important and obtainable is it and what measures appear predictive? Arch Phys Med Rehabil 2004;85:234-9.

Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. Int J Rehabil Res.1981;4:483-92.

Malcolm MP, et al. Repetitive transcranial magnetic stimulation as an adjunct to constraint-induced therapy: an exploratory randomized controlled trial. Am J Phys Med Rehabil. 2007;86(9):707-15.

Málly J, Dinya E. Recovery of motor disability and spasticity in post-stroke after repetitive transcranial magnetic stimulation (rTMS). Brain Res Bull. 2008;1;76(4):388-95.

Mansur CG, et al.A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology. 2005 24;64(10):1802-4.

Morris DM, Uswatte G, Crago JE, Cook EW III, Taub E. The reliability of the Wolf motor function test for assessing upper extremity function after stroke. Arch Phys Med Rehabil . 2001; 82: 750-755.

Ng SS, Hui-Chan CW. The timed up & go test: its reliability and association with lower-limb impairments and locomotor capacities in people with chronic stroke. Arch Phys Med Rehabil 2005;86(8):1641-7.

Nishikiori, O., [Studies on transcranial magnetic stimulation--Part 2. Pathological findings of rabbit brain after long-term stimulation based on characteristics of intracerebral induced voltage]. Nippon Ganka Gakkai Zasshi, 1996. 100(7): p. 489-95.

Nowak DA, et al.Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. Arch Neurol. 2008;65(6):741-7

O'Reardon, J.P., et al., Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial. Biological Psychiatry. In Press, Corrected Proof.

Page, S.J. et al. Clinically important differences for the upper extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. Physical Therapy, 2012; 92: 791-798.

Pascual-Leone, A., et al., No evidence of hearing loss in humans due to transcranial magnetic stimulation. Neurology, 1992. 42(3 Pt 1): p. 647-51.

Pascual-Leone, A., et al., Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. Electroencephalogr Clin Neurophysiol, 1993. 89(2): p. 120-30.

Pomeroy VM, et al.Transcranial magnetic stimulation and muscle contraction to enhance stroke recovery: a randomized proof-of-principle and feasibility investigation. Neurorehabil Neural Repair. 2007;21(6):509-17.

Ravnborg, M., G.M. Knudsen, and M. Blinkenberg, No effect of pulsed magnetic stimulation on the blood-brain barrier in rats. Neuroscience, 1990. 38(1): p. 277.

Rossi S, Cappa SF, Rossini PM. Higher Cognitive Functions: Memory and Reasoning. In: C. Epstein, U. Ziemann, EM Wassermann, V. Walsh, T. Paus, SH Lisanby (Eds). Oxford Handbook of Transcranial Stimulation, Oxford University Press, London, 2007c, pp. 501-516

Rossi S, et al; Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009. 120(12):2008-39.

Stinear CM, et al. Functional potential in chronic stroke patients depends on corticospinaltract integrity. Brain. 2007. 130(Pt 1):170-80

Sung W, et al. Efficacy of coupling inhibitory and facilitatory repetitive transcranial magnetic stimulation to enhance motor recovery in hemiplegic stroke patients. Stroke 2013; 44(5):1375-82

Säisänen L, Pirinen E, Teitti S, Könönen M, Julkunen P, Määttä S, Karhu J. Factors influencing cortical silent period: optimized stimulus location, intensity and muscle contraction.J Neurosci Methods. 2008 Mar 30;169(1):231-8. Epub 2007 Dec 23.

Takeuchi N, et al. Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranical magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. J Rehabil. 2008.

Takeuchi N, et al.Repetitive transcranial magnetic stimulation of the unaffected hemisphere in a patient who was forced to use the affected hand. Am J Phys Med Rehabil. 2008;87(1):74-7.

Takeuchi N, et al. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. Stroke. 2005; 36(12):2681-6.

Takahashi S., et al. Navigated transcranial magnetic stimulation for mapping the motor cortex in patients with rolandic brain tumors. Neurosurg Focus, 2013 34 (4):E3

Tassinari, C.A., et al., Transcranial magnetic stimulation in epileptic patients: usefulness and safety. Neurology, 1990. 40(7): p. 1132-3.

Taub E, Miller NE, Novack TA, et al. Technique to improve chronic motor deficit after stroke. Arch Phys Med Rehabil. 1993; 74: 347-354.

Teng EL, Chui HC. The Modified Mini-Mental State Exam. J Clin Psychiatry 1987;48 (8):314-18.

Thielig S., et al., Functional neuromuscular stimulation to improve severe hand dysfunction after stroke: does inhibitory rTMS enhance therapeutic efficiency? Exp Neurol. 2011. 230(1):149-55.

Traversa et al., A method to monitor motor cortical excitability in human stroke through motor evoked potentials. Brain Res Protocols 1999;4:44-48.

Van der Lee JH, De Groot V, Beckerman H, Wagenaar RC, Lankhorst GJ, Bouter LM. The intra- and interrater reliability of the action research arm test: a practical test of upper extremity function in patients with stroke. Arch Phys Med Rehabil 200182(1):14-9.

Wassermann, E., et al., Seizures in healthy people with repeated "safe" trains of transcranial magnetic stimuli. Lancet, 1996. 347: p. 825.

Wassermann, E.M., Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol, 1998. 108(1): p. 1-16.

Wassermann, E.M., Side effects of repetitive transcranial magnetic stimulation. This article is a US Government work, and, as such, is in the public domain in the United States of America. Depression & Anxiety (1091-4269), 2000. 12(3): p. 124.

Wolf SL, Catlin P, Ellis M, Archer AL, Morgan B, Piacentino A. Assessing Wolf motor function test as outcome measure for research in patients after stroke. Stroke. 2001; 32: 1635-1639.

Wolf SL, Lecraw DE, Barton LA, Jann BB. Forced use of hemiplegic upper extremities to reverse the effect of learned nonuse among chronic stroke and head-injured patients. Exp Neurol. 1989; 104: 104-132.

Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3-9 months after stroke: the EXCITE randomized clinical trial. JAMA. 2006; 296: 2095-2104.

