COVER PAGE

PROTOCOL TITLE:

TheraBracelet: The first and only wearable to instantly improve stroke hand function

PRINCIPAL INVESTIGATOR:

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1.0 Objectives / Specific Aims

- Objectives: To determine the feasibility and safety of using this assistive device, TheraBracelet, every day during waking hours, and to determine if TheraBracelet's instant effects are sustained during prolonged use.
- Design: Community-dwelling chronic stroke survivors will be randomly assigned to either the treatment or control condition for the first month, followed by a 2-week washout period and then crossover to the other condition. In both the treatment and control conditions, participants will be instructed to wear the device for at least 8 hours/day every day during their normal daily activity and come to the laboratory for evaluation prior to and each week of using the device (for a total of 5 evaluations over 4 weeks). The device will deliver vibration (treatment) or no vibration (control). Double- blinding will be possible because the treatment vibration is imperceptible (i.e., subthreshold).
- Primary Aim: Determine the feasibility and safety of using TheraBracelet daily for a month. For feasibility, compliance in using the device will be assessed by weekly self-reports of usage. Hypothesis: TheraBracelet will have a feasibility level comparable to wearing a non-vibrating wristband. To determine safety, participants will be examined at each weekly visit for any worsening of hand sensation, dexterity, grip strength, upper limb pain, spasticity, and wrist skin irritation. Adverse events will be recorded and categorized by severity (minor, moderate, and serious) and device relevance (related to device use or not). Adverse event frequency will be compared between conditions, and with a comparable FDA-approved device, Bioness electrical muscle stimulator. Hypothesis: TheraBracelet will have a safety level equivalent to or better than the comparable FDA-approved assistive device.
- Secondary Aim: Determine the durability of TheraBracelet's instant effect over a month. TheraBracelet's instant effects will be quantified as an increase in the hand touch sensation score, dexterity score, and grip strength with vibration turned on vs. off (with 'on' and 'off' tested in a random order) in each weekly evaluation. Hypothesis: TheraBracelet's instant effects in improving hand function will persist across all weekly evaluations (i.e. desensitization to vibration will not occur during extended daily use over a one-month period). In addition, the broader impact of TheraBracelet will be assessed by comparing self-reported abilities for activities of daily living and quality of life between the treatment and control conditions.

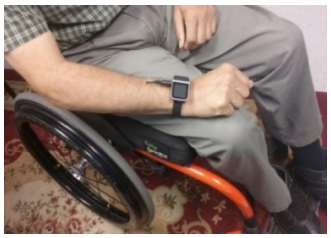
2.0 Background

Stroke is a leading cause of long-term disability in the U.S. More than two thirds of nearly 7 million stroke survivors in the U.S. have persistent hand impairment. This treatment-resistant hand impairment diminishes stroke survivors' abilities for activities of daily living including self-care, hygiene, and employment, which lowers their independence and burdens caregivers. The total cost of stroke from 2005 to 2050 is projected to be $2.2 trillion, with $13 billion annually in indirect costs associated with lost wages. Unfortunately, with the rehabilitation service reimbursement cap, most stroke survivors live with persistent hand impairment for the rest of their lives, with no therapy. Existing devices are impractical for daily home use. The proposed technology aims to fill this gap by providing an assistive device, TheraBracelet, that enhances stroke survivors' hand sensation and dexterity throughout daily living. Our preliminary studies with this vibrating

wristband have shown to instantly improve chronic stroke survivors' touch sensation as well as hand dexterity (Enders et al. 2013; Seo et al. 2014). However, additional research is needed to evaluate the feasibility and safety of TheraBracelet over longer periods of time (e.g. one month) as well as durability of its instant effect. Public health implication is that by improving stroke survivors' abilities for activities of daily living, TheraBracelet intends to increase functional independence and lessen caregiver burdens, which will contribute to increased rates of return to work and productive lifestyle for both stroke survivors and caregivers.

3.0 Intervention to be studied

Device: A stand-alone prototype is composed of an MP3-playing watch and a vibrator (see the pictures below; total weight 40g, watch=3.7cm×5.3cm). Both items are off-the-shelf products (i.e. available to purchase for anyone). The vibrator is attached to the wristband of the watch. The vibrator's wire is connected to the MP3 player via an audio jack. The MP3 player drives the vibrator with its internal battery for at least 22 hours, enabling a full day of use after an overnight charge. The MP3 player/watch is charged using a conventional phone charger. The MP3 player can play any file including the treatment vibration file with white noise vibratory signal at the intensity that is 40% below the sensory threshold (i.e. subthreshold, imperceptible to the participant) and control file with zero amplitude (i.e. no vibration).

