~~**Version Date: March 4, 2021**~~	**Page: 1 of 13**
Subject Name:	**Informed Consent Date:**
Principal Investigators: Dr. Jill M. Wecht, EdD	**VAMC: James J Peters**
Protocol #: WEC-16-050 **Title of Study: Treatment of Post-SCI Hypotension: A Randomized Controlled Study of Usual Care versus Anti-hypotension Therapy**	

INTRODUCTION

You are being asked to participate in a research study that is supported by the James J. Peters Veterans Affairs Medical Center (JJPVAMC). This research study is being performed at the Icahn School of Medicine at Mount Sinai, an affiliate of the JJPVAMC. Before you decide to take part in this study, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive.

Please read the information below closely, and discuss it with your family and friends if you wish. You can also ask one of the study staff members if there is anything that is not clear to you or if you would like more details. Please take your time to decide if you want to participate. If you do decide to take part in this study, your signature on this consent form will show that you received all of the information below, and that you were able to discuss any questions and concerns you had with a member of the study team.

1. Purpose of study and how long it will last:

You are being asked to participate in the study because you have a traumatic spinal cord injury (SCI) and are between the ages of 18 and 89 years of age. The purpose of this research study is to compare usual care treatment of symptomatic hypotension (dizziness, lightheadedness, nausea, blurry vision, passing-out, etc.) to treatment initiated based on low blood pressure (BP) readings (BP<110 mmHg for males and <100 mmHg for females), regardless of symptoms, during acute rehabilitation following your SCI. The medication (midodrine) has been approved for experimental use in this study by the FDA for phase 4 clinical trial. The results will help us to understand if we can minimize or eliminate disruptions to the prescribed rehabilitation program due to low BP during inpatient rehabilitation and explore the safety of initiating treatment for low BP before symptoms arise. If you choose to participate in this study, you understand that there is an approximated time commitment of 6 weeks. It is also required that you to sign both a VA informed consent and Mount Sinai School of Medicine informed consent. A copy of these consent forms will be given to you and a copy will be kept by the research team. This study is sponsored and funded by the National Institute on Disability, Independent Living, and Rehabilitation Research and the Veterans Affairs Rehabilitation Research & Development Service National Center for the Medical Consequences of SCI.

Participants:
You will be one of about 80 participants in this study participating at Icahn School of Medicine at Mount Sinai's Inpatient SCI Rehabilitation Unit.

Inclusions:

- You are between the age of 18-89 years of age
- You experienced traumatic SCI within the past 30 days

- Any level of injury
- non-ventilator dependent
- AIS grade A, B, C, D
- You are an inpatient for the acute SCI rehabilitation program
- You have evidence of hypotension (systolic BP<110 mmHg for males and <100 mmHg for females) measured while sitting for at least two separate measurements

Exclusions: If any of the following statements apply to you, you need only tell the researcher that one or more of the statements pertain to you. To ensure your privacy and confidentiality, you need not reveal which of the statements apply to you. If you choose to tell the investigator which of the statements apply to you, the information will be kept strictly confidential. Please inform the researcher if any of the following statements apply to you.

- You have insufficient English speaking or reading ability to provide informed consent or complete assessments in English
- You have contraindications to the use of midodrine
- You are pregnant
- You are hypertensive in sitting or supine position (systolic BP >140mmHg)

In addition, you may be excluded from participation if you have insufficient mental capacity to independently provide informed consent as determined by clinical staff during your admission to the SCI rehabilitation unit at Mount Sinai.

2. Description of the Study Including Procedures to be Used:

If you consent to participate in this research study, you will remain in the inpatient unit for acute SCI rehabilitation therapy at the Icahn School of Medicine at Mount Sinai located on Floor 2 of the Klingenstein Clinical Center (KCC building). You will be randomized to receive either the usual care treatment or the BP threshold treatment, and you have an equal chance of being assigned to the usual care or the BP threshold treatment groups. The usual care treatment group will receive BP management according to the current practice on the SCI Rehabilitation Unit. The treatment group will receive BP management, regardless of symptoms, to maintain systolic BP (SBP) between 111-135 mmHg for males and 101-135 mmHg for females. For both the usual care and the BP threshold treatment groups, the treatment plan will be driven by a protocol programmed into your Electronic Medical Records (EMR) with strict guidelines for moving from level to level. The protocol will be reviewed daily by a co-investigator who will complete a daily decision tree survey within your medical record. Your doctor will continue to following your

medical care closely and will initiate any necessary clinical intervention in the event of an incidental finding.

Treatment Group **-** if you are randomly assigned to the treatment group you will receive a medication that will increase your BP (midodrine hydrochloride). This treatment will be started based on your low BP, regardless of if you experience symptoms that are associated with low BP (dizziness, lightheadedness, nausea, blurry vision, loss of consciousness, etc.). Before you start on any medication you will receive physical countermeasures to increase BP (abdominal binders, compression stockings, etc.). If your BP remains low after using these countermeasures you will begin to take midodrine 2 or 3 times a day, as appropriate for your BP needs. We will start you at a low dose of midodrine (5 mg) and will monitor your BP several times a day for several days. If your BP remains low (SBP<110 mmHg for males and <100 mmHg for females) we will increase the dose to 10 mg and again monitor your BP several times a day for several days. If your BP still remains low we will increase the dose to 15 mg and again monitor your BP several times a day for several days. We will repeat this procedure until your seated SBP is between 111-135 mmHg. If your blood pressure is not well controlled (seated SBP between 111-135 mmHg) on midodrine or fludrocortisone, you will be prescribed a different medication, droxidopa, to increase your blood pressure. You would be started on this medication at a dose of 100mg 1 or 2 or 3 times a day as appropriate for your blood pressure needs.

Usual Care Group **-** if you are randomly assigned to the usual care group you will receive treatment only if you experience symptoms that are associated with low BP (dizziness, lightheadedness, nausea, blurry vision, loss of consciousness, etc.). Treatment to lessen or eliminate these symptoms of low BP will be guided by your doctors and can include physical countermeasures to increase BP (abdominal binders, comperssion stockings, etc.) and/or medications (midodrine, fludrocortisone, and/or droxidopa).

Testing Protocol **-** Prior to entering the treatment protocol, you will be asked to visit the testing laboratory located on the Inpatient SCI Rehabilitation Unit at Mount Sinai. You will be transferred to a laboratory bed and will remain in the supine position for instrumentation. Three sticky electrodes will be placed on your chest and abdomen area. A BP cuff will be placed around your upper right arm and a finger cuff on the left middle or ring finger. A small Doppler ultrasound probe with ultrasound gel will placed over your left temple to measure cerebral blood flow (CBF). After a period of 20 minutes of quiet rest, a 10-minute sample of supine heart rate (HR), respiration rate (RR), BP and CBF data will be collected. Venous Occlusion Plethysmography (VOP) will be collected while you remain in the supine position for two 5-minute recordings. After the supine data collection, you will be passively moved into a seated position, with the knees and hips at 90° for another 10-minute seated HR, RR, BP and CBF data collection. You

will then be asked to complete two surveys, one related to autonomic dysreflexia (AD) symptoms and another related to orthostatic hypotension (OH) symptoms. In addition to the weekly autonomic functional assessments, participants will have beat-to-beat BP assessments (via the finometer) performed during at least once a week while the participant simultaneously undergoes routine clinical bowel evacuation (standard of care) as well as bladder evacuations (standard of care as well). In addition, if a urodynamic study is clinically indicated and performed/overseen on the unit by the attending physician, an assessment of beat-to-beat finger BP will be simultaneously recorded. The beat-to-beat BP data will be recorded continuously for the entire period of bowel management and bladder management and/or testing. This assessment of beat-to-beat finger BP during bowel and bladder management and/or testing is optional based on subjects' willingness. Participants will also complete weekly surveys of autonomic sensations and control of bladder and bowel function. Finally you will be instrumented with a 24-hour Holter monitor, which will record HR and BP every 20-minutes during the daytime and every 30-minutes at night while you go about your normal daily routine. A log will be kept to record your daily activities, rehabilitation, medications, and eating and sleep/wake times. These procedures will be repeated at weekly intervals (6-8 days apart) and just prior to your discharge.