Xia G, et al., . Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. Int. J.Neuropsychopharmacol., 2008; 11: 119-30

Appendix A NBT PROCEDURES

GENERAL

For the navigated TMS session with NBT, the subject will undergo the MRI to head registration and Motor Threshold and TMS procedures. Each TMS imaging session will begin with aligning the MRI images to the subject's head via the MRI to head co-registration. Subjects will then undergo TMS mapping of the hand motor areas as set out below to localize optimal the motor representation area of hand muscles including the muscle of interest, m.EDC.

ELECTROMYOGRAPHY

EMG leads must be connected to m.EDC and m.APB to facilitate accurate mapping of the m.EDC motor representation areas:

1. Abductor Pollicis Brevis (APB)
2. Extensor Digitorum Communis (EDC)

NOTE: The target muscle(s) should be at rest at all times. Monitor involuntary muscle activity at all times during the examination.

MRI TO HEAD CO-REGISTRATION

Using the nasion and the crus of helix of the ears, landmarks that are visible on both the subject's MRI and the head, the 3D -locations of landmark are measured using a digitizing pen with an optical tracking system. This registration will allow real time monitoring of the coil position without restraining the subjects head during the TMS experiment. The optical tracking system uses a camera to measure the 3D -location of infrared reflectors attached to the coil and subject's head.

BASELINE, TREATMENT VISITS

The motor mapping of the healthy hemisphere will be done during the baseline visit and this location will be utilized in determining the motor threshold and therapy intensity during each treatment visit when rTMS is administered. Motor mapping of the lesioned hemisphere will not be performed. The following list illustrates which procedures are done during the first and subsequent visits. The details of the steps are described in the following sections.

1) Healthy hemisphere
    a) Baseline visit
        i) Hand area motor mapping
            (1) Initial motor mapping
            (2) Initial motor threshold
            (3) Refined mapping
        ii) Therapy dose determination
            (1) Refined motor threshold
        iii) Offline analysis
    b) Following visits
        i) Therapy dose determination
            (1) Refined motor threshold

ii) Therapy delivery

iii) rTMS stimulation

iv) Offline analysis

HEALTHY HEMISPHERE

HAND AREA MOTOR MAPPING

Localization of the cortical representation area for m.EDC at rest is described here.

Attach mapping coil (Nexstim Focal Coil)

Mapping of the motor cortical representation areas and determination of motor thresholds will be done using the Nexstim Focal Coil. Attach the coil to the system if not already connected.

Identifying the rough location of hand motor area

This identification of the rough location of hand motor area is used in determination of the initial motor threshold and as a reference for the actual motor mapping.

1) Identify the hand knob at primary motor cortex, if possible.
   a) Peel the 3D head to a depth where the gyral patterns of neuroanatomy are clearly visible (approximately 20-25 mm)
   b) For reference utilized during mapping place a stimulation target on the motor cortex. The position of the marker is on the medial end of the so called "motor knob" on the central sulcus.
2) Set initial stimulation intensity
   a) Adjust stimulator output so that the software displays stimulation intensity between 80 and 100 V/m (at 25 mm peeling depth).
   b) Give a preparing stimulus pulse on the marker and check the response of the target muscle m.EDC
   c) Give two stimuli are on the target and check m.EDC response latencies (normal 15-25ms) and amplitudes.
      i) **IF YOU GET EMG RESPONSE >500uV**: Lower the stimulation intensity 1 – 2 % of stimulator output and repeat stimulation until the m.EDC peak-to-peak response is in the range of 100-500uV.
      ii) **IF YOU GET EMG RESPONSE <100uV**: Increase the intensity of stimulus until the m.EDC amplitude is 100-500uV.
3) Using the intensity defined in the previous step, continue stimulation by following the central sulcus towards the central fissure so that the stimulus orientation is always perpendicular to the central sulcus and direction frontal. Stimulation is ended when there is no response. This is most likely to happen about 2 cm from the marker. **NOTE:** Make sure that you stimulate also directly over the precentral gyrus. Return to the marker and continue stimulation by following the central sulcus towards the Sylvian fissure so that the stimulation direction is always perpendicular to the central sulcus. Expand the stimulated area until MEP's disappear.
4) Select the largest m.EDC response and set is as Repeat Stimulus.

5) Testing coil orientations:

   a) The first stimulus is given on the repeat stimulus target. This is the zero degree position. Check the EMG response amplitude which is now the reference. Turn off location controlled stimulation. Using the aiming tool to repeat stimulus on the marker, the stimulation on the marker is continued so that after each stimulus the coil is turned 20 degrees left. The m.EDC response amplitude (μV) is checked after each given stimulus. The stimulation is terminated when the response is less than 100μV.

   b) Return to the original orientation on the marker and continue stimulation on the marker so that after every stimulus the coil is turned 20 degrees right. After every stimulus the response amplitude (μV) is checked. Stimulation is terminated when the response is less than 100μV.

   c) The coil orientation giving the best motor response is selected for defining the motor threshold.

Initial motor threshold measurement for defining intensity for motor mapping:

The motor threshold (MT) is defined as the lowest stimulation intensity producing a response in the target muscle (m.Extensor Digitorum Communis, m.EDC) at least in 50% of trials. The presumption is that the motor threshold varies due to the functional state of the brain which may be altered by lesions or medications.

1) Start the MT determination tool from the stimulus defined in the previous step.

2) Stimulate guided by the Aiming Tool as many times as suggested by the software, leaving 3-5 seconds between each stimulus.

3) In the end of the iteration, the software displays the patient's motor threshold value as a percentage of the maximum stimulator output.

Mapping of hand motor area and localization of m.EDC hotspot

Mapping of the cortical representation area of the hand area is now repeated using a stimulator intensity that generates ~ 100-300μV MEPs repeatably at the location where resting motor threshold is determined. Typically this is 110% of the resting motor threshold.

The overall goal is to find a stimulation location, on or near the motor strip, that elicits the largest amplitude EDC MEP during mapping with other relatively large EDC MEPs elicited at the same location or at nearby locations.

