Protocol Title

Study Protocol & Statistical Analysis Plan

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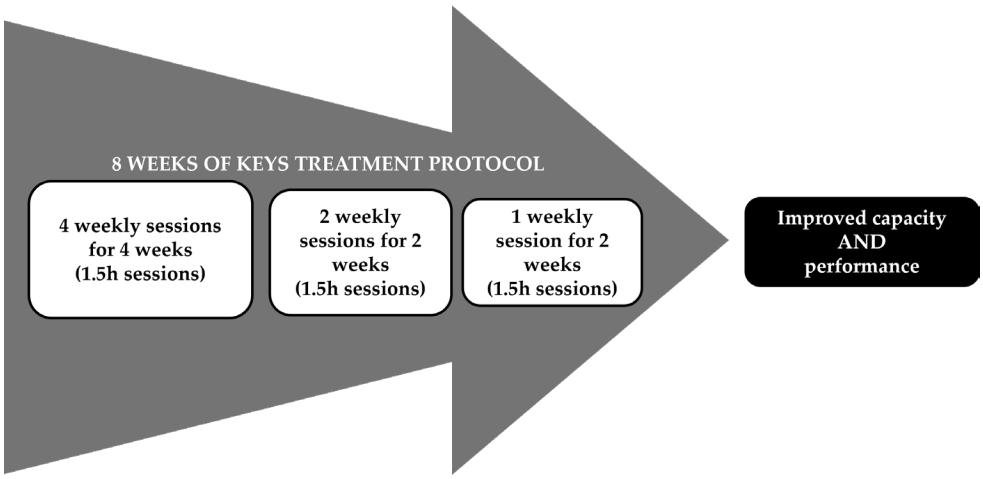
1. STUDY PLAN

Constraint-induced Movement Therapy (CIMT) is a family of techniques that has systematically applied intensive treatment daily over consecutive days, supervised motor training using a technique called shaping, behavioral strategies to improve the use of the affected limb in real life situations called a Transfer Package (TP), and the use of strategies to remind participants to use the affected extremity; including restraint of the non-affected arm. Studies have shown robust evidence on the effect of CIMT in increasing the amount and the quality of use of the paretic UE in daily situations of individuals with stroke.

Despite strong evidence and acceptance in the scientific community, clinical application of CIMT has been challenging. Barriers for its implementation in clinical settings include time needed by therapists, other resources required and lack of payment for the services. With regards to therapists' time, in the traditional CIMT protocol, therapists supervised training for 3.5 hours daily (except for weekends) for a 10 consecutive weekdays period. This level of supervision in highly unusual for traditional rehabilitation clinical settings. The treatment schedule in also incompatible with most insurance reimbursement policies in the US, and in most cases, patients pay for the treatment privately (with little or no insurance reimbursement). Such practices severely limit the number of patients who have access to CIMT. Two lines of evidence have suggested that an alternative CIMT protocol may allow for the essential (or "Key") elements to be delivered in a schedule that better utilizes therapist time and is compatible with payment policies of many US insurance companies. One line of evidence comes from findings that indicate that the original 6-hour supervised training schedule could be shortened to as little as 2-hours/daily without a reduction in outcomes. Additional evidence comes from a study exploring the systematic addition and deletion of the traditional CI therapy protocol elements indicated that when the transfer package was omitted, outcomes related to functional use were reduced by 50%. These findings were also verified by brain imaging studies conducted concurrently that revealed a much-reduced level of brain remodeling in those not receiving the transfer package. These findings highlight the potential effectiveness of the transfer package and continued functional training by the patient while away from clinical supervision. Therefore, the Keys treatment protocol was developed, providing a distributed schedule (1 to 4 times/ week over an 8-week period) instead of consecutively over a 12-day treatment period. Also, patients would be exposed to the behavioral component of the protocol, the transfer package, for an extended period (Figure 1).

