MIRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

General Study Information

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Study Title:
Pilot Study to Establish Use of a Lower Extremity Sleeve and Sequential Compression Pump Device in Patients with Upper Extremity weakness or impaired sensation post Stroke

Protocol version number and date:
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Research Question and Aims

Hypothesis:
We hypothesize that a leg sleeve and Sequential Compression Device (SCD) can be used on the upper extremity (UE), specifically in patients with upper extremity weakness or decreased sensation as a result of cerebral vascular accident (CVA).

Aim 1:
To establish that an SCD and lower extremity (LE) sleeve can be used on a weak or reduced sensation upper extremity post stroke.

Aim 2:
Utilize an existing device – the Kendall SCD™ 700 Series Compression Therapy Pump and leg sleeve system – in a novel way, to establish new practice standards or protocols.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc.*):
The SCD system provides intermittent, pneumatic compression, which facilitates venous return when normal muscle activity is deficient secondary to prolonged immobilization[1]. SCD therapy mimics some aspects of muscle activity that occurs during ambulation, pushing blood proximally to prevent venous stasis and protecting venous valves against venous hypertension [2].

The SCD system also provides sensory stimulation to the limbs. We propose exploring the use of SCDs further for neuro-recruitment and recovery in the hospital as early as but not limited to 24-48 hours post CVA. Tactile stimulation via the SCD system may engage ascending pathways, which terminate in the sensory cortex and are responsible for carrying sensory modalities such as crude touch, pressure, pain and temperature. Activation of the sensory cortex has positive crossover effects on the motor cortex, improving the potential primary outcome of stroke recovery by cortical reorganization[7]. The effects of vibratory stimulation on the sensory cortex have published outcomes [11].

There are two studies from Europe that support the use of SCD's on the UE for the reasons we are suggesting in Aim 3. According to Cambier et al., use of SCDs resulted in improved results for sensory and motor return post stroke[7]. The researchers found that the use of intermittent pneumatic compression in the hemiparetic upper limb post-stroke resulted in improved somatosensation including tactile sensitivity, kinesthetic sensation, and stereognosis. The SCD was placed on subjects 30 minutes a day for a total of 20 treatments over a 4-week time period [11]. This study trialed use of compression devices on subjects' post stroke two to five weeks after stroke occurrence [11]. We are proposing using the SCD on subjects diagnosed with stroke as early as but not limited to 24–48-hour post-injury time frame for a 4-hour period. This is much earlier than prior studies that apply the modality at the two-week post-stroke mark using only 30-minute trials. In the future, if proven safe, this modality may be used to improve sensory-motor function in the weak UE and in subjects with inattention or neglect impairments with hopes to increase awareness of the weakened side of the body post stroke upon admission to the hospital.

Feys et al. performed a single-blind randomized controlled multicenter trial over a period of 6 weeks where 100 subjects either received (experimental group) or did not receive (control group) sensorimotor stim via SCD type device in conjunction with their normal physiotherapy. The sensory stimulation from the SCD was used on subjects for 30 minutes 5 times a week for 6 weeks to test motor recovery improvement post stroke. It was found that the subjects' UE motor function and recovery improved significantly by using additional sensorimotor stimulation supplied by an SCD device in conjunction with conventional methods for stroke rehabilitation in the acute phase [18]. The SCD treatment was most effective on subjects with severe motor deficits, hemianopia and with hemi-attention [18]. The Feys et al study also supports the research on application of an SCD system to the UE in order to establish use for future studies.

Another frequently used modality for neural recovery is electrical stimulation (E-stim)[12]. E-stim provides repetitive stimulation to the nervous system in efforts to facilitate cortical reorganization and functional gains. It is often used in conjunction with conventional therapies and when used together, has shown improved sensory and motor function in patients with subacute, unilateral, ischemic strokes [13]. Yet, e-stim can be painful and is contraindicated for use in patients with sensory impairments as commonly seen in the acute phase of stroke. We suspect application of sensory stimulation via SCD system can provide similar repetitive sensory stimulation early-on, in a more tolerable fashion and independent of sensory deficits.

SCD systems are commonly used in the acute care or hospital setting to aid in the prevention of Venous Thromboembolism (VTE). They are routinely prescribed for use on LEs due to immobility and applied and monitored by nursing staff. Patients in the hospital are at higher risk for VTE secondary to immobility, active disease processes and co-morbidities [3]. Patients with an immobile weakened UE post CVA have similar risks. Mortality from UE DVT may be as high as 48% and mortality related to PE up to about 25%, contributing to approximately 10-35% of hospital deaths [2]. Mortality rates secondary to lower extremity DVT are overall lower, ranging from 13-21% [2].