FDA: The use of the vibrator for this proposed purpose of affecting the hand sensation and/or dexterity has not been approved by the FDA. The vibrator is a general-purpose vibrator, not specifically designed for any particular purpose. Safety of using this vibrator at the proposed intensity (40% below the person's sensory threshold, i.e. imperceptible) for a month has not been studied, and will be studied as a primary aim of the proposed research. Currently there is no vibration exposure guideline for this small level of vibration. People are exposed to higher-intensity, suprathreshold vibration daily (e.g. from a phone, riding a car).

Control/placebo: No vibration will be the control condition. The MP3 player will play a zero-amplitude file, producing no vibration.

4.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria

- Age = 18 or older
- Time since stroke>3 months
- Those with at least some movement in the affected upper limb (The Fugl-Meyer upper limb score is expected to be approximately 20 or higher)
- Able to put on the device at home
- Ability to perform the Box and Block Test with a score greater that zero

Exclusion Criteria

- Comorbidity such as peripheral neuropathy, orthopaedic conditions in the hand
- Compromised skin integrity of the hand/wrist due to long-term use of blood thinners, scars on the hand/wrist from burn or other injury
- Participation in an upper limb rehabilitation program concurrently
- Pregnancy, since swelling is common in pregnancy
- Those whose swelling changes dramatically during the day, which would require constant adjustment of the wristband tightness
- Participant has received Botulinum toxin injection in the past 3 months
- A language barrier or cognitive impairment that precludes following instructions
- Inability or unwillingness of subject or legal guardian/representative to give informed consent

- Screening: Eligibility will be determined based on the potential participant's verbal disclosure.
- Exclusion of children: Children will not be recruited since stroke is rare in children.

5.0 Number of Subjects

The enrollment goal is 24 subjects at the time of randomization. Considering potential ineligibility after enrollment, a total of 30 recruitment is proposed.

6.0 Setting

Research Laboratory

Study Sites

College of Health Professions Research Building, 77 President Street, Charleston SC

7.0 Recruitment Methods

This study will recruit from the Registry for Stroke Recovery (RESTORE-Pro#00037803, IRB approved9/6/14) which is a research tool sponsored by the National Institutes of Health (NIH) Center of Biomedical Research Excellence (COBRE) in Stroke Recovery with subjects consented for future contact to support stroke recovery research conducted at MUSC. RESTORE staff will query the registry for potential subjects and provide the Principal Investigator (PI) with the contact information of subjects who meet their criteria. The PI or research staff will contact subjects to further screen for potential enrollment.

8.0 Consent Process

Informed consent will be obtained from the participant. The consent process will take place when the potential participant comes to the laboratory on a scheduled time agreed upon between the study personnel and the participant. In a private room, the content of the consent will be verbally explained to the participant and the participant will be asked to raise any questions and concerns. If the person requests a waiting period, then one will be

given. If the person desires to consent immediately, then the person will provide consent immediately.

9.0 Study Design / Methods

- Study design: The study will use a 2×2 crossover design. Participants will be randomly assigned to either the treatment or control condition for the first month, followed by a 2-week washout period and then crossover to the other condition. For both conditions, participants will be instructed to wear TheraBracelet on the affected wrist every day for at least 8 hours/day during their daily activity over a month. The device will apply wrist vibration at 60% of the sensory threshold (imperceptible) for the treatment condition, and no vibration for the control condition. The control condition is needed to assess safety of TheraBracelet in comparison to that of simply wearing a wristband, thereby accounting for any worsening of symptoms that may occur as a natural course after stroke. Half the participants will start with the treatment and half with the control (balanced).
- Schedule: One person's participation will be 2.5 month long (= 1 month for one condition, 2 week washout period, 1 month for another condition). For each condition, participants will come to the laboratory once a week for evaluation for a total of 5 times: The 1st visit will entail the baseline evaluation followed by an introduction to using the device. Subsequent visits will be for evaluation after using the device each week. A follow-up assessment will be administered 4-16 weeks after the 10th session if any safety measure has worsened as defined as an adverse event by the 10th visit compared to the 1st visit. The follow-up assessment will evaluate only the measure that has worsened.
- Evaluation will include feasibility, safety, and durability, as detailed below.
- Feasibility: We will compare user compliance in using the device in the treatment vs. control. Compliance will be assessed using self-reports. Participants will bring home a device usage log, record time at which they put on and take off the device every day, and submit the log during the weekly evaluation. Study personnel will record which hand the participant is wearing the device (right vs left) at the beginning of the weekly evaluation session. During their final session, participants will complete a technology acceptance questionnaire to evaluate their experience using the device. Additionally, a pedometer function will be run in the watch to obtain a total number of steps for a week, which can provide a rough estimate of the wear time. Participants will also wear the device while completing a 10-meter walk test during their initial visit. Walking speed and the pedometer reading will be recorded when the test is complete.
- Safety: We will compare the rate of occurrence of adverse events in the treatment vs. control condition. The measures of adverse events will include worsening of hand sensation, hand strength, hand dexterity, upper limb pain level, spasticity, and wrist skin irritation. Specifically, hand sensation will be assessed using the Monofilament Test, the Two-Point Discrimination Test, and verbal report of any numbness and tingling. Hand sensation will be determined to have deteriorated if any of these hand sensation test results declines by a category (e.g. "normal" to "diminished light touch" for the Monofilament Test with a change more than two points; "no" to "yes" for numbness and tingling). Hand strength will be determined to have deteriorated if grip strength declines by more than 20% from the baseline (which is approximately 2 standard deviation of the population grip strength data) and more than minimal