Figure 1. Keys treatment protocol schedule



Project Design and Methods

- Participants: 10 participants with chronic stroke were included in the pilot trial. Individuals were included if they (1) were age 18 years or older; (2) had a stroke at least 6 months prior to enrollment; (3) were able to demonstrate minimum movement criteria of more-affected UE including 10 degrees of wrist extension (starting from a fully flexed position), 10 degrees of thumb abduction, and 10 degrees of extension of two additional fingers at all joints; (4) scored less than 2.5 on the Motor Activity Log (MAL); (5) achieved score of 24 or higher on the Mini Mental State Examination (MMSE); (6) demonstrated the ability to comprehend and answer the Motor Activity Log (MAL) questions; and (7) had not received a botulin toxin injection or adjustments in anti-spasticity drug regimens within 3 months of treatment. Sensory deficits were not an exclusion. Individuals who were not fluent in English were excluded from the study.
- Outcome Measures: *Aim 1* will be assessed using the MAL (Arm use), WMFT (Arm capacity), SIS (Quality of Life), ZDS (Depression) and COPM (Functional activity preference, ability and satisfaction). All measures will be administered immediately pre- treatment, at the end of the 4th week of the intervention (middle of treatment), and at post-treatment. The MAL, SIS, ZDS, and the COPM will also be administered at 3 months post-intervention by telephone.
- Intervention: All participants will receive the Keys intervention protocol over an 8-week intervention period. Specific CI therapy strategies will be delivered as previously described' except for the following modifications: 1) supervised training for 1.5 hours (i.e., 2 shaping tasks), gradually decreasing the number of weekly session over the course of 8

weeks with 4 days/week for the first 4 weeks, 2 days/week for weeks 5 and 6, and 1 day/week for weeks 7 and 8; 2) participants will use the restraint mitt on their less-affected UE for most of their waking hours for the 8 week period; 3) transfer package methods will be modified to accommodate the longer time period between clinic visits; and 4) participants will be asked to independently perform additional movement training for 30 minutes each day at home.

2. STATISTICAL PLAN

Demographic data including age, ethnicity or race, type of stroke, chronicity, affected side and pre-morbid handedness are reported as frequence (percentage), mean and full range. All outcome measures, as well as their units, when each one was administered, and analysis is described below.

Outcome measures	Unit	Administration time points	Reported as	Analysis
MAL AOU	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
MAL QOM	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
COPM Performance	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
COPM Satisfaction	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
WMFT - performance time (s)	Time in seconds	Pre-, during, post-treatment	Median and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
WMFT – Functional Ability Scale	Score on a scale	Pre-, during, post-treatment	Mean and full range	Difference between pre-treatment and the other data points.
SIS - Physical	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
SIS - Memory	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID

SIS - Mood	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
SIS - Communication	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
SIS - ADLs	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
SIS - Mobility	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
SIS - Hand function	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
SIS - Participation	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
SIS - Recovery	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points. Comparison with the MCID
ZDS	Score on a scale	Pre-, during, post-treatment and follow up	Mean and full range	Difference between pre-treatment and the other data points.

MAL = Motor Activity Log; AOU = amount of use; QOM: quality of movement; COPM = Canadian Occupational Performance Measure; WMFT =Wolf Motor Function Test; SIS = Stroke Impact Scale; ZDS = Zung Depression Scale; MCID = Minimal Clinically Important.

CONSENT FORM TO BE PART OF A RESEARCH STUDY

Title of Research: Application of a Reimbursable Form of Constraint Induced Movement Therapy for Upper Extremity Recovery Following Stroke: A Feasibility Study

UAB IRB Protocol #: IRB-300008977

Principal Investigator: Sarah Dos Anjos, OT, PhD

Sponsor: Center for Engagement in Disability Health and Rehabilitation Sciences (CEDHARS) pilot funding.

General Information	You are being asked to take part in a research study. This research study is voluntary, meaning you do not have to take part in it. The procedures, risks, and benefits are fully described further in the consent form.
Purpose	The purpose of the study is to investigate 1) if a distributed protocol of Constraint-Induced Movement Therapy is feasible, and 2) the effects of this protocol in the use of your more affected arm (e.g. the arm affected by the stroke).
Duration & Visits	You will be in this study for 8 weeks. Also, you will be asked to come for one screening visit, 4 assessments visits that will last approximately 3h, each.
Overview of Procedures	This study will include 22 sessions distributed in 8 weeks of exercises for your arm that was affected by the stroke, and the administration of a questionnaire. Each session will last 1.5h. You will also be asked to perform tasks at home to reinforce what has been emphasized in the laboratory. You will be asked to come for a screening visit, and if you are included, there will be 4 evaluation sessions, pre-treatment, 4 weeks after the treatment had started, after the treatment, and 3 months after the end of the treatment project. After the end of the treatments, one of the questionnaires will be administered weekly for the first months after the end of the treatment by phone with two additional questionnaires asked at the fourth week after treatment.
Risks	The most common risks include muscle fatigue and soreness from the exercises you will perform during your visits to the laboratory and at home.
Benefits	You may or may not benefit from the study. You may gain valuable information about how you move your affected arm as well as activities you can do at home using your affected arm.
Alternatives	If you do not want to take part in the study, your alternative is not to

	participate. You may stop at any time.

