VA Department of Veterans Affairs

VA RESEARCH CONSENT FORM

Version Date: May 28, 2020	**Page: 1 of 12**
Subject Name:	**Informed Consent Date:**
Principal Investigator: Jill M. Wecht, EdD	**VAMC: James J Peters**
Protocol #: WEC-17-42 **Title of Study: Dose Response to the Norepinephrine Precursor Droxidopa in Hypotensive Individuals with Spinal Cord Injury (Study 1)**	

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

The purpose of this study is to determine the dose of a medication that raises your blood pressure into the normal range (111-139/70-85 mmHg). The medication (droxidopa), which has been approved for experimental use in this study by the FDA, has anti-hypotensive effects and will be given in increasing doses on successive study visits, depending on your blood pressure responses. You, the investigator and study team will not be blinded to the dose of medication. Your participation will last for no fewer than 1 and no more than 7 visits over the course of about six weeks. Subsequent study visits will be scheduled no less than 2 and no more than 10 days apart.

You are being asked to participate in this research study because you have low blood pressure (hypotension), are between the ages of 18 and 85, and have had a spinal cord injury (SCI) for over one (1) year. This study is sponsored by the National Center for the Medical Consequences of SCI and is funded by the New York Spinal Cord Injury Board IDEA program. You will be one of 50 subjects with SCI screened for eligibility to participate in this study. If you are screened eligible you will be one of approximately 40 subjects with SCI who will participate in this study. This study being conducted at the James J. Peters VA Medical Center (JJP VAMC) and at the Icahn School of Medicine Mount Sinai (ISMMS).

You will be eligible for the screening visit if you meet the following inclusion/exclusion criteria:

Inclusion Criteria:

- SCI between the ages of 18 – 85 years old
  - Any level of injury
  - non-ventilator dependent
  - Any AIS grade of SCI
  - SCI duration > 1 year
  - Wheelchair dependent
- Low blood pressure
  - Males- systolic blood pressure < 110 mmHg and diastolic BP < 70 mmHg
  - Females- systolic blood pressure < 100 mmHg and diastolic BP < 70 mmHg

Exclusion Criteria:

- Current illness or infection
- Individuals with frequent or severe autonomic dysreflexia
  - More than 3 symptomatic events per week
  - BP ≥140/90 mmHg
  - Significant adverse subjective symptoms reporting

- Hypertension
- Any neurological condition other than SCI (Alzheimer's disease, dementia, stroke, multiple sclerosis, Parkinson's disease, etc.)
- History of epilepsy or other seizure disorder
- Liver or kidney disease
- Bladder problems including blockage of the urine and/or weak urine stream.
- Known artery disease, heart failure, AV block, and irregular heartbeat
- Any allergies to droxidopa, asprin, polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide
- Major surgery in the last 30 days
- Pregnant

In addition we would like to review prescription medications that you are taking. Please will be let the research staff know if you are currently taking medications to treat any of the:

- Depression, Schizophrenia, ADHA
- Pain (opioids)
- Infection or illness (antibiotics)
- Erectile dysfunction (Viagra, Cialis, etc.)
- Overactive bladder
- High or low blood pressure
- Migraine headaches
- Malaria
- Ashtma

Please talk to the research staff if you have any questions about your medications; we may contact your doctor to discuss.

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

If you consent to participate in this research study, you will schedule your first visit with a study team member. If you are a participant consenting at ISMMS, you will be asked to sign both VA and ISMMS consent forms. As a subject in this research study, you will be asked to come to the laboratory at the JJPVAMC (7A-13S) or ISMMS Klingenstein Clinical Health Center (KCC) building, Floor 2, between 1 and 7 times for about 5 hours each visit. You will be asked to refrain from caffeine, alcohol, heavy exercise, and smoking for 12 hours prior to arrival and you will refrain from taking sildenafil (Viagra), tadalafil (Cialis), or other similar medications, for 2-days prior to your study visit. You will remain seated in your wheelchair for a minimum of 20 minutes

while the research team applies instrumentation. Three sticky electrodes will be placed on your chest and abdomen area. A blood pressure cuff will be placed around your upper right arm and a small blood pressure cuff will be placed on your left middle or ring finger. Your blood pressure, respiration rate and heart rate will be recorded for 5-minutes while you rest quietly (baseline) before we administer the study medication. After baseline testing you will be asked to swallow a small pill(s) with a glass of water. Blood pressure, respiration rate and heart rate will be monitored for 5-minutes every 15 minutes after you take the medication. For every visit you will receive droxidopa in a dose escalation (increasing doses) manner. The table below displays the medication and dose escalation that will be administered on successive study visits, depending on your blood pressure responses. The medication we have chosen has a short duration of action so any bad reaction should last for a short period of time. But if at any time you feel uncomfortable, we will immediately stop the study medication and all testing and will monitor your heart rate, breathing rate, and blood pressure very closely until you recover.