1) Set the stimulator output to 110% of the motor threshold defined previously

2) Once the stimulation intensity is determined, the rMT determining location should be set as the active stimulation target to overlay a stimulation Grid on cortex.

3) Using the Grid to systematically cover the area to be studied, stimulate along central sulcus, precentral gyrus, postcentral sulcus and precentral sulcus with 2-3 mm spacing of stimuli while keeping the electric field orientation perpendicular to the sulcus. Mapping should proceed with 3 stimuli per grid location, delivered with 3-4s between pulses, until stimulation at locations around the "rim" or outer edge of the map do not produce reproducible MEPs (=at least 2/3 stimuli to location do not elicit a MEP >50 μV).

4) Expand the stimulated area as long as reproducible motor responses emerge.

5) Identify the location giving rise to the largest m.EDC EMG response - the target for rTMS

5.1 Rank the EDC MEPs by amplitude

5.2 Select the MEP with highest amplitude that fills as many of the following criteria as possible

5.2.1 Background EMG was quiet during this stimulation

5.2.2 The location is on or near the motor strip

5.2.3 The other two MEPs generated at this location are also large

5.2.4 There is also a clear resting MEP in APB

5.2.5 The adjacent locations also have strong, repeatable MEPs.

5.3 NOTE: The location chosen may not be the absolute highest amplitude MEP from the mapping. We are trying to find a location that represents the strong center of activation for hand and finger muscles, shown by large repeatable MEPs. We want to avoid selecting an isolated activation center for EDC far from M1, or one that represents a transient high fluctuation in cortical excitability.

6) Test coil orientations in this location as done in initial mapping and select the best motor response is for defining the refined motor threshold

<u>The location defined in the refined mapping including coil orientation testing is considered the hotspot of m.EDC and will be used as the target location for subsequent MT determinations and delivering 1 Hz rTMS therapy.</u>

THERAPY DELIVERY

For rTMS delivery the best coil orientation giving rise to the largest m.EDC response from refined mapping will be used as the coil orientation during rTMS delivery. The rTMS delivery will be performed at 110% of the motor threshold determined at this location in the previous step.

A single 1Hz train consisting of 900 stimuli will be delivered to the hotspot of motor representation area of m.EDC established at the baseline visit.. Active or sham rTMS will be delivered utilizing an active or sham coil, respectively.

Attach the TMS coil appropriate for the subject's randomization group (Nexstim Trial Coil)

Motor threshold measurement for defining intensity for rTMS therapy.

The location defined in the refined mapping including coil orientation testing is considered the hotspot of m.EDC and will be used as the target location for subsequent MT determinations and delivering 1 Hz rTMS therapy.

1) Start the MT determination tool from the stimulus defined in the previous step.

2) Stimulate guided by the Aiming Tool as many times as suggested by the software, leaving 3-5 seconds between each stimulus. For subjects randomized to receive sham stimulation, alternatively accept and reject the results suggested by the NBT software.

3) In the end of the iteration, the software displays the patient's motor threshold value as a percentage of the maximum stimulator output.

RTMS stimulation

1) Select the stimulus corresponding to the largest m.EDC response from refined motor mapping (same stimulus as used as reference during refined MT determination) and set it as Repeat Stimulus

2) Position therapy coil using coil positioning holder to location guided by Aiming Tool

3) Select rTMS sequence containing 900 stimuli at 1 Hz (15 minute duration)

4) Check that the intensity corresponds to 110 % of the refined m.EDC MT defined in previous step

5) Start rTMS sequence and monitor coil position

OFF-LINE ANALYSIS

1) From details of the therapy rTMS sequence review statistics for accuracy of pulses in relation to the reference pulse / first pulse of sequence, i.e. how well the coil stayed in place during the sequence run.

2) From motor mapping, identify optimal m.APB and EDC locations (the stimulus location evoking the largest EMG responses, respectively).

3) Define coil coordinates, coordinates on the chosen stimulation surface (3D-MR image), and coordinates at fixed depth (25 mm from the scalp surface). Review MEP traces and correct the amplitudes and latencies if needed.

4) Capture all stimuli eliciting muscle responses with normal latencies and greater than or equal to 50 μV in relaxed muscles.

5) Make an analysis file to NBT for further studies.

6) Establish a map of motor cortical locations from the analysis file by using the NBT analysis table and its visualization features.

Appendix B Task Oriented Upper Limb Therapy Protocol

Protocol Structure

The therapy program for both investigational and control subjects will be the same. Each subject will attend 18 therapy sessions, each lasting 2 to 2.5 hours (39 treatment hours).

Each session will follow a standard protocol with 4 or 5 phases:

1. Pre-functional Activities (20 minutes) - Therapist chooses 1-2 pre-functional activities listed below based on the patients Chedoke hand or arm level.
2. Rest Break (10 minutes)
3. Low Frequency TMS or Sham TMS (25 minutes) – per TMS protocol.
4. 5-15 minutes wait (to allow for upregulation of motor system)
5. Task-Oriented Functional Activities (60 minutes) – The patient will choose functional activities from the following list of categories based on his or her desired functional goals. The therapist will provide guidance in choosing by suggesting activities according to the patients capacity as determined by the patient's Chedoke Hand or Arm Stage
    a. Wrist and finger activities
    b. Grasp/pinch
    c. Force Modulation/Lift off
    d. Release
    e. Reach to grasp
    f. Fine motor activities

Prefunctional Activities

1. Scapular Stability (Can perform in any position including side lying)

    Chedoke Arm #3:
    a. Place and hold - Subject attempts to hold position of scapula after placement in the plane by therapist (subject can be sitting or in side lying)
    b. Active elevation and depression of scapula with emphasis on depression
    c. Active exercise for middle trapezius - Subject squeezes both scapulas together while keeping arms stable on table or in side lying.
    d. Active exercise for lower trapezius - Subject squeezes scapula together and pushes down. Therapist can provide manual cues. Position at discretion of therapist
    e. D1 extension - emphasizing posterior depression

f. Active exercise for Serratus Anterior
g. Active exercise for Rhomboids

Chedoke Arm # 4, 5 or 6 - Any of the above exercise plus these additional exercises:
a. After alignment of scapula, shoulder flexion between 0 to 50 degrees and attempts to maintain scapula in position
b. Practice stabilizing scapula while performing D2 flexion