detectable change (MDC) (also known as the smallest real difference, Chen et al 2009). Hand dexterity will be determined to have deteriorated if the Nine Hole Peg or Box and Block Test score worsens by more than 20% (approximately 2 standard deviation of the population data) and MDC (Chen et al 2009). Hand strength and dexterity measurement will be performed three times during the baseline testing. Upper limb pain will be assessed using the visual analog pain rating scale (0 to 10). Upper limb pain will be determined to have increased if the pain level indicated on the visual analog pain rating scale increases by more than 2. Spasticity will be show assessed using the Modified Ashworth Scale (MAS). Spasticity will be determined to have worsened if MAS increases by more than 1 point (equivalent to the effect size of botulinum toxin A). Wrist skin irritation and increased swelling, if there is any, will be noted. Rigorous safety criteria will be used in which adverse events will be noted if any of the measures (hand sensation, strength, dexterity, pain, spasticity, skin irritation, swelling) worsens at any of the four evaluation times compared to the baseline. The co-investigator and study neurologist, Dr. Wayne Feng, will meet with each participant in person or via teleconference to interview the participant regarding safety related to wearing the device.

- Durability: The durability of TheraBracelet's instant effect will be examined by assessing TheraBracelet's instant effect in each weekly evaluation and comparing them across. The instant effect will be quantified as increase in the hand touch sensation (Monofilament Test) dexterity scores (Nine Hole Peg and Box and Block Tests) with vibration turned on compared to off, with the 'on' and 'off' tested in a random order, blinded, within a single evaluation session. If TheraBracelet's instant effect is seen for all evaluation times, it will support durability (i.e. desensitization to vibration does not occur). In addition, the impact of TheraBracelet on stroke survivors' self-reported abilities for activities of daily living and quality of life will be assessed. Specifically, the Stroke Impact Scale, SIS (sections of the hand, activities of daily living, and recovery), and Stroke Specific Quality of Life, SS-QoL (sections of the self-care and upper extremity function), will be obtained at weekly evaluations and compared between the two conditions. The Nine Hole Peg and Box and Block Tests will be videoed to ensure the exact start and stop time are recorded. This video will not include the participant's face in order to maintain confidentiality.
- Protection against risk: For fatigue, frequent sufficient breaks will be provided to participants. As for potential skin irritation due to wearing the wristband, the wristband tightness may be adjusted with a new wristband to maximize participant comfort. Participants will be notified if we learn anything that might make them change their mind about participating in the study. Potential risks of deterioration of hand sensation, strength, and dexterity, increased upper limb pain level and spasticity level, and/or wrist skin irritation will be monitored every week during the weekly evaluation when participants come to the laboratory. In fact, these events are the outcome measures of safety for the primary aim of the study. Participants will be informed that they can drop out of the study any time without penalty.

10.0 Data Management

- Confidentiality protection: The data from test results will be de-identified once it has been collected and before it is stored. This means individual results would not be able to be linked to the participant by others who review the results of this research. The linkage between participant codes and identities as well as all other identifiable

information including consent forms will be stored in a locked room and be accessible only to the study personnel.