Table 1: Medication Dose Schedule*

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Dose	Screening	200 mg	300 mg	400 mg	500 mg	600 mg	700 mg	800 mg
Time	1-2 hours	4-5 hours	4-5 hours	4-5 hours	4-5 hours	4-5 hours	4-5 hours	4-5 hours

*Once the target blood pressure is attained (**i.e., males: SBP 111-139; females SBP 101-139 mmHg**), you will not be administered a higher dose of that study medication.

Screening Visit - You will visit the laboratory at the JJPVAMC (7A-13S) or ISMMS Klingenstein Clinical Health Center (KCC) building, Floor 2 to participate in a screening visit to determine your eligibility. If you are taking a vasoconstrictor agent, you will be asked to stop these medications 2 days or 5 half-lives prior to the screening visit, if medically cleared. If you routinely wear compression garments you will be asked to remove these for all testing sessions. The screening vist assessments will include medical intake information, medical history, physical examination, American Spinal Cord Injury Impairment Scale (AIS) classification (if not assessed in the prior 6-months), clinical symptoms survey for OH and AD and brachial BP assessment, recorded one time per minute for 10 minutes while in the seated and supine positions. You will be eligible to participate in Study 1 if your average seated BP meets the WHO definition of hypotension (i.e., SBP $\leq$ 110 mmHg for males or SBP $\leq$ 100 mmHg for females), there is evidence of OH (i.e., orthostatic fall in BP $\geq$20/10 mmHg when you are moved from the supine to the seated position) and if there is no evidence of sustained elevation in BP $\geq$140/100 mmHg in either the supine or seated positions. This visit will take approximately 1-2 hours.

Autonomic Dysreflexia (AD) Symptoms Survey: Will be collected during the screening visit. Autonomic dysreflexia is a condition where blood pressure increases higher than normal, usually because of a painful or non-painful stimulus below the level of your spinal cord injury. Some of the most common causes of AD relate to bowel or bladder fullness, tight clothing, or pressure from being in a position for too long, but there may be other causes that we are not aware of. You will be asked to complete an AD symptoms survey during each study visit, which will be used to determine your experience with AD over the 7-days prior to the study visit. This survey contains questions related to symptoms you may have experienced, information about your blood pressure at that time, and possible causes of the AD. This survey should take approximately 15 minutes to complete

Orthostatic Hypotension (OH) Symptoms Survey - will be collected during the screening 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. This survey should take approximately 15 minutes to complete.

The Visual Analog Fatigue Scale Survey **-** will be used during the screening visit to determine your self-reported history and severity of fatigue. This survey should take approximately 10 minutes to complete.

Table 2: Protocol Timeline

Procedures Table	Screening	Study Visits						
Visit	1	2	3	4	5	6	7	8
Dose	0 mg	200 mg	300 mg	400 mg	500 mg	600 mg	700 mg	800 mg
Medical Intake	X							
Medical History	X							
Physical Exam/AIS	X							
OH/AD Survey	X	X	X	X	X	X	X	X
10 minute Seated BP	X							
10 minute Supine BP	X							
Fatigue Survey	X	X	X	X	X	X	X	X
Seated Brachial BP (15 min interval)		X	X	X	X	X	X	X
Contniuous Finger BP (30 min intervals)		X	X	X	X	X	X	X
Beat-to-Beat Heart Rate (30 min intervals)		X	X	X	X	X	X	X
Side-effects		X	X	X	X	X	X	X

Heart Rate & Respiration Rate **-** Three electrodes (small sticky pads) will be placed on your chest and abdomen to continuously monitor your respiration and heart rate during each study visit. Heart and respiratory rate will be monitored and recorded for 5-minutes during the baseline period and at 30-minute intervals after administration of the study medication.