The table below depicts all of the study procedures that will be performed by VA staff and the time-points each will be recorded.

	Admission	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Discharge
Seated HR & BP	X	X	X	X	X	X	X	X
Supine HR & BP	X	X	X	X	X	X	X	X
Cerebral Blood Flow	X	X	X	X	X	X	X	X
Venous occlusion plethysmography	X	X	X	X	X	X	X	X
24-hour monitoring HR BP	X	X	X	X	X	X	X	X
Bowel/Bladder BP	X	X	X	X	X	X	X	X
AD Symptoms Survey	X	X	X	X	X	X	X	X
OH Symptoms Survey	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X

Heart Rate (HR) & Respiration Rate (RR) - will be monitored using 3 electrodes (small sticky pads) placed on your chest and abdomen. Your HR and RR will be monitored and recorded at admission, discharge and during each weekly study visits. At each visit your HR and RR will be continuously monitored for 10 minutes while you are lying down in bed (supine) and for 10 minutes while seated.

Blood Pressure (BP) **-** will be monitored and recorded from your right upper arm (brachial) using an automated BP cuff and vital sign monitor. Your brachial BP will be monitored and recorded 1 time per minute for 10 minutes while you are supine and for 10 minutes while you are seated. In addition, BP will be monitored on a beat-to-beat basis at your left middle or ring finger for 10 minutes while you are supine and for 10 minutes while you are seated. These BP assessments will be recorded at admission, discharge, during each weekly study visit, and weekly during routine clinical bowel and bladder evacuation.

Cerebral Blood Flow (CBF) - will be monitored and recorded using a small Doppler ultrasound probe (a noninvasive test that measures brain blood flow) with ultrasound gel that will be placed over your left temple to measure blood flow velocity through your middle cerebral artery. The Doppler probe will be held in place with a head harness, which will be tightened so that the probe doesn't move around during testing. CBF velocity will be monitored and recorded for 10 minutes while you are supine and for 10 minutes while you are seated during the admission visit, at weekly intervals and at discharge.

Venous Occlusion Plethysmography (VOP) **–** will be collected while you remain in the supine position, with your right leg propped up on a foam block. A strain gauge (small rubber band) will be placed around your calf at the widest point. A BP cuff will be placed on your ankle and another BP cuff will be placed on the thigh. The ankle cuff will be inflated to about 200 mmHg while the thigh cuff will be inflated to about 50 mmHg. The strain gauge on your calf will record the accumulation of blood and the increase in volume of your lower leg (calf). Once a plateau has been reached (about 3-4 minutes in), the thigh cuff will be deflated, and 60 seconds later the ankle cuff will be released. The procedure will be done twice at admission, each weekly visit and at discharge.

24-Hour Blood Pressure and Heart Rate Monitor - Electrodes will be placed on your left and right shoulder, left and right chest, and one on your abdomen and a cuff will be placed on your upper left or right arm for 24-hour HR & BP data collection. 24-hour HR and BP data will be collected during your usual daily activities at admission, one-time per week and just prior to discharge.

Autonomic Dysreflexia (AD) Symptoms Survey **–** will be collected at each study visit. AD is a condition where BP increases higher than normal, usually because of a painful or non-painful stimulus below the level of your SCI. Some of the most common causes of AD relate to bowel or bladder fullness, tight clothing, or pressure from being in one position for too long, but there may be other causes that we are not aware of. You will be asked to complete a 9 question AD symptoms survey once a week during the weekly testing visit, which will be used to determine your experience with AD over the past 7-days. This survey contains questions related to symptoms you may have experienced, information about your BP at that time, possible causes of the AD, and how frequent these symptoms occur.

Orthostatic Hypotension (OH) Symptoms Survey - will be collected at each study visit. OH is a condition where your BP falls when you change from supine to upright standing or seated position. Symptoms may range from dizziness and light headedness to fatigue and nausea to loss in consciousness. You will be asked to complete a 9 question OH symptoms survey at admission, once a week during your weekly testing visit, and at discharge, which will be used to determine your experience with OH over the past 7-days. This survey contains questions related to symptoms you may have experienced, information about your BP at that time, and how frequent these symptoms occur.

3. Description of any Procedures that may Result in Discomfort or Inconvenience:

You have been told that the study described above may involve the following risks and/or discomforts:

Heart rate and breathing rate: You may experience some discomfort when the electrodes are removed from your skin and some skin irritation at the site of electrode placement.

Blood pressure: You may experience some discomfort when the BP cuffs around your upper arm and finger are inflated.

Brain blood flow: You may experience some discomfort when the head harness is used to secure the ultrasound probe to your head for assessment of brain blood flow.

Venous occlusion plethysmography: You may experience some discomfort from the ankle cuff when it is inflated above your systolic BP.

Passive positional change: You may experience dizziness, lightheadedness or nauseous following a passive change from the supine to seated position. If you feel uncomfortable we may stop the test at any time.

Since this research may have unknown effects on an unborn child and should not be done during pregnancy, it is necessary for a pregnancy test to be done first. To your knowledge you are not pregnant at the present time. You also agree to avoid becoming pregnant (use contraceptives, take precautions against becoming pregnant, etc.) during this study.

For Males, you should know that your female partner should not become pregnant, once you agree to participate in this study. Therefore take all precautions to prevent pregnancy.

4. Expected Risks of Study:

Heart rate and breathing rate: You may experience some skin irritation when the electrodes are removed.

Blood pressure: You may experience some tingling or numbing sensation when the BP cuff around your upper arm and finger are inflated.

Midodrine:

More frequent or worsening of AD symptoms.

Sustained (30+ minutes) elevation in BP (>160/100 mmHg). Clinical staff may move you to the upright seated position, may loosen any tight clothing or braces that you are wearing and may check and empty your bladder and bowel. If your BP remains high for more than 30 minutes you may be provided with a medication to lower your pressure. The medication of choice will be a nitropaste (Nitroglycerin Ointment, 2%) placed one inch on your forehead.

Risks of midodrine (≤8% likely) include blurred vision, cardiac awareness (irregular heartbeat or shortness of breath), headache, pounding in the ears, increased dizziness, slow pulse, fainting, tingling and itching of the scalp, goosebumps, chills, constipation, superficial venous thrombosis (a blood clot in a vein), vascular ischemia (blockage of blood supply in an artery), urinary retention, the urge to urinate, and temporary muscle spasms

Fludrocortisone:

- More frequent or worsening of AD symptoms.
- Sustained (30+ minutes) elevation in blood pressure (>160/100 mmHg). Clinical staff may move you to the upright seated position, may loosen any tight clothing or braces that you are wearing and may check and empty your bladder and bowel. If your blood pressure remains high for more than 30 minutes you may be provided with a medication to lower your pressure. The medication of choice will be a nitropaste (Nitroglycerin Ointment, 2%) placed one inch on your forehead.
- Risks of fludrocortisone include hypertension, swelling, heart enlargement or heart failure, and potassium loss. Much less likely risks include muscle weakness, peptic ulcer, impaired wound healing, seizure, menstrual irregularities, cataracts, elevated blood sugar, allergic skin rash

Nitropaste:

- Bloating or swelling of the face, arms, hands, lower legs, or feet, burning, crawling, itching, numbness, prickling, “pins and needles,” tingling feelings, difficult or labored breathing, feeling faint, dizzy, lightheadedness, feeling of warmth or heat, flushing or redness of the skin, especially on the face and neck, headache, rapid weight gain, sweating, tightness in the chest, tingling of the hands or feet or unusual weight gain or loss. Rare: Bluish-colored lips, fingernails, or palms, dark urine, fever, pale skin, rapid heart rate, sore throat, unusual bleeding or bruising, unusual tiredness or weakness.