2. Scapular Mobility

Chedoke Arm #3:
a. Passive-Scapular Mobilization in D1 and D2 diagonals. Subject is then instructed to move with the therapist
b. Active Assist or resistance to scapular patterns

Chedoke Arm #3 or 4
a. Bilateral Asymmetrical patterns: Chop/reverse chop or Lift/reverse lift
b. Activation of scapular muscles using PNF techniques

3. Strengthening Rotator Cuff (Affected arm should be positioned in external rotation with cubital fossa facing upward)

Chedoke Arm #3:
a. Stretching or soft tissue mobilization of internal rotators
b. Washing a window or wiping table while maintaining external rotation
c. Bilateral Symmetrical D1 or D2 flexion pattern
d. Bilateral Symmetrical D1 or D2 flexion with maximal resistance on the unaffected limb
e. Unilateral D1 or D2 pattern (Active assist, Active, or resistive)
f. Unilateral D1 or D2 with isometric contraction at end ranges
g. Eccentric and Concentric strengthening exercises for shoulder external rotation (can include isometric holds, active assist, gravity eliminated or against gravity). Strengthen with and without abduction

.
Chedoke Arm #4, 5 or 6 - Any of the above exercise plus these additional exercises:
a. Same exercise as above with theraband™ or light free weights
b. Strengthen shoulder abduction without recruitment of upper trapezius
c. Strengthen shoulder flexors
d. Practice shoulder external rotation with abduction
e. Practice shoulder external rotation with flexion

NOTE: The therapist uses maximal resistance. Maximal resistance is not the maximal resistance that the therapist can provide. It is the maximal amount that the subject can handle, while still moving in the pattern without breaking. For some subjects, maximal resistance is active assist.

4. Shoulder Elbow Coupling Phase

   Chedoke Arm #3:
   a. Passive stretching of elbow with shoulder in flexion
   b. Stretching elbow by weight bearing.
   c. Work on shoulder and elbow control in supine (place and hold, active assist, reach to target)
   d. Practice elbow extension in sitting with the hand of the affected arm fixed on the mat
   e. Work on placing hand from lap to table without shoulder elevation and increasing distance of hand placement
   f. Active Assist shoulder and elbow coupling while the arm is supported on table (shoulder flexion, elbow extension). Therapist can provide assistance as needed.

   C*hedok*e *Arm #4 or 5- Any of the above exercises plus these additional exercises*
   a. Work in sifting/side lying/supine or prone on concentric and eccentric shoulder flexion (begin with place and hold and progress to stop and hold).
   b. Throw beanbag towards feet after retrieving it from opposite shoulder
   c. Work on shoulder flexion with elbow extension and hand opening to grasp with varying levels of assistance from the therapist and at various speeds.
   d. Work on moving and coordinating the arm and hand to a target (vary the distance of the target).

   Chedoke Arm #6: - Any of the above exercises plus these additional exercises
   a. Work on the shoulder elbow coupling at varying speeds.

Task Oriented Functional Activities

Note: Functional activities are chosen by the patient in the context of functional goals. Suggested activities are provide by the therapist according to the patient's Chedoke level. Effort should be made to practice these exercises in the context of meaningful functional activities.

1. Wrist and Finger activities

   a. Wrist (and forearm) practice

   Chedoke Hand # 3
   1) Passive stretch of wrist in all planes
   2) Active assist wrist flexion/extension
   3) Wrist extension/flexion with gravity eliminated
   4) Wrist extension against gravity
   5) Place and hold in wrist extension and flexion against gravity
   6) Isotonic wrist extension and flexion with graded resistance
   7) PNF movements D1 or D2 with distal focus on wrist

Chedoke Hand 3 & 4

1) Pushing ball, dough or other round object on surface with wrist and fingers in extension
2) Active or Active assist radial abduction and adduction of wrist
3) Passive stretch of forearm into supination
4) Active assist forearm into supination/pronatoin

Chedoke Hand 4, 5, & 6 *(or when patient is able to all of the preceding activities)*

1) Place and hold forearm in various degrees of supination and pronation.
2) Isotonic supination and pronation with isometric holds at end ranges
3) Isotonic supination and pronation with graded resistance
4) Practice drawing figure-of-eight on paper with a marker or pen with focused use of wrist rotation.

b. Finger Activities

Chedoke Hand #3

1) In standing by a table the patient passively stretches the wrist and finger flexors by bearing weight on table with wrist and fingers in extension and shoulder in external rotation (this can be taught to the patient and carried out at home several times a day)
2) Active Flexion and extension of fingers
3) Extended fingers of the affected hand hold a ruler firmly while unaffected hand draws lines.
4)

Chedoke Hand #4(or when patient is able to all of the preceding activities)

1) Gross finger flexion and extension exercises
2) lndividual finger flexion and extension exercises (may include blocking exercises)
3) Isometric holds for finger extension
4) Finger abduction/adduction
5) Exercises for lumbricals (start out in full finger flexion and assume intrinsic plus position)

c. Exercises for thumb in all planes

Chedoke Hland ***#5*** *&* ***6***

1) Opposition of thumb to digits II, III, IV, and V — then hold small object between thumb and each digit (one digit at a time). Therapist can apply resistance to hold.
2) Lift fingers off table
3) Practice finger tapping - use all four fingers and then one at a time.

2. Graded upper limb activities to improve grasp and pinch

Note: A variety of objects should be used for the functional activities. The objects should be various sizes, weights, shapes or textures. Weighted objects may be

easier than light ones because of greater ease in modulating force. Objects should be graded to patient's ability. Grasping should be practiced using both pronated grasp and grasp in the neutral position.