A study done by Rokosh et al., reports in 2018 a 1.8% incidence of UE DVT in acute inpatients. Thirty five out of 83 patients were detected in a 7-month time frame. Persons with medical comorbidities such as coronary artery disease (CAD) and congestive heart failure (CHF) were more likely to have UE DVT vs LE DVT [4]. Part of the explanation for this was possibly that SCD's are used on the LE's as part of the prevention protocol for DVT and this study suggests that there is reason to research developing and adopting LE management strategies for the UE [4]. There was also a higher incidence of concomitant malignancy with the patients with UE DVT. Twenty six of the 35 UE's were provoked VTE (77.1%) secondary to recent surgery and/or indwelling catheterization in patients with prolonged immobilization. Neurosurgical procedures were one of two most associated with postoperative VTE [4]. It was found that 96 of the patients with DVT had the following characteristics: atrial fibrillation 17.7%, hypertension 61.5%, hyperlipidemia 38.5%, and specifically neurologic malignancy 50%, neurosurgery 26.5%, prolonged immobilization 32.4%, and central venous catheters 35.1% [4]. These characteristics are directly relevant to the population we are studying and strongly supports the use of the SCD on an immobile and weakened UE to help prevent DVT. Same admission mortality for patients with VTE was 13.5% [4]. Patients with UE DVT had significantly higher all-cause mortality (28.5%) than patients with LE DVT (4.9%) which also correlates with the finding that patients with UE DVT were found to have more comorbidities [4]. This study did not suggest that UE DVT itself was a direct cause of higher mortality rather it suggested there may be an overall increased thrombotic risk or a more severe global inflammatory state in these patients [4]. The statistics from two studies support the use of SCDs on the immobile UE to help prevent VTE and mortality from DVT in the UE [2,4].

SCDs have been used since the 1970s for VTE prevention and are the leading choice for DVT and PE prevention [5]. As compared to compression stockings and pharmacological methods, SCDs are as effective, without causing discomfort and complications of bleeding often seen in alternative means of prophylaxis [2]. The risk of developing a DVT or PE is as high as 15% in the first few weeks post stroke due to stagnant blood. Nerves surrounding blood vessels in the hemiparetic limb do not work well which can cause a negative impact on blood flow causing increased risk for blood clots and a pro-inflammatory hypercoagulable state of blood [3]. Studies have shown, use of SCDs in lower extremities day 0-3 post stroke, along with patient mobility, have been effective in reducing the risk for DVT and possibly improving survival rates amongst this population [2,6].

By using SCDs on the immobile UE there is a potential to further reduce this risk, once proving the ability to use on the UE.

There is a paucity of research on the safety of using the SCD system on the immobile UE, as compared to the lower extremity. We have found one study, performed by Mayo Clinic, on the effectiveness of SCDs and prevention of blood clots in the upper extremity with placement of a central line catheter which found it to be unsafe. Thus, it is contraindicated to use an SCD system on an extremity in which a central line catheter is placed [7]. Further research is needed on the use of SCD's on UEs without central lines.

SCD utility may go beyond the hemodynamic benefit. Our initial thought and long-term objective are to use SCD's to assist with post-CVA recovery particularly with patients with inattention. The first principle of neuroplasticity states, failure to drive specific brain functions can lead to functional degradation [8]. Therefore, neural circuits not actively engaged in task performance for an extended period degrade. Bernhardt et al. suggests the greatest opportunity for structural change is early on post stroke [9]. Given the importance of timing and repetition to neuroplasticity, the SCD could be a source of repetitive stimulation in the acute post CVA population.

CVA patients who are alone in their rooms most of the time do not have the social support to assist with their recovery. This modality would serve as a sensory feedback or alert system for improved awareness of the neglected limb/side of the body. It could potentially be a safe intervention for nurses to easily apply and take off that they are familiar with using and understand well. Spatial neglect has been estimated conservatively to be present in at least 30% of the CVA survivors in the US [10]. It is estimated that there is a total annual incidence of 239,000 people with neglect in the acute phase post CVA and 10% of these will experience symptoms in the chronic phase [10]. The direct and indirect cost in the USA post-CVA as of 2009, according to the American Heart Association, is about 68.9 billion dollars and is associated with longer than average length of hospital stays, increased family burden, higher requirements for assistance and skilled nursing placement[10]. The use of SCD's as a new intervention to shorten recovery time of this complex patient population could be very beneficial for preserving precious economic resources.