- Statistical analysis: For Primary Aim of feasibility and safety, we will compare rates of compliance and device-related adverse events between the treatment and control conditions using the test of non-inferiority. For safety, we will analyze the data using the "intent to treat" paradigm. The meaningful difference in adverse events to detect between the treatment and control is 20% for the following reason. For a regulatory approval, a safety level similar to a comparable FDA-approved device is desired. One such device, with availability of safety data, is a Bioness electrical stimulator for foot drop: It has a 21% higher likelihood for adverse events compared to a standard ankle foot orthosis (Kluding et al. 2013). Based on power analysis below, we will be sufficiently powered to statistically discern different rates of adverse events if more than 3 out of 24 participants experience adverse events in the treatment vs. control condition. In other words, if 3 or less participants out of 24 experience adverse events in the treatment vs. control condition, we will deem TheraBracelet safe for the purpose of an FDA approval. We will verify that there is no order effect using exact binomial tests.
- For feasibility, compliance will be defined as participants' use of the device for at least half the prescribed time. The reason is that 4 hours/day is still a substantial use of this assistive device in daily living, and will provide sufficiently useful information about feasibility of TheraBracelet. Similarly with the analysis for safety, if 3 or less participants out of 24 are incompliant in the treatment vs. control, we will conclude that TheraBracelet is as feasible as wearing a non-vibrating wristband. The cumulative hours of device usage will also be examined for both conditions to inform the general usage trend.
- For the secondary outcome of durability of TheraBracelet's instant effect, the hypothesis will be tested using repeated measures ANOVA for each hand function measure, with factors of vibration (on/off), condition (treatment/control), evaluation time (1-5), and their interactions. A significant main effect of vibration, with improved hand function with vibration on vs. off, with non-significant interactions of vibration×evaluation time and vibration×condition, would indicate durability over a month. In contrast, a lesser extent or abolishment of the instant effect toward the later evaluations or for the treatment condition, with significant interactions of vibration×evaluation time or vibration×condition, would indicate desensitization. In that case, the time point at which the instant effect wanes will be examined using Tukey type posthoc pairwise comparisons.
- A possibility exists that instant enhancement of hand function with TheraBracelet may trigger more use of the affected hand in daily living, which, when accumulated over time, might lead to improvement of the innate hand function (without vibration). This is analogous to cane users who may walk more with canes than without, and thus build greater lower limb abilities over time. Thus, change in the innate hand function will be examined. A significant effect of condition×evaluation time, with greater improvement of the innate hand function for the treatment vs. control, will suggest a therapeutic effect of TheraBracelet for secondary investigation.
- Impact of TheraBracelet on activities of daily living and quality of life will be assessed using repeated measures ANOVA for the SIS and SS-QoL, with the main effect of condition.

- Power analysis: The sample size for the primary outcome of safety was determined for testing hypothesis of non-inferiority using a 2×2 crossover at 80% power and 5% significance level. A sample size of 24 (12 in each condition at randomization) provides sufficient power to conclude non-inferiority within a difference in adverse events of 20% between the discordant pairs (those who are safe with control but unsafe with treatment vs. those with the opposite), assuming a total of 10% discordance rate (proportion of participants with different responses for the two conditions) and a 90% safe rate for the control. That is, we will be powered to statistically conclude non-inferiority (hence safety) if 3 or less out of 24 participants have adverse events in treatment vs. control. For the Secondary Aim involving repeated measures ANOVA, with the effect size of f=0.25 for the Box and Block from our previous study,(Seo et al., 2014) a sample size of 19 is needed assuming a conservative correlation of 0.3 across evaluation times, for 80% power and 5% significance level. Thus, we will aim to obtain data from 24 participants. Considering that some may be found ineligible after enrollment, a total of 30 recruitment is proposed.
- Data sharing: Only de-identified coded data will be reported and/or shared with the public in publications, in ClinicalTrials.gov, or upon written request.

11.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

- Data and Safety Monitoring Board (DSMB): The primary purpose of the DSMB is to ensure the safety of participants and the validity and integrity of data collected during the study. By having the DSMB, safety concerns will be addressed objectively, in a timely manner. If the intervention definitively has safety concerns, the DSMB may recommend stopping the study early.
- The DSMB will be composed of (1) a board certified physician with expertise in stroke management, (2) a registered and licensed occupational therapist with expertise in stroke rehabilitation, and (3) a biostatistician with expertise in design and analysis of clinical trials.
- The responsibilities of the DSMB are as follows. Prior to any enrollment, the DSMB will review the study design, protocol, recruitment/enrollment plan, statistical analysis plan, and data safety monitoring plan, and document the agreement or recommendation. Once the enrollment begins, the DSMB will convene every 3 months to review the safety data (i.e. worsening of hand sensation, hand strength, hand dexterity, upper limb pain level, upper extremity spasticity, and wrist skin irritation, and any other adverse events regardless of whether it is related to the device use or not) as well as the enrollment data including any discontinuation of participation in the study with or without adverse events, new enrollments, and progression of the enrollees' participation in the study. The DSMB will review the aggregated summary data as well as the individual participants' data (de-identified). The DSMB will provide recommendations for any adverse events and safety concerns. The DSMB will also provide a report to the IRB to summarize oversight activities, recommendations, and any concerns regarding participant safety.
- The DSMB will have access to coded (de-identified) data but not identifiable data. While the experimenters and participants are double-blinded to the condition assignment information during the study progression, the DSMB will have access to the condition assignment information during the study progression in order to assess

the safety of the TheraBracelet vibration in comparison to that of simply wearing a wristband (i.e. control) and separately assess other safety issues such as assessments.