Chedoke Hand #3

a. Strengthen weak grasp by pulling a rolled towel through the hand in radial direction and asking the subject to squeeze and then release
b. Practice holding forearm in neutral position while supported by table
c. Practice holding object that is placed in hand by therapist while arm is supported by table (can use any type of grasp or pinch)
d. Placed object in subject's hand and practice holding close to body while standing/walking
e. Practice moving the arm with object placed in hand(s) with arm supported on table (with and without vision) *
f. Placed object in subject's hand(s) and practice holding free in space*
g. Hold onto jar with affected hand and unscrew lid with unaffected one

Chedoke #4 (or when patient is able to do the preceding activities)

a. Strengthen thumb in radial abduction to increase stability
b. Subject holds object and moves thumb up and down object surface while maintaining grasp
c. Subject holds small pill bottle in hand and uses thumb to lift lid while maintaining grasp
d. Increase strength of intrinsics (lumbricals, abductors, and adductors) as needed. Start with placing hand in position and asking subject to hold.
e. Grasp object on table that is supported by therapist (therapist is holding/stabilizing the object)
f. Grasp bean bag on table

Chedoke #5 (or when patient is able to do the preceding activities)

a. Grasp object without support by therapist
b. Grasp object with eyes closed (may help increase hand opening)
c. Practice grasp/pinch using a variety of objects
d. Hold onto jar with unaffected hand and unscrew lid with affected. Vary diameter of jars and work up to peanut butter jar.
e. Grasp an object and then change the weight of it (e.g. grasp a cup and therapist can pour liquid into it or subject can pour with unaffected hand).

Chedoke #6 (or when patient is able to all of the preceding activities)

a. Practice pouring water from one container to another. Starting at tabletop and then progress to free space. Also, vary size of container. Start with a large glass and progress to pouring with small glasses. Vary the quantity of liquid.
b. Work on repetitive grasp and release of one object increasing speed.
c. Work on reaching maximum grip or pinch as fast as possible using dynamometer or pinch gauge
d. Apply resistance to wrist extensors while subject is holding/grasping object. Ask subject to hold
e. Strengthen grip and pinch with theraputty or other resistive equipment
f. Train to grasp an object and then rotate it (e.g. pick up box of cereal and then rotate

box to pour cereal in bowl

3. Graded activities to improve force modulation and lift off.

Note: These activities require coupling of grip and vertical load force. These should be practiced to improve lifting of an object or maintaining an object in hand when it is difficult for themThe therapist should use various types of grasps and objects

Chedoke Hand #3

a. Hold object in unaffected hand lift off of table, then attempt with affected hand
b. Place object in subject's hand, which is lifted off table. Subject attempts to hold objects while elbow is on table
c. As above with a cylindrical or large object using both hands.
d. Same as A with forearm and elbow resting on table — lift object (which has been placed in hand by therapist) off table two inches and hold. Elbow remains on table
e. Subject grasps or places object requiring bilateral use in both hands with forearm free in space. Object is pressed down into the table prior to lift off. (ex. objects could include pan or pitcher filled with water, etc)
f. Work on the above with vision occluded
g. Place object in subject's hand (subject can also place it with unaffected hand) and change weight of object (pour water into a cup, add items to a tray)

Chedoke# 4, 5 and 6, (or when the patient is able to perform the preceding activities).

a. Practice gripping dynamometer, pinch meter, blood pressure cuff or any instrument with visual feedback to vary levels of force - *(Hand can be placed on dynamometer. Since subject should be able to see scale, dynamometer should be turned around and the adjustable bar should be placed in the web space)*
b. In standing, reach for object on table. Press down into table prior to lift off
c. Stroke the affected wrist with unaffected hand while lifting object

4. Graded Activities for Release

Chedoke Hand # 3

a. Passive stretch of finger flexors w/wrist in extension
b. Practice holding 1 or 2 lb weight in hand and then lowering it onto mat or floor and releasing (holding weight enables relaxation of long finger flexors). Thumb should be in extended position. Forearm can be neutral or pronated
c. After grasping rolled towel, relax finger flexors. Therapist can position towel in the air so that subject's arm is slightly raised. Use gravity.
d. Practice holding a large ball with two hands and then letting go
e. Pass object from one hand to another
f. Throw objects underhand toward a target on the floor.

g. Release of a supported object on table following pronated grasp by using tenodesis effect

Chedoke Hand #4 (or when patient is able to all of the preceding activities)

a. Release of a medium width cylindrical object (can or glass) that is externally supported (on table or countertop) with the therapist's hand stabilizing the object. Therapist's hand should be on top of the can while the subject attempts to release his/her hand, which is gripping sides of can. Therapist maintains hold on can while subject releases. Task will be easiest at this level since less force modulation is required for this task.
b. The same as above with different object widths
c. Release of an unsupported object but subject's arm is supported by table

Chedoke # 5 (or when patient is able to do all of the preceding activities)
a. Release with the object on the table but with the arm in free space
b. Release of small ball onto floor using increased velocity
c. Throw ball overhand into a safe area (e.g. corner of room) and progress to throw with therapist catching the ball.

d. Release of objects into progressively smaller spaces
e. Using both hands, grasp/release a dowel using hand over hand (up/down & crossovers)
f. Release of objects using two targets of different height (e.g. shelves)
g. Transport an object and then release.
h. Release object into crowded environment without changing position of other objects
i. Release object on to a moving target (rolling cart). Subject is standing. Therapist is walking with cart

Chedoke Hand # 6 (or when patient is able to do all of the preceding activities)
a. Practice release with increasing speed requirements
b. Practice release of objects after orientation of hand has to change (thumb facing ceiling while putting mail in mail slot).