Purpose of the Research Study

We are asking you to take part in a pilot research study. The purpose of the pilot study is to evaluate 1) whether a structure of the Constraint-Induced Movement Therapy (CIMT) protocol is feasible, and 2) its effect on motor function and use of the arm affected by the stroke. The new therapy is named Keys Treatment. This therapy includes all of the components in CIMT but is delivered over a distributed schedule in fewer hours each day. CIMT involves repeating intensive exercises with your impaired arm (the arm more-affected after stroke) and using your impaired arm for everyday activities. In numerous studies of CIMT at UAB and in research studies around the world, it has been found that CIMT has helped improve motor function of the impaired arm of stroke patients.

Study Participation & Procedures

Before participating in the research study, you will be examined by a team member who specializes in physical rehabilitation. They will determine if you are a good fit for the study. They will ask you questions about your medical history, take vital signs, and measure your ability to move your arms. The results of the evaluations can disqualify you from participating in the research if you do not meet the minimum requirements. If your arm function or health status changes after this evaluation, you may be dismissed from participating in the study. Therefore, you are encouraged not to change how you use your impaired arm between the screening evaluation and the start of treatment. If you qualify for and agree to join this study, you will be enrolled in the study.

- You will come in for initial screening, pre-treatment testing, periodic testing, and final testing.
- Treatment will occur for up to 1.5 hours each session over 8 weeks with 4 days per week for Weeks 1,2,3, and 4; then treatment tapers to 2 days per week for Weeks 5 and 6, then 1 day per week for Weeks 7 and 8.
- On the last day of treatment, a face-to-face individual interview will be conducted. The interview will be audio recorded and transcribed verbatim afterwards. The interview questions will explore your perceptions and opinions regarding the treatment protocol you participated in.
- The research team will administer one questionnaire once a week for 4 weeks over the phone or through an online link to an electronic form.
- If you are entered and complete the entire study, you will be in the study for approximately 5 months, including training sessions, and evaluation visits.

Before the treatment period begins, your ability to move your arms will be tested and several questionnaires and motor tests will be given. Testing will take place about one week before treatment starts. The first day you participate in the study, researchers will ask you to complete testing questionnaires which measure your use of the impaired arm at home, ability to think, opinion about the treatments you have received in the past, and quality of life. You will also be asked to complete motor testing that measures the speed and quality of your arm movements. The questionnaires and motor testing will include:

- Motor Activity Log (MAL; measures how well and how much the impaired arm is used in your everyday life)
- Canadian Occupational Performance Measure (COPM; rating how well and how satisfied you are for tasks that are important to you)
- Wolf Motor Function Test (WMFT; arm motor skills)
- Participant Opinion Survey (expectations about and satisfaction with treatment)
- Stroke Impact Scale (SIS; quality of life)
- Mini-Mental State Examination (MMSE; thinking skills)
- Zung Depression Inventory (ZDS; mood)

Some of the questionnaires might be administered by telephone or mail. Some of the tests will be videotaped.

Treatment will begin on your third visit to the laboratory. Sessions will last up to 1.5 hours each day to complete the treatment procedures that will include:
- arm training (personalized to focus on your needs)
- arm training using everyday activities

A portion of each session, 15 minutes on average, will be spent going over a set of techniques that help you carry over improvements from the laboratory to the home. In addition, at the beginning of treatment, you will be evaluated for any specialized equipment, such as a built-up spoon or spill proof mug that will help maximize the potential for improved use of the arm. These aids may change as needed throughout the treatment.

The therapy will also involve wearing a safety mitt about 90% of the time during the hours of the day that you are awake. The mitt is so that you do not use your stronger arm. You will remove the mitt before going to bed, and you will put it on in the morning. You will also be able to remove the mitt to carry out necessary bathroom functions and whenever it is not safe to keep it on. While your unimpaired arm is in the mitt, you are to make every effort to use your impaired arm as much as possible.

You will be asked to do some homework when out of the treatment setting. You will be asked to:
- sign an agreement to carry out the homework and other aspects of the training
- do some homework assignments when out of the treatment setting
- keep a daily home diary, and
- talk to your therapist about problems that you face in implementing the homework during treatment, during the calls that will be conducted weekly for 4 weeks after the end of the protocol.

After you complete treatment, you will repeat the testing you did before treatment, i.e., motor testing and questionnaires. In addition, The MAL, SIS, COPM, and ZDS will also be administered at 3 months after your treatment by telephone. If you live with a family member or have a professional caregiver, they may be asked to help you to participate in this research study. If you are asked to wear a mitt at home, your family member or caregiver will be asked to be present and assist you when you practice using your impaired arm.