Mayo Clinic Jacksonville (MCJ) admits approximately 10 patients per week with a diagnosis of stroke. Current practice aims to perform skilled physical and/or occupational therapy evaluations within 24 hours of a physician order being placed. This allows us to capture this critical time frame and intervene early.

Currently patients are encouraged to wear and use the SCDs on the LE for at least 18 hours a day, or as much as possible, whether in bed or chair, unless care or patient activities (i.e. bathing, walking) require their removal [9]. To test the use of a LE sleeve and SCD system for use on the UE, we will assess patient tolerance for approximately 4 hours in a single day. For this study, such repetitive cortical stimulation of the brain using an SCD could supplement reduced stimulation that occurs secondary to immobility and inattention.

Covidien is the manufacturer of the Kendall SCD™ 700 Sequential Compression System, currently utilized at MCJ. They do not manufacture sleeves for the UE, just LE sleeves. This system is preset to provide compression that lasts approximately eleven seconds per cycle, starting distally and ending proximally, in wave-like fashion. The amount of peak pressure is approximately 45 mmHg for the calf [1].

Current use of compression therapy in the UE is most recognized for lymphedema management. The sleeves used for such treatment(s) are generally large, covering the entire arm and upper chest of the involved side. Pressures of 40-50 mmHg, and in some cases up to 60 mmHg, are provided. Such devices and pressures have been proven to be well tolerated [14]. As previously noted, our current SCD systems apply less than 50 mmHg, supporting our hypothesis that a leg sleeve and sequential compression device (SCD) can be used on the UE.

Additionally, blood pressure cuffs are used interchangeably between UEs and LEs. When applied to the arm or calf following standard safety protocols, including proper sizing/fit, studies support the safety and effectiveness of multi-site use [14].

Our vision of creating an enriched environment for the patient in the acute hospital setting post-stroke requires an inexpensive and non-labor-intensive intervention to progress the recovery of this patient population sooner. An SCD can be used over the course of their acute hospital stay, potentially providing improved functional outcomes for sensory-motor recovery, increased hemi-body awareness, and prevention of blood clots and edema in the UE. Several studies have demonstrated that an enriched environment with a well-coordinated multidisciplinary team providing specific interventions specialized for CVA populations result in neural plasticity that improves their performance and positively impacts disability levels after CVA [13]. These CVA Rehabilitation programs, known as "stroke unit care," should include meaningful, repetitive, intensive, and task-specific movement training in an enriched environment to promote functional recovery [13]. The use of SCD's could be a new intervention available to all post CVA patients that would provide gentle repetitive stimulation and would promote the enriched environment we hope to continue to create in the acute hospital setting [11].

Research and reliable evidence on SCD use in the UE in the hospital setting is scarce. However, SCD use in the LEs over the past 45-50 years has been well tolerated with little to no adverse effects [5]. Once use of a sleeve and SCD is determined, studies investigating the potential benefits can follow. This can possibly lead to new post CVA rehabilitation protocols and allow for further development of enriched environments for hospital patients in acute care.

Study Design and Methods

Methods:

Study Design or Overview:

This will be a pilot study with an enrollment goal of 20 patients post stroke with a weak or sensory impaired UE. Mayo Clinic Florida received approximately 39 patients with stroke diagnosis per month according to records taken from January through October of 2019. Patients will be evaluated as routine standard part of care where standard chart review will be done and then patients will be screened for study inclusion for appropriateness for

participation in this study using the Brief Interview of Mental Status (BIMS) with scores > or = to 13 indicating intact cognition. If the patient does not score > or = to a 13 they will not be included in this study. If patient consent is obtained the patient will be enrolled in this study. Baseline data will be collected including pain, edema, nail bed color, sensation, skin integrity, grip strength and movement of the hemiparetic UE and photo taken prior to application of the sleeve and upon completion of 2nd check. The NIH score will be recorded as well at baseline. The patient's arm will be checked approximately every 2 hours following, for a total of approximately four hours recording pain, edema, nail bed color, sensation, skin integrity, movement, and patient tolerance during every check. Adverse effects attributable to sleeve usage will warrant removal of the SCD sleeve. These include, but are not limited to, compromised skin integrity, pain, patient intolerance, and increased edema or cyanosis. Subjects to which the SCD sleeve is removed will no longer be included in the study.