Blood Pressure **-** Blood pressure will be monitored and recorded from your right upper arm using standard procedures at 1-minute intervals during baseline and at 15-minute intervals after administration of the study medication. Finger blood pressure will be monitored continuously from your left middle or ring finger on a beat-to-beat basis during the baseline period. Beat-to-beat blood pressure will be recorded for 5-minutes at 30-minute intervals throughout the 4-hour observation period after administration of the study medication. Blood pressure will be taken every 30-minutes by a trained clinical research coordinator and will be reviewed by the study physician Dr. William Bauman and the clinical monitor Dr. Noam Harel.

Side-Effects Survey **–** The most common side-effects reported with droxidopa are headache (>10%) dizziness (4% to 10%) nausea (9%) hypertension (2% to 7%) and fatigue. In addition, subjects may report: feeling feverish, muscle cramps, confusion and uncontrolled movements. Therefore, you will be asked questions related to these known side-effects during each study visit. This survey contains questions related to symptoms you may have experienced, information about your blood pressure at that time, and possible causes of symptoms that may be related to the study medication. This survey should take approximately 10 minutes to complete.

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 discomforts:

- You may experience some discomfort when electrodes are removed from your skin and some skin irritation at the site of electrode placement.
- You may experience some discomfort when the blood pressure cuffs around your upper arm and your finger are inflated.
- 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.

4. Expected Risks of Study:

- The monitoring of heart rate, breathing rate, and blood pressure are all non-invasive measurements and are not associated with any known risks.
- Your blood pressure may be elevated above what is considered to be the normal range (>140/90 mm Hg) following administration of the study medication (i.e.,droxidopa). If this happens, we will take action to help reduce your blood pressure; we will loosen any tight clothing or braces that you may be wearing; we will shift your position in your wheelchair, and we will help you check and empty your bladder or bowel. If your blood pressure remains high for more than 30 minutes after we take these measures, we will provide medication to lower your blood pressure. The medication of choice will be sub-lingual (under the tongue) nitroglycerin. You will be asked to remina in the laboratory until your blood pressure has returned to baseline levels and the study doctors will monitor you and your blood pressure until it is safe for you to go home.
- If after 4-hours of testing if your BP remains elevated above baseline (SBP +10 mmHg), **but not in the hypertensive range** (<139/89 mmHg), you will be sent home with a 24-hour BP monitor, which will be programmed to obtain BP readings every 20 minutes during the day and at 30-minute intervals during the night. Study coordinator or the PI will follow-up with phone calls to you while you are at home to asses any side effects and document BP changes.
- You will be asked to immediately report any significant adverse event you may feel after leaving the laboratory. Symptoms which you should be particularly aware of include: headache, pounding in the ears, blurry vision, nausea, goosebumps, chills and spasms; please alert the research staff if you experience any of these symptoms in greater frequency or severity during the experiment or after you leave the laboratory.
- In order to lower the possible risks of interaction between the study medications and other medications you may be taking, you may be asked to avoid taking prescription medications on the day of the study, which should be approved by your primary physician.
- There may be interactions between the study medication and prescription medications you my be taking. In order to lower the risk to you the research staff will monitor your medications and may contact your doctor if needed. Medications prescribed for conditions not mentioned in the exclusion criteria, may have minor or moderate risks, (meaning the effects are considered tolerable and in most cases there is no need for medical intervention), and may be permitted, but decisions about your study participation should be made by study personnel in conjunction with you and your doctor.
- Symptoms of autonomic dysreflexia (AD) may become more frequent or worse while taking the study medication droxidopa.
- Common side effects of the study medication are dizziness, nausea, blurred vision, headache, bladder pain, difficulty, painful, and/or burning urination. Also, an urge to urinate or urine retention.

- **Droxidopa** risks (≤8% likely) include: slow or fast heartbeat, pounding in the ears, low back or side pain, and nervousness.
- 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.

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 information learned may help others.

6. Other Treatments Available:
Participation in the study is voluntary and you understand that the only alternative is to not participate.

7. Use of Research Results:
We 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. Wecht and her study team. De-identified electronic data will be stored on secured VA networks, behind VA firewalls, in access-restricted folders. Coded physical data will be stored at the JJP VA Medical Center in locked file cabinets behind locked doors. Access to the research materials generated from the study will be restricted to Dr. Wecht's research team. Records will be retained according to National Archives and Records Administration, in accordance with Records Schedule RCS-10-1.

□_____ By checking this box and initialing, you agree to be contacted by the Principal Investigator or her investigative team at a future date for additional studies being conducted in the National Center for the Medical Consequences of SCI.

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 Bronx VAMC (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 the Office for Human Research Protections (OHRP).