Droxidopa:

- More frequent or worsening of AD symptoms.o Sustained (30+ minutes) elevation in blood pressure (>160/100 mmHg). Clinical staff may move subject to the upright seated position, may loosen any tight clothing or braces that the subject is wearing and may check and empty the subject's bladder and bowel. If subject's blood pressure remains high for more than 30 minutes the subject may be provided with a medication to lower his/her pressure. The medication of choice will be a nitropaste (Nitroglycerin Ointment, 2%) placed one inch on the subject's forehead
- Droxidopa risks (≤8% likely) include: slow or fast heartbeat, pounding in the ears, low back or side pain, nervousness, dizziness, nausea, blurred vision, headache, bladder pain, difficulty, painful, and/or burning urination. Also, an urge to urinate or urine retention.

Since his research may have unknown effects on an unborn child and should not be done during pregnancy, it is necessary for a pregnancy test to be done first. To your knowledge you are not pregnant at the present time. You also agree to avoid becoming pregnant (use contraceptives, take precautions against becoming pregnant, etc.) during this study.

As with any research, there may be unforeseen risks and discomforts. A medical doctor associated with the study will be available to treat any medical emergency that may develop.

5. Expected Benefits of the Study

There may be no direct benefit to you from this study, but any information that the researchers get from this study may help others.

6. Other Treatments Available:

Participation in the study is voluntary and your alternative is to not participate and seek clinical advice from your doctor.

7. Use of Research Results:

The researchers will let you and your physician know of any significant new findings made during this study which may affect your willingness to participate. All research material generated from the study will remain in the possession of Dr. Jill M. Wecht and her study team at the JJP VAMC. Your medical records will be maintained according to this medical center's requirements and all electronic and hardcopy.

~~**Version Date: March 4, 2021**~~	**Page: 9 of 13**
Subject Name:	**Informed Consent Date:**
Principal Investigators: Dr. Jill M. Wecht, EdD	**VAMC: James J Peters**
Protocol #: WEC-16-050 **Title of Study: Treatment of Post-SCI Hypotension: A Randomized Controlled Study of Usual Care versus Anti-hypotension Therapy**	

All electronic and hardcopy Research Records will be retained according to National Archives and Records Administration, Records Schedule RCS-10-1.

Your research records will be maintained according to the requirements of the JJPVAMC as follows:

Data Collection, Storage, and Transfer:

- Your coded electronic data will be collected on VA computers that are not connected to the internet and will be transferred to a VA issued encrypted thumb drive for transfer to a secure password-protected VA environment.
- Your coded electronic data without your name, or other identifying information, will be stored on secured networks, behind electronic security systems, in access-restricted folders.
- Your coded electronic data will be stored on a secure VA network.
- Hard copies of your data will be stored in a locked file cabinet behind 2 locked doors at the VA and the keys will be kept with VA staff associated with the study.
- Data are transferred to the VA in the following manner
  - Hard copies will be hand delivered to the VA by VA staff.
  - Electronic copies will be sent over PKI-encrypted VA email, if necessary, to be stored on the VA intranet behind the VA firewall.

Access to the research materials generated from the study will be restricted to Dr. Jill M. Wecht and her study team. If results of this study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent. No information by which you can be identified will be released or published unless required by law. In order to comply with federal regulations, research records identifying you may be reviewed by the following:

Authorized representatives of the JJPVAMC (e.g. Institutional Review Board, Research Compliance Officer) and VA, including the Office of Research Oversight (ORO), Federal Agencies such as the Government Accounting Office (GAO), VA Office of Inspector General (OIG), Food and Drug Administration (FDA) and Office for Human Research Protections (OHRP) may have access to your research records. Because this research involves articles regulated by the FDA, the FDA may choose to inspect and copy medical or research records that identify individual research subjects.

If this study was initiated on or after March 7, 2012, a description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will include a summary of the results. You can search this web site at any time.

8. Special Circumstances:

~~**Version Date: March 4, 2021**~~	**Page: 10 of 13**
Subject Name:	**Informed Consent Date:**
Principal Investigators: Dr. Jill M. Wecht, EdD	**VAMC: James J Peters**
Protocol #: WEC-16-050 **Title of Study: Treatment of Post-SCI Hypotension: A Randomized Controlled Study of Usual Care versus Anti-hypotension Therapy**	

Because you are participating in a study at the Mount Sinai School of Medicine, your private health information (PHI) from this study will not be placed in the VA patient record system.

9. Compensation and/or Treatment in the Event of Injury:

In case of an emergency, necessary medical treatment to a research subject injured by participation in a research project approved will be provided at Mount Sinai School of Medicine and conducted under the supervision of one or more MSSM employees. Further information about compensation and medical treatment may be obtained from the medical administration service at Mount Sinai School of Medicine.

10. Voluntary Participation:

You are not required to take part in this study; your participation is entirely voluntary. You can refuse to participate in this study or withdraw your participation in this study after you consent without penalty or loss of VA or other benefits to which you are entitled.

11. Termination of Participation:

You can refuse to participate now or you can withdraw from the study at any time after giving your consent. This will not interfere with your regular medical treatment, if you are a patient. The investigator also has the right to withdraw you from the study at any time for reasons including, but not limited to, medical concerns (your health and safety are in jeopardy with continued participation in the study), non-compliance (you miss several scheduled appointments without notification) and protocol deviations (exclusion/inclusion criteria change and you are no longer eligible to participate).

12. Costs and Reimbursements:

As a veteran or non-veteran, you will not be charged for any treatments or procedures that are part of this study. For veterans who are required to pay co-payments for medical care and services provided by VA, these co-payments will continue to apply for medical care and services provided by VA that are not part of this study.

You will not receive any compensation for your participation in this study.

13. Contact Person(s):

To obtain answers to questions about the research, report or seek treatment for a research-related injury, or to voice concerns or complaints about the research contact the following:

- **During the Day: Dr. Jill M. Wecht (718) 584-9000 ext. 3122**
- **After Hours: Dr. Jill M. Wecht (201) 390-0487 or Dr. William A. Bauman at (914) 329-4772**

~~**Version Date: March 4, 2021**~~	**Page: 11 of 13**
Subject Name:	**Informed Consent Date:**
Principal Investigators: Dr. Jill M. Wecht, EdD	**VAMC: James J Peters**
Protocol #: WEC-16-050 **Title of Study: Treatment of Post-SCI Hypotension: A Randomized Controlled Study of Usual Care versus Anti-hypotension Therapy**	

I understand that should I wish to discuss my participation in this study with any other doctor or layperson, I can contact Mary Sano, Ph.D., Associate Chief of Staff (ACOS) R&D Program at the JJP VAMC by requesting an appointment at (718) 741-4228 hospital extension 4228, first floor in the research building, Room 1F-01 If I have questions, concerns, and/or complaints or to offer input.