Application of LE SCD Sleeve:
Calf size LE SCD sleeve will be placed on the weak or sensory impaired UE below the cubital fossa and may include the hand if necessary. The patient's arm will be placed on a pillow providing support to the shoulder and arm keeping elbow extended. The sleeve will be applied with the standard approach/application to the calf when applied with adequate 2 finger spacing between the SCD sleeve and skin of the UE [2]. Patients will otherwise be allowed to move their arm as able freely while wearing the SCD sleeve.

Step -by –Step Schedule:

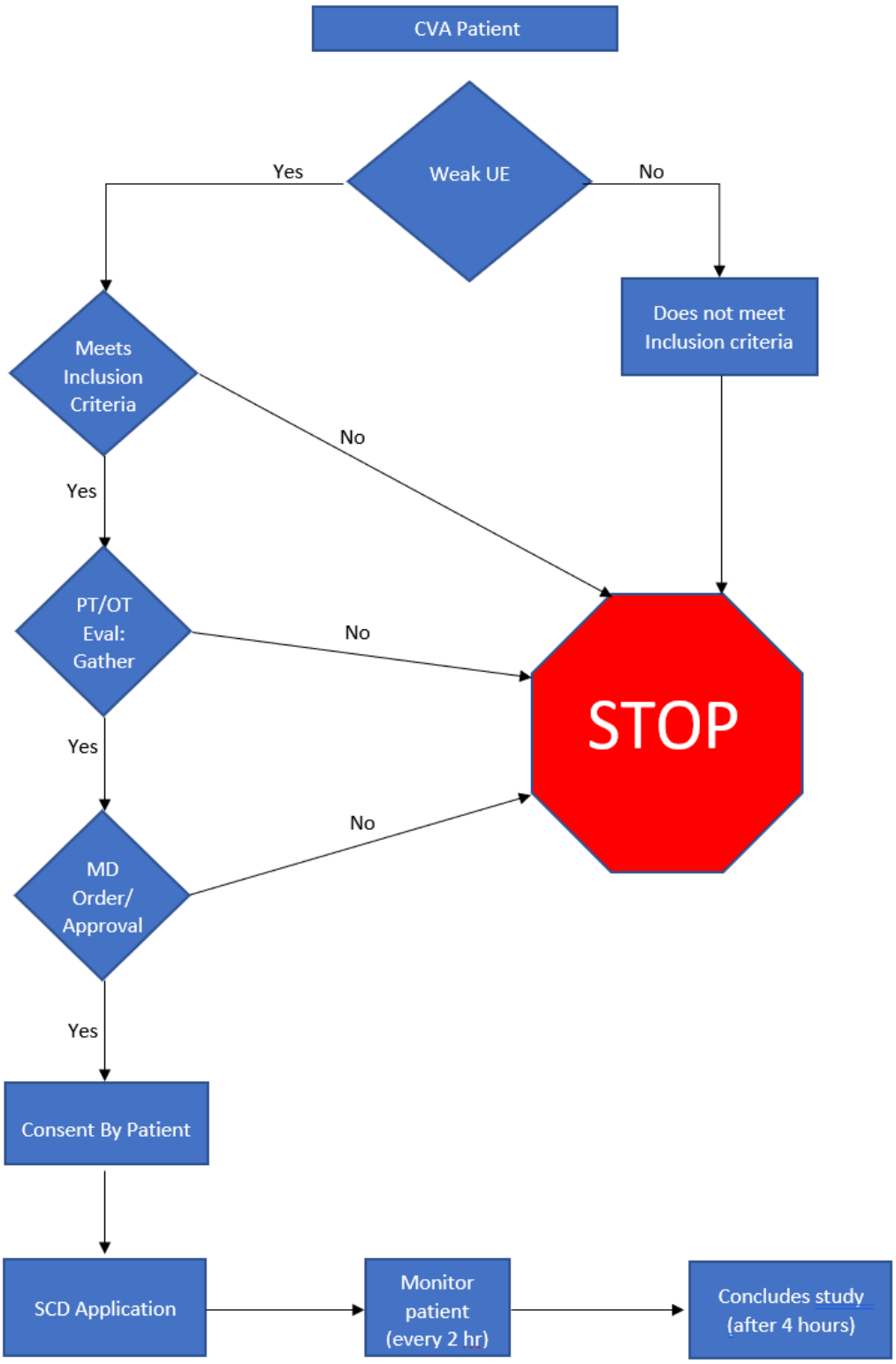
1. Order for PT or OT services received, OT and PT evaluations will be completed
2. PT/OT will screen during OT/PT evaluation process and perform standard protocol chart review for potential patient inclusion into this study and order will be obtained for inclusion by MD
3. MD will place an order in the chart for the SCD and sleeve to be placed on the affected UE
4. Reason for SCD study and risks will be explained; and once all questions by patient are answered satisfactorily, informed consent will be signed by patient
5. Baseline skin and neurovascular assessment performed and documented by PT or OT prior to placement of SCD sleeve on patient (Picture of UE taken pre application and attached to chart):
    a. Patient tolerance of wearing sleeve
    b. Pain
    c. Edema
    d. Nail bed color
    e. Skin integrity
    f. Sensation
    g. NIH Motor Arm subsection #5 score
    h. BIMS score
    i. NIH stroke scale score
    j. Grip strength measure hand dynamometer
6. Measure circumference of affected forearm using tape measure to determine size of SCD sleeve
7. Placement of SCD sleeve on affected UE below cubital fossa, document patient initial tolerance and start time (T_i).
8. Subsequent UE checks to occur as follows, for a total of approximately four hours wearing time*:

    - 1st check – approximately 2 hours (h)after initial application (i.e. T_1).
        1. Take sleeve off patient, assess arm, obtain data (a.-g.), and document findings.

- 2nd check - approximately 2 hours (h) later (i.e. $T_1 + 2h = T_2$).
    1. Take sleeve off patient, assess arm, obtain data (a.-g.) and document findings (take post picture of UE and attach to chart).

* Any adverse effects, including patient tolerance, attributable to sleeve usage will warrant removal of SCD sleeve

Time (T)	T_i Baseline	T_1 1st check	T_2 2nd check
Patient tolerance "Are you tolerating this sleeve (Y/N)?"			
Pain (VAS)			
Edema (Girth)			
Nail bed color			
Skin integrity (Intact/Impaired)			
Sensation (Intact/Impaired)			
Motor Arm subsection of NIH			
Hand Dynamometer			
BIMS score			
NIH stroke scale score			


CVA Patient
Weak UE
Yes
No
Does not meet Inclusion criteria
Meets Inclusion Criteria
No
Yes
PT/OT Eval: Gather
No
STOP
Yes
MD Order/ Approval
No
Yes
Consent By Patient
SCD Application
Monitor patient (every 2 hr)
Concludes study (after 4 hours)

Subject Remuneration:
Subjects will not be provided a monetary incentive.

Sample Size:
The sample size of this pilot study will be 20 subjects. The average number of subjects when testing the use or effectiveness of a device is commonly between 10-40 subjects. This study is within the average range for this type of study.

Data Collection May Include:

1. Age
2. Gender
3. Race
4. Diagnosis
  a. type of stroke
  b. location of stroke
5. Vitals (reviewed and considered for inclusion criteria, not included in data collection chart)
6. Medical History (including a family history of thrombosis, coagulopathy, blood clots, or clotting disorders) (reviewed and considered for inclusion criteria, not included in data collection chart)
7. Affected UE pain using Visual Analog Scale (VAS) 1-10 Pain Scale
8. Affected UE nail bed color (normal, cold, dusky or bluish)
9. Affected UE strength using Motor Arm Subscale # 5 of the NIH stroke scale
10. Affected UE sensation using cotton swab and dermatome points (C2-T2) documenting Intact or Impaired
11. Affected UE edema using arm circumference measurement proximal to wrist crease and 5 inches distal to cubital fossa and for size of sleeve needed using tape measure in inches as follows:

Medium	<21 inches
Large	<26 inches

12. Affected UE skin integrity documenting Intact or Impaired (describing redness, rash or bruising and area of arm if present)
13. BIMS score
14. Most recent NIH stroke scale score documented in chart prior to application of sleeve
15. Grip strength measured via hand grip dynamometer.

Data Handling:
Data will be entered into Redcap data collection system.

Feasibility and Time Frame:
From January through October 2019 Mayo Clinic Florida averaged 39 patients with a stroke diagnosis per month with varying degrees of immobility in their affected UE. Due to the high number of stroke patients with UE weakness, decreased sensation and/or immobility, we feel this study has good general feasibility at attaining enrollment in a reasonable timeframe. We anticipate completing this study in 1-3 months, enrolling 4-5 eligible persons to be studied per week for a total of 20 subjects acquired in a 1–3-month time frame. Feasibility is good for this project.