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 not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

8. Special Circumstances:
If you are a patient, a copy of this consent form will be placed in your medical record.

9. Compensation and/or Treatment in the Event of Injury:
The VA must provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or more VA employees. Further information about compensation and medical treatment may be obtained from the medical administration service at this VA medical center. A veteran-participant does not have to pay for care received as a participant in a research project, except in accordance with federal law that certain veterans have to pay co-payments for medical care and services provided by the VA.

10. Voluntary Participation:
You are not required to take part in this study; your participation is entirely voluntary. You can refuse to participate or withdraw your participation in this study after you consent without penalty or loss of VA or other benefits to which you are entitled. During the course of the study, you will be told about any new findings within the investigation or about information reported in the literature or reported verbally to the investigators that might affect your willingness to remain in the study. A signed copy of this consent form will be given to you.

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. Reimbursement typically takes 6-8 weeks to arrive by Electronic Transfer Fund (EFT) and 12-14 weeks to arrive by check. You understand that if you choose to receive reimbursement through EFT, you will be required to provide the research staff information that includes; name of your bank, routing number and account number.

You have been told that you will receive up to $375 for participation in this research study according to the following schedule:

- Screening - $25.00
- Visit 1 (200 mg)- $50
- Visit 2 (300 mg)- $50
- Visit 3 (400 mg)- $50
- Visit 4 (500 mg)- $50
- Visit 5 (600 mg)- $50
- Visit 6 (700 mg)- $50
- Visit 7 (800 mg)- $50

You understand that payment will be processed after each study visit based on the above schedule, and that you will be paid for each study visit you attend and complete. You understand that if you cannot complete all study visits you will be paid for the testing sessions that you complete.

13. Contact Person(s):
If you have any questions, at any time, about this research, or want to discuss any possible study-related injuries, please call telephone number 718-584-9000, ext. 3122 for Dr. Wecht. In addition after-hours you can contact Dr. Wecht at (201) 390-0487 or one of the medical doctors affiliated with this study: JJP VAMC: Dr. William Bauman at (914) 329-4772 and ISMMS: Dr. Miguel Escalon (979) 739-6228.

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. ACOS/R&D Program 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:
You have read or have had read to you all of the above. Dr. Jill M. Wecht, EdD or her delegate has explained the study to you and answered all of my questions. You have been told of the risks or discomforts and possible benefits of the study. You have been informed 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.

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 Conse	Date

VERBAL CONSENT IF THE PARTICIPANT LACKS UPPER LIMB FUNCTIONS 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.

Person Obtaining Consent: _____

Signature: _____

Date: _____

Witness Name: _____

Signature: _____

Date: _____

Version Date: May 28, 2020	**Page: 1 of 12**
Subject Name:	**Informed Consent Date:**
Principal Investigator: Jill M. Wecht, EdD	**VAMC: James J Peters**

Protocol #: WEC-17-42
Title of Study: Dose Response to the Norepinephrine Precursor Droxidopa in Hypotensive Individuals with Spinal Cord Injury (Study 2)

1. Purpose of study and how long it will last:
The purpose of this study is to measure blood pressure and blood flow to the brain while you are lying down (supine) and during a head-up tilt (HUT) maneuver before and after the administration of the study medication, which increased your blood pressure in Study 1. You will be asked to visit the laboratory on 2 separate days and the medication (droxidopa), which has been approved for experimental use in this study by the FDA for phase 2 clinical trial, will be given to you as a pill on 1 of the study visits. On the other study visit you will be given an identical pill, which will be a placebo (no medication). This is a randomized double-blinded, placebo control trial, as such, neither you nor the study investigators will know what the pill contains on each of the 2 study visits.

You are being asked to participate in this research study because you are between the age of 18 and 85, and you have had SCI for over one (1) year. This study is sponsored by National Center for the Medical Consequences of Spinal Cord Injury (SCI) and funded by the New York Spinal Cord Injury Board IDEA program.