RESEARCH SUBJECTS' RIGHTS: I have read or have had read to me all of the above. Dr. Jill Wecht or her delegate has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I understand that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

~~**Version Date: March 4, 2021**~~	**Page: 12 of 13**
Subject Name:	**Informed Consent Date:**
Principal Investigators: Dr. Jill M. Wecht, EdD	**VAMC: James J Peters**
Protocol #: WEC-16-050 **Title of Study: Treatment of Post-SCI Hypotension: A Randomized Controlled Study of Usual Care versus Anti-hypotension Therapy**	

The results of this study may be published, but my records will not be revealed unless required by law. This study has been explained to me. I have had a chance to ask questions. I voluntarily consent to participate in this study. I will receive a signed copy of this consent form.

_____	_____	
Subject Signature	Date	Time
_____	_____	_____
Person Obtaining Informed Consent (Print Name) (Investigator or Delegate as Indicated on Assurance Page)	Signature of Person Obtaining Informed Consent	Date

VERBAL CONSENT IF THE PARTICIPANT LACKS UPPER LIMB FUNCTION TO COMFORTABLY WRITE

_____ is unable to sign the consent form due to impaired arm function. I certify that I have carefully explained the purpose and nature of this research to him/her in appropriate language and he/she has had an opportunity to discuss it with me in detail. I have answered all of his/her questions and he/she has consented to participate in this research. I, therefore, am signing the consent form to document that he/she has given his/her consent to participate in this research study.

~~**Version Date: March 4, 2021**~~	**Page: 13 of 13**
Subject Name:	**Informed Consent Date:**
Principal Investigators: Dr. Jill M. Wecht, EdD	**VAMC: James J Peters**
Protocol #: WEC-16-050 **Title of Study: Treatment of Post-SCI Hypotension: A Randomized Controlled Study of Usual Care versus Anti-hypotension Therapy**	

Person Obtaining Consent:

Name: _____

Signature: _____

Date: _____

Witness Name: _____

Signature: _____

Date: _____

B. SITE-SPECIFIC RESEARCH PROJECT: **TREATMENT OF POST-SCI HYPOTENSION: A RANDOMIZED CONTROLLED STUDY OF USUAL CARE VERSUS ANTI-HYPOTENSION THERAPY**

1. IMPORTANCE OF THE PROBLEM

Shrinking lengths of stay for acute inpatient rehabilitation make taking advantage of the available time allowed for acute rehabilitation essential. From 1973 to 2014 the median length of stay for an admission to acute rehabilitation for traumatic SCI decreased from 98 to 36 days within the SCI Model Systems. Given this decreased length of stay for acute rehabilitation, there is a critical need for persons with SCI to optimize their time in therapy. However, on average patients with SCI during acute rehabilitation miss about 2.5 hours (17%) of scheduled therapy time per week of which a 'medical' complication was the most commonly reported cause.[17] Furthermore, it is appreciated that during the scheduled therapy time individuals need to be able to participate in the prescribed therapeutic plan to the best of their ability in order to maximize functional outcomes. An alteration or disruption in the optimal therapy plan, while not identified as missed therapy, has the potential to adversely impact outcomes, which may be proportional to the amount of the therapy plan that was affected.

One prevalent medical complication that can limit optimal participation in therapy is hypotension, particularly OH, which is frequently encountered especially among people with high cord lesions, but may also hinder rehabilitation efforts in individuals with low cord lesions. OH is defined as a decrease in systolic BP of 20mmHg or more, or a reduction in diastolic blood pressure of 10mmHg or more, upon changing body position from a supine position to an upright posture, regardless of the presence of symptoms.[18] In 2000, Illman et al. reported nearly three quarters of persons with acute SCI (levels of injury ranging from C2-L3) demonstrated OH during acute physical therapy rehabilitation.[19] It is important to note that symptoms of OH may or may not relate to orthostatic BP changes[20] and, while nearly half (43%) of the orthostatic episodes adversely impacted the prescribed therapy plans during acute rehabilitation following SCI, not all patients were symptomatic.[19] Another investigation reported a prevalence of OH in persons with high thoracic and cervical lesions of 74% within the first days and weeks after injury with systolic BP being significantly lower in those with cervical (107±2 mmHg) as compared to high thoracic (125±7 mmHg) lesions.[21]

On the SCI Rehabilitation Unit, we have similarly found that more than half of individuals with traumatic SCI are impacted by symptomatic hypotension. We recently conducted a survey of newly injured patients over a two-week interval and noted that 10 out of 18 persons with traumatic SCI experienced some interruption (21-100%) in their rehabilitation plan due to symptomatic hypotension. Specific examples of how this manifested included individuals 'not being able to sit fully upright in a wheelchair', 'not being able to work on seated balance due to an inability to tolerate upright postures', 'not being able to work on transfers due to an inability to sit upright', and 'not being able to work on standing or walking due to an inability to tolerate standing'. While the individuals did not miss therapy per se their therapeutic plan was restricted to activities that could be performed in a reclined position or for only short periods in a sitting or standing position. There were several instances where the plan was changed from being functionally oriented to one consisting of non-functional activities where symptomatic OH would not pose a significant barrier such as strengthening and stretching exercises performed in the supine position on a mat.

While treatment strategies for OH have been identified for use in persons with acute SCI, the field of SCI medicine lacks a gold standard for treatment thresholds and well-defined outcome parameters. Comprehensively documenting the impact of OH during acute rehabilitation and identifying the effects of two different treatment approaches on therapy participation and adherence to an intended rehabilitation plan could have a significant impact on clinical practice in the acute rehabilitation setting following SCI.

2. REVIEW OF THE LITERATURE

OH following SCI is well described in the literature and is known to be more common in persons with tetraplegia than in persons with paraplegia.[19,21-23] Not only is this condition evident in the acute period, it persists in a significant number of individuals for many years.[23,24] Decentralized adrenergic vascular tone[25] and significantly reduced resting norepinephrine level[26] is believed to be responsible for the loss of reflex vasoconstriction and hypotension following SCI.[22,23,25] Further, pooling of blood in the lower extremities in conjunction with hypotension and OH may result in a reduction in CBF, which then presents as the signs and symptoms of OH.[22,23,25] However, it has been documented that the absence of symptoms, does not mean that OH cannot have negative effects on CBF velocity, therapy tolerance and medical status. In fact we recently reported significantly reduced seated CBF in hypotensive individuals with chronic SCI compared to relatively hypotensive age-matched non-SCI control cohort.[27,28]

We recently conducted a retrospective review of all traumatic SCI admissions to the SCI Rehabilitation Unit for 2014-2015. We reviewed the medical record for blood pressure (BP) values that reflected hypotension, which was defined by the World Health Organization in 1978 as a systolic BP ≤ 110 mmHg for males & ≤ 100 mmHg for females, regardless of diastolic BP.[29] The findings suggest that hypotension was present in 34% in individuals with cervical SCI, compared to 22% in those with high thoracic (T1-T5) and 15% of those with low thoracic (T6 and below) lesions. It is important to emphasize that these data were collected in the ***supine*** position and reflect hypotension. It is highly likely that the prevalence of hypotension and OH will be substantially increased in the seated position, as previously described.[19]