- Reporting of safety data: All safety data including adverse events will be reported to the DSMB, IRB, and relevant funding agencies. Summative safety data will be reported in ClinicalTrials.gov and in publications. Following the guidelines, we will register this study in ClinicalTrials.gov as soon as the study commences (at the latest within 21 days after the first participant is enrolled) and report results including all adverse events as soon as the study is completed (at the latest within12 months of the trial's primary completion date). To protect participants' confidentiality, personally identifiable information will not be used for reporting. Only de-identified or aggregated data will be used for reporting.
- Endpoint: Participants will be assured of their right to discontinue their participation in the study at any time. In addition, the study physician, Dr. Feng, may recommend discontinuation of participation if his/her adverse event is deemed to warrant discontinuation, without breaking the double-blinding. However, the condition assignment information will be available to the DSMB to make appropriate judgment during the study progression.

12.0 Risks to Subjects

There is a slight risk for loss of confidentiality. There is a minor risk of physical and mental fatigue from engaging in the study activity. The treatment a person receives at one time point may be less beneficial than the other study treatment. There is a minor risk of skin irritation from wearing the wristband and/or from vibration. There is a minor risk of discomfort in moving the arm/hand due to the weight of the device on the wrist, although the device weighs only 40g. Potential risks that may be associated with use of wrist vibration all day every day for a month will be tested as the primary outcome measures of safety within the study. These risks are: deterioration of hand sensation, strength, and dexterity, increased upper limb pain level, spasticity level, and/or wrist skin irritation. Occurrence of these adverse events are expected to be rare because the intensity of vibration used in TheraBracelet is subliminal while we are exposed to higher-intensity, suprathreshold vibration daily (e.g. from a phone). TheraBracelet has also been used during hand task practices in chronic stroke survivors for a total of 6 hours over 2 weeks without reportable adverse events in the PI's current study. However, there has not been a study that focuses on safety of TheraBracelet. Currently there is no known information regarding any side effects associated with using this small imperceptible (unfelt) level of vibration all day every day for a month. Currently there is no vibration exposure guideline for this small level of vibration.

13.0 Potential Benefits to Subjects or Others

There may be no benefit from participating in this study. The potential benefit is that the vibration the person receives may help their hand function in daily living, although this cannot be guaranteed. The vibration the person receives may increase their innate hand function (without vibration) over time (assessed as secondary investigation under Secondary Aim), although this cannot be guaranteed. The knowledge regarding the potential of using unperceivable vibration as a daily assistive or therapeutic option is important to increase quality of life of people who had a stroke and may benefit stroke survivors in general. The risks are deemed reasonable in relation to the potential gain of knowledge regarding this technology's feasibility, safety, and efficacy in potentially enhancing hand function and quality of life.

14.0 Sharing of Data

The RESTORE registry (Pro#00037803), from which this study may recruit subjects, also serves as a data analysis tool by which interdisciplinary teams may share data across projects and provide MUSC's stroke recovery research community with a more complete registry with key stroke elements. Some subjects may have participated or will participate in other stroke related research studies at MUSC. Sharing data from this and other stroke research studies with RESTORE will allow for more targeted recruitment efforts in the future and could reduce the burden placed on subjects by reducing the duplicative efforts of collecting common data and physical function assessments requested by multiple studies and storing them in one centralized and secure location.

Subjects are informed in the consent process if they enroll into the RESTORE registry, their data from this study will be shared. Those who have participated in other stroke research will be asked to sign a Release of Study Records form to share data with RESTORE if they did not already authorize release. Subjects will be asked to sign a HIPAA authorization stating their health information may be disclosed to MUSC investigators requiring their data for their research projects upon approval by an Institutional Review Board.

15.0 Devices

The vibrators and watches will be stored in the laboratory and will be provided to the participants by the study personnel. The participants will use the device at home by themselves, and return the device to the study personnel when the 1-month period is completed. The device does not have an IDE.

References

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