5. Activities for Reach and Grasp Sequence

Chedoke *Hand # 3*
a. Subject uses both hands to push wheelchair or cart (hands grasping handle, forearm in neutral position and/or pronated)
b. Subject is sitting and reaches to down to target close to floor. Gravity may help to release tone. Object is placed in hand by therapist. Subjects grasps it and brings it up to lap.
c. Subject is sitting in chair and uses both hands to hold a dowel and simulate paddling a conoe starting on affected side and then moving to unaffected side.
d. Place hand on faucet with arm supported on sink and practice turning water off and on
e. Train the affected arm to reach and point without grasp) to a target while the arm is fully supported on a table. Start this task by positioning target in the unaffected space (affected arm uses adduction and crosses midline)
f. Progress to reaching straight forward in line with the shoulder while arm is supported on table
g. Reach away from midline with shoulder abduction while arm is supported on table

h. Wipe a table using horizontal adduction and abduction
i. Subject holds on to handle of pan or other object and slides it across table
j. Train hand to mouth movement while holding a cup unilaterally. Use different types of cups including plastic drinking glass, paper cup and coffee cup with a handle.
k. Train eccentric control of reach with object placed in hand
l. Use affected arm to open /close door. Hand can be placed on handle. Or handle can be grasped
m. Open close drawer with affected hand. Hand position as above
n. Practice reaching and turning on a light switch. (can use unrefined grasp)
o. Train to move arm free in space with object already placed in hand
p. As above but with bilateral use (ex. tennis racket, golf club, baseball bat etc)

Chedoke Hand # 4 (or when patient is able to do all of the preceding activities)

a. Subject is in side lying or standing and holds a paint roller and then moves it up the wall while depressing the scapula. Can begin with active assist
b. Work on reach and grasp with gravity assisting by placing target close to floor
c. Work on reaching across midline (using shoulder adduction) and grasping an object with arm free in space
d. Work on reaching in sagittal plane (arm in line with shoulder) and grasping an object with arm free in space
e. Work on reaching away from midline and grasping an object with arm free in space

Chedoke Hand # 4 & 5 (or when patient is able to do all of the preceding activities)

a. Work on reaching slowly and having subject attend to thumb position after receiving information on target (vision of target occluded)
b. Work on reaching to a target which is visible but with no vision of the arm
c. Work on reaching to various targets using slow movements interspersed with fast reaching movements

Chedoke Hand # 5 & 6 (or when patient is able to do all of the preceding activities)

a. Work on moving the arm through a maze of objects while holding an object
b. Train to reach and grasp an object from areas with many objects without knocking over these other objects. (e.g. kitchen cabinet, refrigerator or table with many objects placed near the one which is the target object)
c. Reach/grasp with increasing speed
d. Reach/grasp a moving object from a rolling cart (Subject is standing or walking. Therapist rolls cart with objects and subject grabs object from cart)

1. Fine Motor Exercise/Activities **(**Categorized according to activity and type of precision grasp)

Chedoke Hand # 3 or 4 — Lateral Pinch

a. Practice pouring from a container with a handle (tea kettle or pitcher)
b. Practice stuffing envelopes
c. Set a table using affected hand to place flatware

d. Practice counting bills while holding bills with unaffected hand
e. Practice putting key into lock
f. Practice opening door with key
g. Practice zipping and unzipping on dressing board, clothing, pocket book, etc.
h. Practice unwrapping thread around spool using affected hand to hold thread (can
i. downgrade by using yarn)
j. Play cards — shuffling and dealing
k. Practice opening containers with small lids (soda bottles)
l. Hold and drink with cup with handle
m. File nails with emery board
n. Cut with large scissors
o. Cut with small scissors
p. Pinch, place and release closepins
q. Practice pulling cap off pen

Chedoke Hand # 5 – Three jaw chuck

a. Pick up ring from table — place on unaffected finger-remove ring
b. Pick up, shake, and roll dice
c. Pick up keys placed in pocket of pants
d. Hold sugar packet with affected hand; practice opening packet
e. Practice picking up salt shaker, turning over & gently shaking
f. Practice holding teacup

Chedoke Hand # 5 & 6 – Pincer grasp

a. Turn pages of photo album, progress to newspaper or magazine
b. Place/Remove pegs to/from pegboard (small ones)
c. Pick up pennies from table
d. Stack coins on table
e. Pick up coins placed in pocket of pants
f. Practice stacking checkers or playing checkers
g. Practice picking up beans
h. Place pegs in a peg board using tweezers
i. Pick up cotton balls

Chedoke Hand #4, 5, & 6 – Tripod grasp

a. Practice tracing
b. Practice drawing shapes
c. Practice writing
d. Practice drawing with a guide (ruler or stencil)
e. Practice using fork or spoon during feeding

Chedoke Hand # 5 & 6 – Refind hand movement

a. Practice buttoning/unbuttoning appropriate clothing.
b. Sort, clip and fold paper
c. Practice opening & closing locks
d. Screw/unscrew nuts and bolts in varying sizes
e. Use Valpar 9 to screw/unscrew
f. Practice typing the home row

g. Use affected hand to practice typing words that are only used by one hand. For example: RIGHT: you, mill, pill, nil, him, no; LEFT: dear, as, tear, bed, tease, cave, rave, save, rat, pop, kill
h. Practice two handed typing exercise

Chedoke Han # 5 & 6 – In hand manipulation activities

a. Practice picking up coinsfrom pocket of pants.
b. Move coins from fingertips to palm
c. Pick up coins from table and hold in palm of hand. Feed the coins back out to thumb and index finger and place on table
d. Practice moving a pen or other object at fingertips
e. Practice twirling a pencil
f. Rotate a paperclip at fingertips
g. Practice twirling a baton
h. Practice changing position of spoon, knife or fork in hand
i. Practice finding specific keys from a key ring with multiple keys
j. Turning over pegs in Minnesota Rate of Manipulation Test
k. Train release of single object from hand which is holding more than one object
l. Any of the above activities without vision
m. Any of the above with increasing speed

Patient selected Activities of daily Living

The subject selects 2 activities of daily living during the initial assessments that they feel they cannot perform confidently with impaired upper limb. The level of confidence on the 10 point confidence scale of performance should be 5 or less for these tasks. These will be the target functional tasks addressed during the therapy program during the last 30 minutes of therapy daily. In any given therapy session, none, one or both of the tasks may be practiced with emphasis on advancing skill and use of the involved upper limb. The therapist and subject together will problem solve on how to perform the activities using the impaired arm and hand. The activities of daily living should not be graded by using the easiest possible compensatory method. Rather, the activities should be therapeutic for the subject as well as functional with the goal to advance skill on the task. Therapeutic, in this case, refers to facilitating greater use of the involved upper limb. The first section below is a list of possibilities for utilizing the upper extremity during the any of the ADLs. The next section lists a selected number of ADLs and describe possibilities for activity grading. This list is not intended to be exhaustive. These or other activities may be adapted by changing the position, objects, task requirements, or motor patterns of the subject.