Although most hypotensive individuals with SCI appear to be asymptomatic there is ample evidence in the general medical literature supporting associations between chronic asymptomatic hypotension and adverse changes in mood,[30-33] cognitive function[34-37] and increased morbidity and mortality;[38-40] findings which may apply to the Individuals with SCI and may adversely affect therapy adherence. Confirmatory evidence carried out in our laboratory suggests that asymptomatic individuals with chronic SCI who met the World Health Organization definition of hypotension perform significantly more poorly on cognitive tasks of working memory and attention processing compared to normotensive individuals with SCI.[6] It is important to note that all study subjects with SCI were chronically injured (2-39 years) and the two SCI groups were matched for positive history of traumatic brain injury.[6] Evidence of causality between hypotension and cognitive dysfunction has been documented in the general medical literature with findings of improved cognitive performance following acute increases in BP with midodrine.[41-43] The association between hypotension and cognitive impairment is thought to reflect alterations in CBF velocity because individuals with chronic hypotension have substantially reduced CBF velocity compared to matched normotensive controls.[44,45] Increases in CBF velocity secondary to increase in BP has been reported in the general medical literature[41] and we found a similar association in hypotensive individuals with SCI following administration of midodrine and L-NAME.[28,46]

The deleterious effects of hypotension and OH, not only impacts cognition, but also in predisposes individuals to a greater risk of developing pressure ulcers. This increased risk is the result of reduced tissue perfusion and an increased dependence on the renin-angiotensin system that results from renal hypoperfusion. The current usual care approach in the management of OH is to implement therapeutic interventions in stages, dependent upon the severity of symptoms, and not on BP measurements in the absence of symptoms.[23,47]

Most commonly both non-pharmacologic and pharmacologic interventions are utilized in the treatment of symptomatic OH in those with SCI. Non-pharmacologic options include compression stockings, abdominal binders, liberalization of salt intake, and electrical stimulation, while the two most frequently used pharmacologic options are midodrine and fludrocortisone. However, there is little evidence to support the wide spread use of these options to treat hypotension and OH in acute rehabilitation following SCI. Of the existing studies there is level II evidence that suggests midodrine at high doses (≥10 mg) and functional electrical stimulation can be helpful in treating OH post-SCI.[23,47,48] There are very few, underpowered studies in SCI on any of the aforementioned non-pharmaceutical interventions. Thus the standard of care to treat hypotension and OH following SCI is based on clinical judgment rather than on evidenced-based medicine as there is no established guideline for standard medication usage or titration for the treatment of hypotension and OH during acute rehabilitation following SCI.

Midodrine hydrochloride [d,1-alpha-(2'5'-dimethoxyphenyl)-β-(glycinamidoethanol); $C_{12}H_{19}N_2O_4Cl$] is an alpha agonist which, when taken orally, binds to the alpha receptor on the vascular walls, mimicking the actions of norepinephrine by causing vasoconstriction and increasing BP. Because the increased prevalence of hypotension and OH in persons with SCI is thought to reflect low adrenergic tone, midodrine has been most commonly recommended for clinical use in individuals with symptomatic hypotension.[23,47,48] Midodrine is a pro-drug that undergoes enzymatic hydrolysis in the systemic circulation to form the active metabolite desglymidodrine, and is nearly completely absorbed after oral administration,[49] even in models of neurogenic OH in which gastroparesis is common.[50] It has been shown that midodrine does not cross the blood brain barrier and, therefore, is not associated with central nervous system effects.[51] A few relatively small multi-center, randomized placebo-controlled clinical trials have been conducted to determine the efficacy of midodrine to treat symptomatic OH in various models of autonomic failure, and compared to placebo, 10 mg midodrine increased standing BP and improved symptoms of dizziness and light-headedness during standing.[50,52-54] Of note, energy level was improved and symptoms of depression were reduced in individuals randomized to midodrine compared to placebo.[52]

Available data on the effects of midodrine on BP in individuals with SCI include three case reports,[47,48,55] one randomized placebo-controlled trial in 4 individuals with tetraplegia,[56] a dose titration, open label trial, in 10 individuals with tetraplegia,[57] and 4 publications describing the effects of midodrine (10 mg) on BP and

CBF.[28,46,58,59] The three case studies in acute SCI report improved orthostatic BP responses and significant lessening of the symptoms of syncope.[47,48,55] The laboratory assessments provide preliminary evidence on the efficacy of midodrine to raise BP,[46,56,57] and we reported improved orthostatic BP responses to head-up tilt that corresponded to an attenuated fall in CBF following administration of midodrine in hypotensive subjects with tetraplegia.[46,57] In addition, Phillips et al. reported that increases in BP following midodrine administration were associated with improved cognitive performance in individuals with SCI above T6.[59] While midodrine appears to be effective at increasing BP in the Individuals with SCI, the question remains as to the clinical significance of sustained elevation in BP as well as the safety of this agent in treatment of asymptomatic hypotension and OH during acute rehabilitation following SCI. In addition, data are lacking which describe the effects of midodrine on BP changes during autonomic dysreflexia (AD) in the acute rehabilitation setting. However, several studies report comparable increases in BP during ejaculation with and without midodrine in males with chronic SCI.[60-62] It should be noted that subjects reported increased severity of headaches and negative AD symptoms with midodrine compared to ejaculation alone.[60]

The available data describing the effect of midodrine on BP in individuals with SCI have reported responses to a single dose during a laboratory or clinical visit. To our knowledge there has not been an intervention trial, documenting changes in BP in response to midodrine over the course of several weeks following clinically relevant 2 or 3 times per day administration. Furthermore, most of the available data characterizes a handful of brachial BP values in the seated position following midodrine, and none have documented the effect of midodrine over the course of a normal day in ether the acute in-patient or chronic out-patient individuals with SCI. However, BP instability is well described in persons with SCI,[63] particularly in those with high cord lesions, and while midodrine may be safe and effective following a single dose in the seated position, effects on BP during activities of daily living, such as transfers, bladder voiding and bowel evacuation, over the course of 24-hours has not been described. Therefore documenting the effects of midodrine over the course of several representative 24-hour periods during acute rehabilitation following SCI will provide unprecedented evidence of the safety and efficacy of this agent in support of wide-spread applicability.

3. OBJECTIVE AND SPECIFIC AIMS

The objective of this proof-of-concept safety and efficacy trial is to compare anti-hypotension treatment

initiated based upon a BP threshold, regardless of symptoms, to usual care treatment of symptomatic hypotension during acute rehabilitation following SCI.

Primary Hypothesis: SCI inpatients in the BP threshold treatment group (pharmacological hypotension management initiated when systolic BP<110 mmHg for males and <100 mmHg for females) will have less interrupted therapy time than the usual care control group (i.e., those treated for symptomatic hypotension only).

Aim 1: To compare BP threshold treatment and control groups for differences in therapy time spent actively involved in the prescribed rehabilitation program during the inpatient rehabilitation stay *(efficacy #1)*

Secondary Hypothesis: SCI inpatients in the treatment condition (hypotension management with SBP<110 mmHg for males and <100 mmHg for females) will have less cumulative time spent outside the normotensive range than the usual care control condition (i.e., those treated symptomatically).

Aim 2: To compare BP threshold treatment and control groups for differences in cumulative time spent outside of normotensive range, based on twice-weekly 24-hour BP observations**:**

Aim 2A: Compare time spent at a systolic BP > 140 mmHg (safety #1)

Aim 2B: Compare time spent at a systolic BP < 110 mmHg for males and < 100 mmHg for females (efficacy #2)

Exploratory Hypothesis 1: SCI inpatients in the BP threshold treatment group (pharmacological hypotension management initiated when systolic BP<110 mmHg for males and <100 mmHg for females) will report fewer symptoms of OH and AD than the usual care control group (i.e., those treated for symptomatic hypotension only).