You will be one of approxmately 25 subjects with SCI who will participate in this study at one of two sites, 1) the James J. Peters VA Medical Center (JJP VAMC) and 2) the Icahn School of Medicine Mount Sinai (ISMMS). The time allotted for your participation in each of the 2 study visits will be 4-5 hours, which will occur over the course of about two weeks. Prior to study participation you will be screened for the following:

Inclusion Criteria:
- Participation in Study 1
- SCI between the ages of 18 – 85 years old
  - Any level of injury
  - non-ventilator dependent
  - Any AIS grade of SCI
  - SCI duration > 1 year
  - Wheelchair dependent
- Low blood pressure
  - Males- systolic blood pressure (SBP) < 110 mmHg and diastolic BP (DBP) < 70 mmHg
  - Females- SBP < 100 mmHg and DBP < 70 mmHg

Exclusion Criteria:

- Individuals who did not respond to droxidopa with a normal seated SBP in Study 1
- Current illness or infection
- Individuals with frequent or severe autonomic dysreflexia
    - More than 3 symptomatic events per week
    - BP ≥140/90 mmHg
    - Significant adverse subjective symptoms reporting
- Hypertension
- Any neurological condition other than SCI (Alzheimer's disease, dementia, stroke, multiple sclerosis, Parkinson's disease, etc.)
- History of epilepsy or other seizure disorder
- Liver or kidney disease
- Bladder problems including blockage of the urine and/or weak urine stream.
- Known artery disease, heart failure, AV block, and irregular heartbeat
- Any allergies to droxidopa, asprin, polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide
- Major surgery in the last 30 days
- Pregnant

In addition we would like to review prescription medications that you are taking. Please will be let the research staff know if you are currently taking medications to treat any of the:

- Depression, Schizophrenia, ADHA
- Pain (opioids)
- Infection or illness (antibiotics)
- Erectile dysfunction (Viagra, Cialis, etc.)
- Overactive bladder
- High or low blood pressure
- Migraine headaches
- Malaria
- Ashtma

Please talk to the research staff if you have any questions about your medications; we may contact your doctor to discuss.

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

If you consent to participate in this research study, you will schedule your first visit with a study team member. If you are a participant consenting at ISMMS, you will be asked to sign both VA and ISMMS consent forms. As a subject in this research study, you will be asked to come to the laboratory at the JJPVAMC (7A-13S) or ISMMS Klingenstein Clinical Health Center (KCC) building, Floor 2, for 2 visits for about 5 hours each visit.

You will be asked to refrain from caffeine, alcohol, heavy exercise, and smoking for 12 hours prior to arrival and you will refrain from taking sildenafil (Viagra), tadalafil (Cialis), or other similar medications, for 2-days prior to each of your study visits.

You will remain seated in your wheelchair for a minimum of 20 minutes while the research team applies instrumentation. Three sticky electrodes will be placed on your chest and abdomen area to monitor your heart rate (HR) and respiratory (breathing) rate (RR). A blood pressure cuff will be placed around your upper right arm and a small blood pressure cuff will be placed on your left middle or ring finger. We will place a plastic harness on your head, apply gel to your forehead and place an ultrasound probe against your head to monitor cerebral blood flow velocity (CBFv). A catheter (small plastic tube) will be placed in a vein in your arm for blood draws to measure plasma renin activity, aldosterone and norepinephrine concentrations. After instrumentation you will be transferred to the supine position (on the tilt table) for a 10-minute period of quiet rest and baseline supine data collection and a blood draw (20 mL) prior to administration of the study medication. Following the baseline data collection you will be you will be asked to swallow either droxidopa or placebo with a glass of water and will remain in the supine position for 60 minutes.

You will be given the dose of medication that raised your blood pressure into the normal range (i.e., males: 111-139 mmHg; females: 101-139 mmHg) in Study 1.

While you are in the supine position your heart rate, respiratory rate, finger blood pressure and blood flow to the brain will be monitored continuously for 5-minutes at 0, 25 and 55 minutes and brachial BP will be monitored and recorded at 0, 10, 20, 30, 40, 50 and 60 minutes. A second blood sample will be drawn from the catheter in your arm (20 mL).

The HUT maneuver will be initiated 60 minutes after drug/placebo administration and you will remain in the 70° HUT position for 30 minutes or until you have symptoms including but not limited to: dizziness, lightheadedness, nausea, blurred vision. Heart rate, respiratory rate, finger blood pressure and blood flow to the brain will be monitored continuously for 5-minutes at 0, 10 and 20 minutes during the HUT and brachial BP will be monitored and recorded at 0, 5, 10, 15, 20, 25 and 30 minutes. Additionally, you will be asked

questions related to the symptoms of OH at 10 minute intervals during the sustained HUT maneuver. A third blood sample will be drawn from the catheter in your arm (20 mL).