Strengths:
This is a pilot study. Study investigators have direct, inpatient access at Mayo Clinic Florida. The therapy department has adequate staffing levels to meet the demands of patient care for this study. A PubMed search found only a few published studies to date, demonstrating both safety and positive outcomes associated with using SCDs on hemiparetic UEs[11]. Our study will examine further the benefit and use for a potentially more generalized usage. SCDs have been safely used for over 40 years on the LE's with very good outcomes regarding prevention of DVT in all patient populations and all age groups[5]. SCDs are safely used on patients with lymphedema on their UEs with good outcomes. Our study will only include cognitively intact patients as evidenced by BIMS score who will be able to sufficiently communicate tolerance of wearing an SCD. There will be no costs involved for this study.

Limitations:
Mayo Clinic currently utilizes the Kendall SCD™ 700 Series Compression Therapy Pump and leg sleeve which is not intended for UE use. Further, this system does not have an adjustable pressure setting, as this is set by the manufacturer. The Kendall SCD™ 700 Series is pre-set at a pressure of 45 mmHg[1]. We believe this inability to adjust the pressure should not pose a problem. Extrapolating other SCD devices meant for the UE, 35-45 mmHg is a routine pressure for sustained pressure during UE lymphedema treatment and the Kendall SCD 700 series is pre-set at this level[1,15]. Pressures up to 50 mmHg have been found safe for sustained usage [15]. This pressure is well tolerated when comparable devices were used on the UE. Similarly we feel the calf sleeve size is not necessarily a problem if the device is donned properly with adequate standard application (should be able to place 2 fingers between the SCD sleeve and the patient's arm[2]) and is monitored regularly. Further blood pressure cuffs are used for both UE and LE interchangeably with no adverse effect [16].

Subject Information

Target accrual:
Target sample size is 20 subjects.

Subject population (children, adults, groups):
Study population is adults, ages 18-100 years of age. Population to be studied includes patients admitted to MCJ, post-stroke with a hemiparetic upper extremity.

Inclusion Criteria:
Adults post stroke admitted to MCJ, with a weak upper extremity, or diminished sensation, which provide consent of participation by self-agreement. Patients with a weak or sensory impaired UE will be determined using the NIH Motor Arm subsection from the NIH scale and score a 1-4, dynamometry for hand grip strength or sensation deficits using the AISA C2-T2 standard points. Patients who have received thrombolytic therapeutic medicine > 13 hours (per site specific policy) will not be excluded from inclusion in this study. Patients who score > or = to 13 on the BIMS to ensure intact cognition.

Exclusion Criteria:

Inability to provide consent of participation; subjects with aphasia or the inability to effectively communicate their pain consistently or with questionable cognitive reliability scoring <13 on the BIMS (will be excluded), has an existing invasive line (PICC line, central venous catheter, AV fistula or AV graft); recent surgery or vein ligation in the involved extremity; recent skin graft in the involved extremity; confirmed DVT in the affected, upper extremity including axillary or subclavian veins; open or active wounds or infection in the involved extremity; upper extremity ischemia, gangrene, cellulitis or severe arteriosclerosis in the affected upper extremity; status-post axillary lymph node dissection on the involved side; congestive heart failure (CHF) acute exacerbation; acute edema of unknown etiology in the involved upper extremity; subjects with extreme deformity of the affected upper extremity; subjects with an acute kidney injury; subjects who are hemodynamically unstable[1,7,17]; subjects under age 18 and over age 100; and patients who have received thrombolytic therapeutic medicine administered <13 hours (per site specific policy) prior to application of SCD sleeve. Women confirmed pregnant at the time of admission will be excluded.

Biospecimens

Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8-week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☐ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

Data Analysis

Power Statement:
The primary aim is use and tolerability which in twenty subjects should be adequately powered to eighty percent.

Data Analysis Plan:
The data will be largely descriptive around the aims in terms of age, gender, type of stroke, NIH stroke scale severity, weak upper extremity and other laboratory data from the electronic medical record retrospectively.

Endpoints:
Primary:
To establish that a leg sleeve and SCD can be used on a weak or sensory impaired UE post stroke and is tolerable to the patient 100% of the time.

Secondary:

Exploratory, to facilitate neuro-recruitment and recovery, which may improve sensory/motor function and attention to involved hemi-body and environment, as well as the prevention of blood clots and edema.

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