NOTE: THE THERAPIST DOES NOT NEED TO FOLLOW THESE SUGGESTIONS AS THEY ARE MEANT ONLY AS GUIDELINES. IN ADDITION THE THERAPIST AND SUBJECT MAY SELECT OTHER FUNCTIONAL ACTIVITIES NOT LISTED, BUT WHEN DOING SO THEY SHOULD USE A SIMILARLY DESIGNED TASK-ORIENTED APPROACH.

Possibilities for utilizing the upper extremity during any ADL

1. Use of the involved UE to hold an object against the body

2. Use of the involved UE as a support for balance while performing an activity
3. Use of the involved UE as a placed gross stabilizer (stabilizes an object) while performing bimanually (hand is placed on to object with assistance of other hand)
4. Use of the involved UE as an active gross stabilizer while performing bimanually (arm/hand lifts itself to stabilize object)
5. Use of the involved UE as a refined stabilizer (using some type of pinch grasp) to stabilize a small object
6. Use of the involved UE as a gross assist (pulling up pants with both hands)
7. Use of involved UE as a refined assist during bilateral activities (buttoning pants)
8. Use of the involved UE to hold assistive device while walking
9. Use of the involved UE to carry an object while walking
10. Use of the involved UE to hold and move an object during a bilateral activity (golf swing)
11. Use of the involved upper extremity to perform isolated movement during a bimanual task (putting involved arm in sleeve and then straightening the elbow)
12. Use of the involved UE as a dominant while performing a task requiring gross or cylindrical grasp (drinking from a cup)
13. Use of the involved upper extremity as a dominant during a task requiring lateral pinch, pincer grasp, lateral pinch or tripod (writing)
14. Use of the involved upper extremity during complex bilateral task requiring individual finger movement (typing, playing piano)

Grading activities of daily living

1. Upper Extremity Dressing
    a. Button up shirt or jacket (Adapted from Trombly, 1995).
        1) To don shirt, put shirt on lap, label facing up and collar next to abdomen with shirttail draped over knees. Place affected upper extremity in corresponding sleeve first. After affected arm is fully in sleeve, grasp collar (with affected hand) at point closest to unaffected side. Hold tightly to collar, lean forward, and bring the collar and shirt around the affected side and behind the neck to the unaffected side. Put unaffected arm in the other sleeve. Lean forward, straighten shirt over shoulders, pull back down and straighten under affected axilla. Use affected upper extremity as much as possible. (Therapist may initially assist with this movement of shirt to back of neck). Use affected hand to stabilize one side of jacket while the unaffected hand places buttons in buttonholes**. OR**
        2) As above, but buttonhook is used with affected hand holding buttonhook. **OR**
        3) As above, but learn to manipulate buttons using both hands reciprocally.

2. Pullover
    a. Place affected upper extremity in corresponding sleeve first. After affected arm is fully in sleeve, place unaffected arm into corresponding sleeve with help from affected arm. Use both arms to simultaneously pull overhead. Pull down shirt using both hands.

3. Lower Body Dressing
    a. Pants

1) Sit. Move the unaffected leg beyond midline for balance (if necessary). Cross affected leg over unaffected leg. Using the affected or both hands, pull trousers onto the affected leg up to the knee. Uncross legs. Put unaffected leg in other pant leg. Pull pants over knees using both hands. Stand up while stabilizing pants with affected hand in pocket or in belt loop. Lean against stable surface and pull up pants using both hands. OR
2) As above but use affected hand to stabilize by holding cane or propping on table. Use unaffected to pull pants over hips. OR
3) As above but, if subject has difficulty with sit to stand, remain in sitting and pull pants over hips by shifting hips side to side. Use both upper extremities.

b. Shoes and Socks
1) Sit. Move the unaffected leg beyond midline for balance (if necessary). Cross affected leg over unaffected leg. Pick up sock with both hands and (using bilateral symmetrical movement) pull sock over foot. Do the same with shoes. Use adapted velcro shoes, elastic laces, or tie shoes using both hands. Do not use one handed shoe tying. OR
2) Sit. Place affected leg on stool. Pick up sock with both hands and (using bilateral symmetrical movement) pull sock over foot. Do as above with shoes. OR
3) Sit. Place affected leg on stool. Pick up sock with both hands and (using bilateral symmetrical movement) pull sock over foot. Use affected hand to hold shoehorn while donning shoes.

4. Brushing Teeth
a. Have subject hold toothbrush with unaffected hand and place toothpaste on sink or table, use affected hand to squeeze toothpaste onto toothbrush **OR**
b. As above but affected hand holding tooth paste **OR**
c. Have subject hold toothbrush with affected hand and unaffected squeezes toothpaste. Built up grip can be used. Practice brushing teeth with affected hand.

5. Blow Drying Hair
a. Have subject hold blow dryer in the affected hand with affected elbow stabilized on table (seated) OR
b. Affected hand holds blow dryer but arm is not stabilized on table OR
c. Have subject hold blow dryer in unaffected hand and affected upper extremity (with elbow stabilized on table) holds brush (seated position) OR
d. Practice the above with both extremities free in space.

6. Making the Bed
a. Make the bed using both extremities completing one corner at a time. Can use affected extremity as stabilizer, gross assist, and refined assist or as dominant.
b. Have patient strip and remake the bed utilizing both upper extremities during the task.

7. Vacuuming
a. Subject can vacuum with both upper extremities utilizing bilateral symmetrical movement **OR**
b. Vacuum with affected arm only. Can use lightweight sweeper, cordless hand held vacuum or regular lightweight vacuum.

8. Sweeping
    a. Have subject sweep with both hands with affected hand on top of broom and unaffected in middle. Use a dustpan with an extended handle. **OR**
    b. Have subject use affected hand to sweep into an extended dustpan while the unaffected hand holds the dustpan.