After completion of the HUT maneuver you will be transferred to your wheelchair for continued monitoring of your seated HR, RR, SBP and CBFv for 3 hours or until your SBP returns to within ±10 mmHg of your baseline SBP, which ever comes last. You will be asked questions pertaining to the side-effects of droxidopa, symptoms related to autonomic dysreflexia and orthostatic hypotension, and fatigue.

Heart Rate & Respiration Rate : Three electrodes (small sticky pads) will be placed on your chest and abdomen to continuously monitor your heart rate and respiratory rate during each study visit according to the study time line.

Study 2: Protocol Timeline

Time Point		Pre-1	Pre-2	Drug	Post-1	Post-2	Post-3	Post-4	Post-5
Time (min)		0-20	20-30	30	30-60	60-120	120-180	180-240	240-300
Position		Supine				HUT	Seated		
Heart Rate	instrumentation	x		x	x	x	x	x	x
Breathing Rate		x		x	x	x	x	x	x
Drug administration			x						
Beat-to-beat BP		x		x	x	x	x	x	x
Manual BP		x		x	x	x	x	x	x
CBFv		x		x	x	x	x	x	x
HUT Test					x				
Blood draws		x		x	x				x
Fatigue Survey		x		x	x				x
AD/OH Survey		x		x	x	x	x	x	x
Side-Effects Survey				x	x	x	x	x	x

Blood Pressure: Blood pressure will be monitored and recorded from your right upper arm using standard procedures and finger blood pressure will be monitored continuously from your left middle or ring finger on a beat-to-beat basis according to the study time line. Blood pressure will be taken every 30-minutes by a

trained clinical research coordinator and will be reviewed by the study physician Dr. William Bauman and the clinical monitor Dr. Noam Harel.

Cerebral Blood Flow: CBF will be monitored and recorded using a small transcranial Doppler ultrasound probe (a noninvasive test that measures brain blood flow) with ultrasound gel that will be placed over your left or right 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 dosent move around during testing.

Head Up Tilt (HUT): The HUT maneuver will be initiated after the 60 minutes of supine observation and you will be held at 70° HUT position for 30 minutes or until you report any symptom of intolerance.

Plasma Blood Draws: We will draw blood from a vein in your arm 4 times throughout the study to monitor changes in plasma concentrations of substances in your body that control blood pressure. These substances include: plasma renin activity, aldosterone and norepinephrine.

Autonomic Dysreflexia (AD) Symptoms Survey: Will be collected during the both study visits. Autonomic dysreflexia is a condition where blood pressure increases higher than normal, usually because of a painful or non-painful stimulus below the level of your spinal cord injury. Some of the most common causes of AD relate to bowel or bladder fullness, tight clothing, or pressure from being in a position for too long, but there may be other causes that we are not aware of. You will be asked to complete an AD symptoms survey during each study visit, which will be used to determine your experience with AD over the 7-days prior to the study visit. This survey contains questions related to symptoms you may have experienced, information about your blood pressure at that time, and possible causes of the AD. This survey should take approximately 15 minutes to complete

Orthostatic Hypotension (OH) Symptoms Survey - will be collected during both study visits. 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. This survey should take approximately 15 minutes to complete.

Side-Effects Survey **-** The most common side-effects reported with droxidopa are headache (> 10%) dizziness (4-10%) nausea (9%) hypertension (2-7%) and fatigue. In addition, subjects may report: feeling feverish, muscle cramps, confusion and uncontrolled movements. Therefore, you will be asked questions related to these known side-effects during both study visits. This survey contains questions related to symptoms you may have experienced, information about your blood pressure at that time, and possible causes of symptoms that may be related to the study medication. This survey should take approximately 10 minutes to complete.

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 discomforts:

- You may experience some discomfort when electrodes are removed from skin and some skin irritation at the site of electrode placement.
- You may experience some discomfort when the blood pressure cuffs around your upper arm and your finger is inflated.
- You may feel discomfort with the harness around your head that is used to secure the ultrasound probe to your head for assessment of brain blood flow.
- You may experience pain as the intravenous catheter is placed in a vein in your arm.
- When the tilt table is adjusted to 70° you may feel uncomfortable, lightheaded, dizzy and/or nauseous. If any symptom becomes too discomforting we will return the table to the supine position.
- 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.
- You may experience some discomfort when the needle is being placed in your arm vein during the blood draws.