Risks and Discomforts

While your less-affected arm is restrained you may feel anxious and frustrated. These feelings may be stressful. However, researchers will watch you closely to make sure you do not get hurt. There is a low risk that you may be cut or bruised while performing the training tasks. The therapists working on this study have extensive experience with designing safe training tasks, and the risk is low. You may also feel tired or fatigued during training for your impaired arm or may experience pain. The therapist will monitor your activity levels and provide rest breaks as needed to prevent feelings of fatigue or pain from becoming excessive. The only small chance of serious injury may occur if loss of balance occurs when wearing the safety mitt. The mitt leaves the less-affected arm free to swing to maintain balance while walking. If you did fall, it would be available for defense. In case of emergencies or in situations where you feel at risk of falling, you can remove the safety mitt -- but only under those circumstances. Otherwise, you are to keep the padded mitt on for the agreed-upon period. You may risk being recognized from the video recordings done for this study by the individuals who will rate your motor performance. This is an unlikely event. Moreover, these individuals will be trained to respect the confidentiality of study participants. You may risk disclosure of the information collected for this study, if, for example, a hacker breaks into the computer systems where the study data are stored. This is an unlikely event because of the information collected for this study will be stored securely.

Benefits

You may not benefit directly from taking part in this study. However, this study may improve spontaneous use of your more-affected arm in the life setting, through using a safely performed motor intervention. Your participation may provide valuable information to the medical community about the treatment of stroke.

Alternatives

Your alternative is to not participate in the study.

Confidentiality and Authorization to Use and Disclose Information for Research Purposes

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The principal investigator must get your authorization (permission) to use or give out any health information that might identify you.

What protected health information may be used and/or given to others?
All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of any kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills; any other information related to or collected for use in the research study,

regardless of whether the information was collected for research or non-research (e.g., treatment) purposes; records about any study drug you received or about study devices used; and consent forms from past studies that might be in your medical record.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who may use and give out this information?
Information about your health may be used and given to others by the principal investigator and staff. They might see the research information during and after the study.

Who might get this information?
All individuals/entities listed in the informed consent document(s), including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere). Your information may also be given to the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor, or are providing support to the sponsor (e.g., contract research organization).

Information about you and your health which might identify you may be given to:

- The Office for Human Research Protections (OHRP)
- The UAB Institutional Review Board (IRB). An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- The UAB Center of Engagement in Disability health and Rehabilitation Sciences (CEDHARS)

Why will this information be used and/or given to others?
Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

What if I decide not to give permission to use and give out my health information?
By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

May I review or copy the information obtained from me or created about me?
You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your information until after the research is completed.

May I withdraw or revoke (cancel) my permission?
Yes, but this permission will not stop automatically. The use of your personal health information will continue until you cancel your permission.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others?
If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others. Including others outside of UAB, without your permission.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in it. If you decide not to be in the study, you will not lose any benefits you are otherwise owed.

You are free to withdraw from this study at any time. Your choice to leave the study will not affect your relationship with this institution. Contact the study PI, Dr. Sarah dos Anjos if you want to withdraw from the study.

You may be removed from the removed from the study without your consent if the sponsor ends the study if the study PI decides it is not in the best interest of your health, or if you are not following the study rules.

Cost of Participation

There will be no costs to you for participation in the research.

Payment for Participation

There is no compensation for participation in this study.

Payment for Research-Related Injuries

UAB has not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

New Findings

You will be told by the Dr Sarah Dos Anjos or the study staff if new information becomes available that might affect your choice to stay in the study.

Optional Research

We would like your permission to keep your private information (data containing personal information) collected in this study for future research. We would like your permission to contact you for future research. The future research may be similar to this study or may be completely different. Your private information will be stored indefinitely or until used.

Your private information will be labeled with a code that only the study staff can link back to you. Results of any future research will not be given to you or your doctor.

You can take part in this study even if you decide not to let us keep your private information for future research. You can decline participation in any future research you are contacted for.

If you give us permission now to keep your private information and, you can change your mind later and ask us to destroy it. However, once we have analyzed your private information and data, we may not be able to take it out of our future research.

We may share your private information, so that others can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your private information with other researchers, we will not be able to get it back.

Future research use of your private information will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of future research on your private information. Allowing us to do future research on your private information will not benefit you directly.

The private information used for future research may be used for commercial profit. There are no plans to provide financial compensation to you should this occur.

Initial your choice below:

___ I agree to allow my private information to be kept and used for future research

___ I do not agree to allow my private information to be kept and used for future research.

___ I agree to be contacted for participation in future research

___ I do not agree to be contacted for participation in future research

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact the study doctor. You may contact Dr. Sarah Dos Anjos at (205) 934-7323 or smanjos@uab.edu.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

_____

Signature of Participant or Legally Authorized Representative Date

_____

Signature of Person Obtaining Consent Date