Aim 3: To compare BP threshold treatment and usual care control groups for differences in self-reported symptoms of OH and AD based on once weekly assessments**:**

Exploratory Aim 3A: To compare groups on OH symptoms by survey (efficacy #3)

Exploratory Aim 3B: To compare groups on AD symptoms by survey (safety #2)

Exploratory Hypothesis 4: SCI inpatients in the BP threshold treatment group (pharmacological hypotension management initiated when systolic BP<110 mmHg for males and <100 mmHg for females) will have increased seated CBF velocity compared to the usual care control group (i.e., those treated for symptomatic hypotension only).

Exploratory Aim 4: To compare treatment and control groups for seated CBF velocity assessed one time per week (efficacy #4).

4. STUDY DESIGN

The proposed investigation will utilize a two-group randomized design. Subjects that agree to participate will be randomly assigned to either the BP threshold treatment group or to the usual care group. Block randomization will be provided for sub-groupings of subjects based on level of lesion as: cervical lesions (C1-C8); high thoracic lesions (T1-T5) and low thoracic lesions (T6-T12). Although use of a placebo control is often used to help ensure blinding of subjects and reduce bias in study designs similar to this, it was thought not possible in this particular study as both groups will potentially be receiving the same active intervention, the difference being only when the intervention is given if at all. Furthermore it would not ensure blinding to give a placebo to the usual care group who will only receive the usual care interventions if symptomatic.

GROUP ASSIGNMENT

Individuals randomized to the usual care group will receive BP management according to the current practice on the SCI Rehabilitation Unit as outlined in Figure 2.

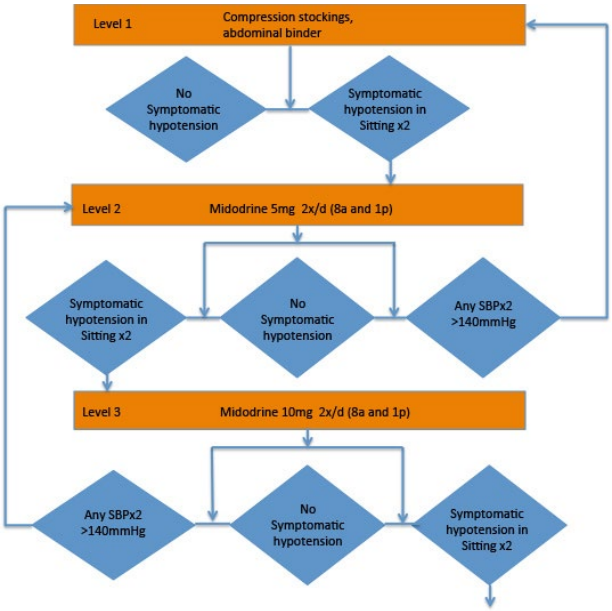

Figure 2. Usual Care Group: Advancement from one level to another will occur no sooner than every 2 days. While not identified on figure, the advancement can continue to **Level 4** (Midodrine 15mg 2x/d), **Level 5** (Midodrine 20mg 2x/d), **Level 6** (Midodrine 20mg 2x/d + Fludrocortisone 0.1mg 2x/d), and **Level 7** (Midodrine 20mg 2x/d + Fludrocortisone 0.2mg 2x/d).

Individuals assigned to the BP threshold treatment group will receive BP management, regardless of symptoms, to maintain systolic BP between 111-135 mmHg for males and 101- 135 mmHg for females for the duration of their in-patient hospital stay. The BP management algorithm is outlined in Figure 3.

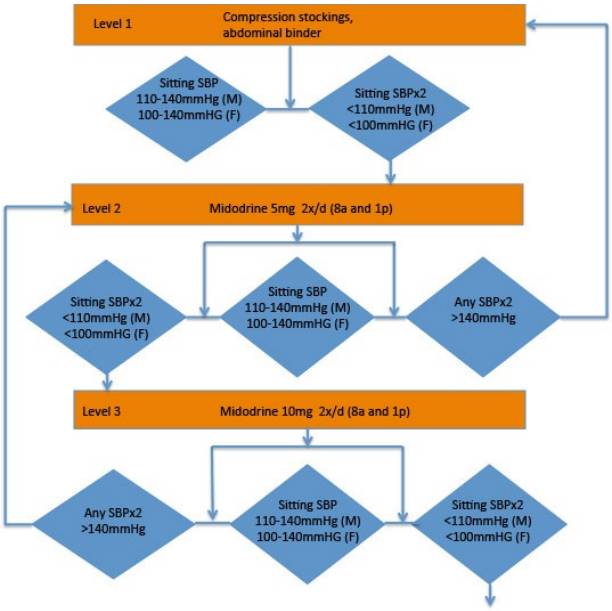

Figure 3. Treatment Group: Advancement from one level to another will occur no sooner than every 2 days. While not identified on figure, the advancement can continue to **Level 4** (Midodrine 15mg 2x/d), **Level 5** (Midodrine 20mg 2x/d), **Level 6** (Midodrine 20mg 2x/d + Fludrocortisone 0.1mg 2x/d), and **Level 7** (Midodrine 20mg 2x/d + Fludrocortisone 0.2mg 2x/d).

The treatment algorithm for both the usual care and BP threshold treatment groups will be driven by a protocol programmed into the EMR with strict parameters for moving from level to level. The protocol will be reviewed daily by a coinvestigator who will complete a daily decision tree survey within the EMR.

INCLUSION AND EXCLUSION CRITERIA.

Participants will include 60 individuals aged 18- 89 with traumatic SCI who:

- Have evidence of hypotension (systolic BP <110 mmHg for males and < 100 mmHg for females) measured in sitting for at least two separate measurements

Individuals will be excluded if they:

- Have insufficient mental capacity to independently provide informed consent
- Have insufficient English speaking or reading ability to provide informed consent or complete assessments in English
- Have contraindications to the use of midodrine
- Are pregnant
- Are hypertensive in sitting or supine position (systolic BP >140 mmHg)

***Note**: If a potentially eligible participant is actively being treated for hypotension or hypertension, these medications will be stopped, if medically indicated, prior to rescreening.*

RECRUITMENT STRATEGY AND INFORMED CONSENT PROCESS.

All individuals with traumatic SCI admitted to the SCI Rehabilitation Unit have their BP taken as per standard of care. Those individuals with a recorded BP <110 for males and <100 for females will be identified by the study co-investigators who are the attending physicians for all the persons with SCI admitted to the SCI Rehabilitation Unit. Potential subjects will receive a brief explanation of the study's objectives, procedures, risks, and benefits from a member of the research team, and will be provided a consent form for their review. The research team will address questions and informed consent will be documented using an IRB-approved consent form. If medically indicated, individuals who screen out due to use of an anti-hypotensive or anti-hypertensive agent will be allowed to taper off these medications and then be rescreened.

DATA COLLECTION PROCEDURES

Baseline Testing: Subjects will visit the testing laboratory on the SCI Rehabilitation Unit for baseline data collection, prior to initiation of the treatment protocol. Upon arrival, subjects will be placed in the supine position

on an adjustable surface for instrumentation, which will be conducted in a quiet, dimly lit, thermo-neutral testing environment. After a 20-minute period of quiet rest, a 10-minute sample of supine heart rate (HR), respiratory rate, BP and CBF velocity data will be collected. Venous occlusion plethysmography (Vop) will be collected in the supine position for two 5-minute periods. After the supine data collection, subjects will be passively moved into the seated position, with the knees and hips at 90°, for the 10-minute seated data collection period. Subjects will be asked to complete two surveys related to AD and OH symptomology. Finally, subjects will be fitted with a 24-hour HR and BP monitor and will be asked to go about their normal routine. A record of all daily activities including rehabilitation, medications, eating and sleep/wake times will be logged. This testing session should take approximately 1 hour.