4. Expected Risks of Study:

- The monitoring of heart rate, breathing rate, and blood pressure are all non-invasive measurements and are not associated with any known risks.
- There is a riak of a bruise at the site of the blood draw and infection if the site is not kept clean.
- Your blood pressure may be elevated above what is considered to be the normal range (>140/90 mm Hg) following administration of the study medication (i.e.,droxidopa). If this happens, we will take action to help reduce your blood pressure; we will loosen any tight clothing or braces that you may be wearing; we will shift your position in your wheelchair, and we will help you check and empty your bladder or bowel. If your blood pressure remains high for more than 30 minutes after we take these measures, we will provide medication to lower your blood pressure. The medication of choice

will be sub-lingual (under the tongue) nitroglycerin. You will be asked to remina in the laboratory until your blood pressure has returned to baselin levels and the study doctors will monitor you and your blood pressure until it is safe for you to go home.

- If after 4-hours of testing if your BP remains elevated above baseline (SBP +10 mmHg), **but not in the hypertensive range** (<139/89 mmHg), you will be sent home with a 24-hour BP monitor, whichwill be programmed to obtain BP readings every 20 minutes during the day and at 30-minute intervals during the night. Study coordinator or the PI will follow-up with phone calls to you while you are at home to asses any side effects and document BP changes.
- You will be asked to immediately report any significant adverse event you may feel after leaving the laboratory. Symptoms which you should be particularly aware of include: headache, pounding in the ears, blurry vision, nausea, goosebumps, chills and spasms; please alert the research staff if you experience any of these symptoms in greater frequency or severity during the experiment or after you leave the laboratory.
- In order to lower the possible risks of interaction between the study medications and other medications you may be taking, you may be asked to avoid taking prescription medications on the day of the study, which should be approved by your primary physician.
- There may be interactions between the study medication and prescription medications you my be taking. In order to lower the risk to you the research staff will monitor your medications and may contact your doctor if needed. Medications prescribed for conditions not mentioned in the exclusion criteria, may have minor or moderate risks, (meaning the effects are considered tolerable and in most cases there is no need for medical intervention), and may be permitted, but decisions about your study participation should be made by study personnel in conjunction with you and your doctor.
- Symptoms of autonomic dysreflexia (AD) may become more frequent or worse while taking the study medication droxidopa.
- Common side effects of the study medication are dizziness, nausea, blurred vision, headache, bladder pain, difficulty, painful, and/or burning urination. Also, an urge to urinate or urine retention.
- **Droxidopa** risks (≤8% likely) include: slow or fast heartbeat, pounding in the ears, low back or side pain, and nervousness.
- 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.

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 information learned may help others.

6. Other Treatments Available:
Participation in the study is voluntary and you understand that the only alternative is to not participate.

7. Use of Research Results:
We 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. Wecht and her study team. De-identified electronic data will be stored on secured VA networks, behind VA firewalls, in access-restricted folders. Coded physical data will be stored at the JJP VAMC in locked file cabinets behind locked doors. Access to the research materials generated from the study will be restricted to Dr. Wecht's research team. Records will be retained according to National Archives and Records Administration, in accordance with Records Schedule RCS-10-1.

□_____ By checking this box and initialing, you agree to be contacted by the Principal Investigator or her investigative team at a future date for additional studies being conducted in the National Center for the Medical Consequences of SCI.

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 Bronx VAMC (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 the Office for Human Research Protections (OHRP).

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 not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

8. Special Circumstances:
If you are a patient, a copy of this consent form will be placed in your medical record.

9. Compensation and/or Treatment in the Event of Injury:
The VA must provide necessary medical treatment to a research subject injured by participation in a research project approved by a VA R&D Committee and conducted under the supervision of one or more VA employees. Further information about compensation and medical treatment may be obtained from the medical administration service at this VA medical center. A veteran-participant does not have to pay for care received as a participant in a research project, except in accordance with federal law that certain veterans have to pay co-payments for medical care and services provided by the VA.

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. During the course of the study, you will be told about any new findings within the investigation or about information reported in the literature or reported verbally to the investigators that might affect your willingness to remain in the study. A signed copy of this consent form will be given to you.

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. Reimbursement typically takes 6-8 weeks to arrive by Electronic Transfer Fund (EFT) and 12-14 weeks to arrive by check. You understand that if you choose to receive reimbursement through EFT, you will be required to provide the research staff information that includes; name of your bank, routing number and account number.