9. Mixing
    a. Stabilize the bowl with the affected hand and dycem under bowl. The thumb is over the lip of the bowl and the fingers on the side. **OR**
    b. As above without dycem. **OR**
    c. Holding the bowl against the body with the affected arm cradling the bowl and stabilizing it against the body **OR**
    d. Use dycem to stabilize. Place both hands on spoon one on top of the other (not clasped together). Mix using bilateral symmetrical movements. **OR**
    e. Stabilize the bowl with the unaffected arm. Mix with affected. Vary the thickness of the substance (can start out with water).

10. Cutting/Peeling
    a. Stabilize food against table or cutting board with affected hand while cutting or peeling with unaffected hand. Food should be held between thumb and index finger against web space. Start out with soft foods (tomato, cucumber) and progress to hard foods (carrot). Can also utilize dycem to assist with stabilization and work towards no dycem **OR**
    b. Hold food on cutting board with unaffected hand. Slice food with affected hand. Assess for safety (Start with banana. Can progress to harder foods.)
    c. Cut or peel with affected hand using built up grip

11. Opening Containers
    a. On the table with dycem, Stabilize the container in the affected hand between the thumb and index finger in the web space and remove the lid with the unaffected hand **OR**
    b. Same as above, without dycem **OR**
    c. Same as above, but hold in the affected hand off the table **OR**
    d. Stabilize the container in the unaffected hand and utilize the affected hand to open the caps

12. Retrieving Items from the Cupboard
    a. Have patient place the affected arm onto the counter top for weight bearing while retrieving items from the shelves with the unaffected hand.
    b. Have the patient retrieve small diameter and light objects from the cupboard with the affected hand.
    c. Have the patient retrieve larger and heavier objects from the cupboard with the affected hand.

13. Washing Dishes
    a. Hold the dishes in the affected hand while affected arm is supported on counter. Wash with unaffected one. **OR**
    b. Hold dishes in affected hand with arm in free space. Wash with unaffected hand. **OR**

c. Hold dishes in unaffected hand. Wash with affected hand. Both forearms are resting on sink. **OR**
d. Hold dishes in unaffected hand and wash them with the affected hand with both forearms off supportive surfaces.
e.

14. Ironing Clothes
    a. *Initially, can practice without turning iron on. Do not turn on iron if subject has sensory loss or is unsafe.*
    b. Place item on ironing board using both hands. Use affected arm on one of the ends to stabilize clothing while ironing with unaffected arm. **OR**
    c. As above, but ironing with affected arm

15. Folding Laundry
    a. Use table surface to hold clothes as you fold. Use affected extremity as gross assist while folding OR
    b. Fold clothes free in space. Use affected extremity as gross assist. OR
    c. Fold clothes on table top using both upper extremities together OR
    d. Fold clothes free in space with both upper extremities. OR
    e. Put clothing on hangers using table to support clothes OR
    f. Put clothing on hangers without table support

16. Putting Clothes in Drawers
    a. Patient should open and close drawers with affected hand.
    b. Place clothes in drawers with both hands holding onto clothing
    c. Place clothes in drawers utilizing only the affected hand.

17. Using the Telephone
    a. Have the subject hold the phone between thumb and index finger in the affected hand while dialing with the unaffected. **OR**
    b. Have the subject hold the phone in the unaffected hand while dialing with affected one. Can use adapted dial pad with large numbers.

18. Writing (if affected hand is the dominant one)
    a. Write large letters or play tick-tack-toe on a chalkboard using affected hand
    b. Write name on chalkboard
    c. Play tick-tack-toe using affected hand on table. Built up grip can be used
    d. Draw large loops on paper that is placed on a table. Gradually decrease size of loops.
    e. Trace shapes
    f. Print letters
    g. Write numbers
    h. Print name
    i. Write 3 letter words
    j. Sign name
    k. Write a short sentence

19. Money Management
    a. Bills

1) Have patient use the affected hand to hold dollar bills while the unaffected hand counts them out
2) Have the unaffected hand hold onto the bills while the affected hand counts them out.

b. Coins: Start with quarters and move to dimes.
1) Pick up and hold change in the affected hand not allowing the coins to fall out of the palm.
2) Hold the coins in the palm of the affected hand and feed them out one at a time utilizing the thumb and index finger.
3) Stack the coins on top of each other utilizing the affected hand.
4) Find coins in pocket using the affected hand

20. Typing
a. Type one handed with affected hand hitting the keys
b. Utilize both hands during typing tasks

21. Calculator Use
a. This may be graded by using a larger calculator and then moving to a smaller one.
b. Use affected hand to hold onto the calculator while the unaffected hand punches in the numbers
c. Use the unaffected hand to hold onto the calculator while the affected hand punches in the numbers
d. Use the affected hand to punch the numbers while the calculator is on the table.

REFERENCES

Carr, J.H. & Shephard, R.B. (1987). A motor relearning programme for stroke (2nd ed.). Rockville, MD: Aspen Systems.

Charness, A.L. (1999). Strategies to Optimize Upper Extremity Function in the Patient with Neurological Dysfunction. Course Text for Continuing Education: Rehabilitation Institute of Chicago, Chicago, IL. -

Ernhardt, R.P. (1982). Developmental hand dysfunction: Theory, assessment & treatment. Tucson: Therapy Skill Builders.

Haugen, J.B. & Mathiowetz, V. (1995). Remediating motor behaviors through contemporary approaches: The contemporary task-oriented approach. In C.A. Trombly (Ed.) Occupational Therapy for Physical Dysfunction. 4th ed. Boston: Williams & Wilkins.

Trombly, C.A. (1995). Retraining basic and instrumental activities of daily living. In C.A. Trombly (Ed.) Occupational therapy for physical dysfunction, 4th ed. Boston: Williams & Wilkins.

Voss, D.E. lonta, M.K. & Myers, B.J. (1985) Proprioceptive neuromuscular facilitation: Patterns and techniques. (3rd ed.) New York: Harper.