Daily Testing: Every day supine and seated BP measurements will be performed at least three times per day. These BP assessments will be recorded in the supine and seated positions in the subject's room by a patient care associate who is blind to the study arm allocation. For every scheduled physical and occupational therapy session, the treating therapist will be asked to complete a brief 6 question survey to document if that session was altered, disrupted, or missed due to hypotension (*Therapist Reported Version)*. The subject will also be asked to complete a brief survey to determine if from their perspective the session was altered, disrupted or missed due to hypotension (*Subject Reported Version)*. In addition, every day a co-investigator and the attending physician for that subject will complete an EMR review of queried BP values within the previous 24 hours, symptoms of low BP, adverse events related to high or low BP, and will review (and act upon for the usual care arm) the protocol treatment decision tree.

Weekly Testing: At weekly intervals of between 6 and 8 days, subjects will be asked to visit the testing laboratory on the SCI Rehabilitation Unit. Procedures for the weekly testing sessions will be the same as for the *Baseline Testing*. The 24-hour BP assessment will be conducted twice weekly.

Discharge Testing: At discharge subjects will undergo similar testing as described during the *Baseline* and *Weekly Testing* with the addition of the Patient Global Impression of Change survey, which will be administered by the Mount Sinai Site Research Assistant.

Table 3: Administration of Measures by Study Visit.

	Admission - Baseline	Week 1	Week 2	Week 3	Week x	Discharge

Daily Altered, Disrupted, or Missed Therapy Time Survey- **Therapist Reported Version**		5-7X	5-7X	5-7X	5-7X	X
Daily Altered, Disrupted, or Missed Therapy Time Survey- **Subject Reported Version**		5-7X	5-7X	5-7X	5-7X	X
Daily Decision Tree	X	5-7X	5-7X	5-7X	5-7X	X
Daily Seated BP	X	21X	21X	21X	21X	X
Daily Supine BP	X	21X	21X	21X	21X	X
Cerebral Blood Flow	X	X	X	X	X	X
Venous occlusion plethysmography	X	X	X	X	X	X
24-hour monitoring HR BP	X	2X	2X	2X	2X	X
Patient Global Impression of Change						X
AD Symptoms Survey	X	X	X	X	X	X
OH Symptoms Survey	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

Daily

Assessments:

- **Altered, Disrupted, or Missed Therapy Time Survey- <u>Therapist Reported</u>** – A survey has been developed to document, any alteration, disruption, or missed time in the therapy plan for all therapy sessions over the duration of the LOS. The number of interruptions per session, the percentage of time, and total time affected will be captured. In addition the reasons for the altered, disrupted, or missed therapy will be documented. The data will be collected for the expected plan and for a plan (if low BP is the cause of the altered time) that would be expected if hypotension were not an issue. This survey will be completed by the therapist who will be blinded to group allocation.
- **Altered, Disrupted, or Missed Therapy Time Survey- <u>Subject Reported</u>**- A survey has been developed to document any alteration, disruption, or missed time in the therapy plan for all therapy sessions and the subject reported reasons for this. This survey will capture in addition subject reported data regarding therapy adherence such as ‘I was expected to work on ‘XYZ’ but could not due to ‘QRS’.
- **Decision Tree**- A checklist will be completed by the attending physician (co-investigator or covering physician) who sees that subject that day. The checklist queries for BP values, symptoms of low BP, adverse events related to high or low BP, and includes a protocol treatment decision tree. This will be incorporated into the hospital EMR.
- **Seated BP**- Brachial BP will be measured by a trained clinician in the highest tolerated upright position

at least three times per day using an automated blood pressure cuff.

- **Supine BP**- Brachial BP will be measured by a trained clinician in the supine position at least three times using an automated blood pressure cuff.

Once Weekly Assessments:

- **Heart Rate & Respiration Rate** - A three lead electrocardiogram will be used to determine HR and autonomic cardiac control with HR variability, with the recording electrode in the V5 position (RESP1EKG: Impedance Pneumograph, UFI 545 Main St. Suite C-2, Moro Bay, CA 93442). HR and respiratory rate data will be monitored for 10-minutes in the supine and 10-minutes in the seated positions during the baseline assessment, at weekly intervals throughout the in-patient LOS and at discharge. The electrocardiogram data will be viewed in real-time and stored on a secured desktop computer for future analysis using LabVIEW graphical software for instrumentation (National Instruments, Austin, TX, USA).
- **Blood Pressure:**
    - *Brachial BP* (GE Healthcare Information Tech; Milwaukee, WI; # PRO Series 400) will be measured by automated auscultation using standardized procedures at 1-minute intervals during the 10-minute supine and seated assessments at baseline, weekly intervals and at discharge.
    - *Beat-to-beat finger BP* will be monitored continuously using photoplethysmography (Finometer ® MIDI Model-2; Finopres Medical Systems B.V. Amsterdam, The Netherlands) at the finger arteriolar for assessment of BP variability and baroreceptor reflex activity. Beat-to-beat BP data will be monitored continuously for 10-minutes in the supine and 10-minutes in the seated positions at baseline, weekly intervals and at discharge. Finger BP data will be viewed in real-time and stored on a secured desktop computer for future analysis using LabVIEW graphical software for instrumentation (National Instruments, Austin, TX, USA).
- **Transcranial Doppler Ultrasound** - CBF velocity will be monitored weekly for 10-minutes in the supine and 10-minutes in the seated positions using a transcranial Doppler (TCD) ultrasound (Terumo Cardiovascular Systems 1311 Valencia Avenue Tustin, CA 92780-6447) to visualize the middle cerebral artery (MCA). The TCD probe will be operated at a frequency of 2.0 MHz to visualize the left

and right MCA through the temporal window, which will be identified by the depth (45-55 mm), sound and direction of flow (towards the probe), as evidenced by the color and spectral waveform. Once the MCA has been visualized a head-harness will be used to secure the probe position for the duration of testing. MCA CBF velocity (cm/sec) will be calculated as [peak systolic velocity + (2* end diastolic velocity)]/3, which is an accepted surrogate of CBF.[64-66] TCD signals will be viewed in real time and will be channeled and stored on a hard-drive for future analysis using customized data acquisition and analysis programs written with LabVIEW graphical software for instrumentation.

- **Venous occlusion plethysmography (Vop)** - We will use standard equipment; a rapid cuff inflator, plethysmograph, and rubber strain gauge (D.E. Hokanson, Inc., Bellevue, WA, 98005). Subjects will be supine with their dominant-side leg elevated at heart level. A tape cloth will be used to measure the widest circumference on their calf, a strain gauge 2cm smaller than the widest circumference measured will be placed on their calf. A small inflatable cuff will be placed just above the ankle; a second cuff will be wrapped around the thigh at its midpoint. The ankle cuff is inflated to suprasystolic pressure (≈200mmHg) while the thigh cuff is rapidly inflated just below diastolic pressure (≈50mmHg). The strain gauge will measure the change in volume, outputting the data to our autonomic data collection cart. The cuff will remain inflated until a plateau in volume change is observed, the cuffs will then be deflated and we will continue monitoring the change in blood volume until it returns to resting values. The test will be repeated two more times.
- **Adverse Events Survey-** A checklist will be reviewed with subjects and the treating physician on a weekly basis to evaluate for adverse events potentially related to the interventions.
- **Vancouver Autonomic Dysfunction Surveys:**
    - **AD Symptoms Survey-** A 9 question survey which queries about the subjects about potential manifestations of autonomic dysreflexia. The survey questions pertain symptoms of AD ranging from sweating and pounding headache to chills and goose bumps and asks the participant during what activities these symptoms occur and with what frequency.
    - **OH Symptoms Survey-** A 9-question survey which queries about the subjects about potential manifestations of hypotension and OH. The survey questions pertain to the symptoms of hypotension and OH ranging from dizziness and light headedness to fatigue and nausea, and

asks the participant during what activities these symptoms occur and with what frequency.

Twice Weekly Assessment:

- **24-hour BP assessment-** Subjects will be instrumented with a 24-hour HR and BP monitor (Vasomedical Biox® Model 2301 Combined Ambulatory ECG and Blood Pressure Recorder (BIOX INSTRUMENTS CO., LTD. 4/5 Taihu Bldg. No. 45-1 LiangXi Road Wuxi, Jiangsu 214062 P.R. China), which will record HR and BP 3 times/hour during the daytime and 2 times per hour during the nighttime. Date on 24-hour HR and BP will be recorded throughout the activities of daily living, including transfers, therapy time, meals, and voiding. Monitoring will be scheduled to co-inside with these activities at least once per week during the in-patient stay.

Discharge Assessment:

- **Patient global impression of change.** In measuring outcomes in intervention studies, transition ratings have been used to assess the subjects' experience of change.[67-69] Guyatt et al. as along with others has suggested these ratings be used to supplement "objective" outcome measures.[68] In a global change or global transition rating, the individual expresses how much better or worse the problem being treated seems to him/her in comparison to another time point. In this investigation, the Patient Global Impression of Change rating at Discharge, will take the form of, "Taking into account only your ability to not be lightheaded or have other symptoms of low blood pressure while you are sitting or standing, are you feeling you are able to do all you are capable of doing during therapy now as compared to when you first arrived?" If the individual states that there is no change, then the rating is complete. If he or she is worse or better, the individual is asked to quantify the magnitude of the change on a seven-point scale (1-very much better; 2-better; 3-somewhat better; 4-unchanged; 5-somewhat worse; 6-worse; 7-very much worse).

5. DATA ANALYSIS

The primary outcome variable is altered, disrupted, or missed time lost in therapy due to hypotensive episodes. The recorded data will be converted to a percent time lost, which is then averaged over the LOS in days for each subject. Differences in percent time altered, disrupted, or missed between BP threshold treatment and usual care groups will be statistically analyzed using a two-tailed independent t-test. In addition,

the 95% confidence interval for the difference between groups and the associated effect size (Cohen's D) will be calculated.

The secondary outcome (Aim 2) of cumulative time spent outside the normotensive range, (i.e., time spent at a SBP > 140mmHg, time spent < 110mmHg for males and < 100mmHg for females) and the exploratory outcome of group differences in seated CBFv (Exploratory Aim 4), will be collectively analyzed using the multivariate Hotelling's T^2 analysis with an alpha level of 0.05. Where appropriate, the data will undergo a transformation (e.g., log, square root) if marked deviations from normality (Z for skewness and/or kurtosis > |2.0|) are evident. In addition, potential covariate relationships will be explored between treatment approach and each of the dependent variables, age, level of lesion, American Spinal Injury Association (ASIA) Impairment Scale classification, and previous medical diagnoses by building separate univariate regression models. For Exploratory Aim 3A and 3B, the counts of symptoms of OH and AD will be analyzed using Poisson tests.

Statistical Power

Based on pilot data collected in our facility, we estimate that at power=0.80 and alpha=0.05, a sample size of 34 subjects per group will allow us to detect a 15 percentage point difference in therapy time altered, disrupted, or missed between groups.

6. PERSONNEL

Jill M. Wecht, Ed.D., is the Principal Investigator for the site specific project. She will be responsible for all scientific, administrative, human subjects and logistical issues related to the trial. She will train staff, ensure procedures are completed according to protocol, monitor adherence to timelines, and will lead the preparation of reports, publications and presentations. Joseph P. Weir, Ph.D., Professor and Chair of the Department of Health, Sport, and Exercise Sciences at the University of Kansas will perform all the statistical analysis. Thomas Bryce, M.D. and Miguel Escalon, M.D. as Co-Investigators will refer patients to the study and ensure that the interventions are prescribed appropriately per usual care for the usual care group and that the protocol is followed for the BP Threshold treatment arm for all enrolled subjects. Drs. Bryce and Escalon will monitor subjects for adverse events on a daily basis. Both investigators will be unblinded to group allocation. Mastanna Eraifej will be the Research Coordinator for the project, she will perform, under the supervision of Dr. Wecht,

weekly cardiovascular autonomic testing and the TCD ultrasounds for CBF velocity. Ms. Eraifej is based at the Bronx VA and will come to Mount Sinai for the weekly evaluations, and will be completely blinded to subject group allocation. Jacqueline Gurevich will be the Mount Sinai Site Research Assistant for the project who will assist in obtaining informed consents, collecting data via questionnaires, managing study data files, and other administrative support activities required for the successful implementation of the project. She will be blinded to group allocation as well.

7. TIMETABLE

A timetable for this investigation is enclosed as Table 4. Recruitment and data collection are expected to be complete by year 4, allowing 1 year for data analysis and reporting.

Table 4: Project Timetable.

Year	1				2				3				4				5			
Quarter	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*
Refine protocol	x																			
Train Research Staff	x																			
Obtain IRB approvals	x			x				x				x				x			x	
Recruit and enroll subjects	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Collect and process data		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Analyze data											x	x	x	x	x	x	x	x	x	x
Prepare NIDILRR reports			x				x				x	x			x				x	
Prepare publications presentations												x							x	x

8. OUTCOMES, OUTPUTS, DISSEMINATION AND KNOWLEDGE TRANSLATION

The core short-term outcome of this study will be preliminary data on the impact of symptomatic treatment versus anti-hypotensive therapy initiated regardless of symptoms, as well as information needed to design a future large- scale clinical trial to provide evidence for the use of anti-hypotension therapy initiated based on BP, regardless of symptoms, as a new paradigm of care during acute in-patient rehabilitation following SCI.

Results of the study will be disseminated via several outputs to promote more effective treatment of hypotension experienced by individuals with SCI. A paper discussing findings from the study and

recommendations for future research will be prepared in year 5, and will be submitted for publication in an SCI-focused journal such as the *Journal of Spinal Cord Medicine* or *Spinal Cord*. Presentations discussing the impacts of the interventions tested and lessons learned for future study planning will be made at scientific conferences of rehabilitation specialists (e.g. American Congress of Rehabilitation Medicine (ACRM), American Spinal Injury Association (ASIA)) in Year 5. Information about study progress and findings will be shared with the SCI community via newsletter articles and/or web postings.

9. STAGE OF RESEARCH

This project fits the Exploration and Discovery stage of research. We will discover if we can limit alterations and disruptions to prescribed rehabilitation therapies due to hypotension during inpatient rehabilitation by initiating anti-hypotension treatment based upon a BP threshold rather than the usual care treatment of only symptomatic hypotension. We will also explore the safety of initiating treatment for hypotension before it becomes symptomatic. In combination, these study outputs will expand the evidence for when anti-hypotension treatment should be initiated in persons with SCI and hypotension.