You have been told that you will receive up to $100 for participation in this research study according to the following schedule:

- Visit 1 - $50.00
- Visit 2 - $50.00

You understand that payment will be processed after each study visit based on the above schedule, and that you will be paid for each study visit you attend and complete. You understand that if you cannot complete all study visits you will be paid for the testing sessions that you complete.

13. Contact Person(s):
If you have any questions, at any time, about this research, or want to discuss any possible study-related injuries, please call telephone number 718-584-9000, ext. 3122 for Dr. Wecht. In addition after-hours you can contact Dr. Wecht at (201) 390-0487 or one of the medical doctors affiliated with this study: JJP VAMC: Dr. William Bauman at (914) 329-4772 and ISMMS: Dr. Miguel Escalon (979) 739-6228.

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. ACOS/R&D Program 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.

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Subject Name:	**Informed Consent Date:**
Principal Investigator: Jill M. Wecht, EdD	**VAMC: James J Peters**

Protocol #: WEC-17-42
Title of Study: Dose Response to the Norepinephrine Precursor Droxidopa in Hypotensive Individuals with Spinal Cord Injury (Study 2)

RESEARCH SUBJECTS' RIGHTS:
You have read or have had read to you all of the above. Dr. Jill M. Wecht, EdD or her delegate has explained the study to you and answered all of my questions. You have been told of the risks or discomforts and possible benefits of the study. You have been informed 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.

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 Conse	Date

VERBAL CONSENT IF THE PARTICIPANT LACKS UPPER LIMB FUNCTIONS 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.

Person Obtaining Consent: _____

Signature: _____

Date: _____

Witness Name: _____

Signature: _____

Date: _____

PART II

A Research Protocol must be submitted with this application.

A. LAY RESEARCH SUMMARY

Provide 1-2 paragraphs explaining the Research in lay terms, including the specific study aim, any important background information to explain why the research is important, what will be done, and how results will be analyzed.

The goal of this study is to determine the efficacy of the drug Droxidopa (Northera) in increasing blood pressure in subject with hypotension, low blood pressure, which is classified as blood pressure less than 110/70 in males and 100/70 in females. The first aim is to determine the proportion of subject with SCI who have a normotensive response to Droxidopa. The second is to determine the proportion of subject with SCHI who express a hypertensive response to Droxidopa. A Normal blood pressure ranges from 111-139 in males and 101-139 in females and a hypertensive blood pressure is anything higher than 140 in males and females.
The study would take place in James J. Peters VA Medical Center (JJPVAMC),The Icahn School of Medicine at Mount Sinai (ISMMS) in Manhattan, New York and The Kessler Foundation (KF) at the Kessler Institute for Rehabilitation in West Orange, NJ.

B. PROTOCOL SUMMARY

A. Provide a brief (200-250 word) summary of background information for physician/scientistsList total # of subjects approved for enrollment by the IRB.
List total number of subjects enrolled (Signed a consent form) over the life of this study. List total number of subjects enrolled(Signed a consent form) in the current approval period. List total number of subjects terminated form study (Lost to follow-up, terminated by PI, withdrew consent, etc.). List total number of subjects that have completed all study tasks/procedures and follow-up visits. List total number of subjects currently receiving study treatment or participating in study activities.:

Interruption of sympathetic cardiovascular autonomic regulation following spinal cord injury (SCI) is associated with significantly reduced plasma norepinephrine (NE) levels, hypotension and orthostatic hypotension (OH), particularly in individuals with high cord lesions. [1-4] Although the incidence of hypotension is reported to be as high as 70% in persons with cervical lesions (i.e., tetraplegia), the vast majority of these individuals remains asymptomatic and, therefore, does not raise clinical concern, or prompt intervention [5, 6]. While it is appreciated that clinicians are faced with substantial challenges in managing blood pressure (BP) in persons with SCI, contrary to the prevailing belief, asymptomatic hypotension and OH are not benign conditions. Reports suggest that asymptomatic hypotensive individuals with SCI may have subclinical cognitive dysfunction affecting memory and attention processing [7-11] and increased incidence of fatigue and depression compared to normotensive individuals with SCI. [7] It must be appreciated that to date, there are no FDA approved pharmaceutical options proven to be safe and effective for treatment of hypotension and OH in the SCI population. Until 2014, midodrine hydrochloride was the only agent with FDA approval for treatment of symptomatic neurogenic OH (NOH). Midodrine, an alpha-agonist, is the most commonly prescribed agent used to treat symptomatic hypotension in the SCI population despite a lack of convincing evidence of safety or efficacy. [12] In 2014 droxidopa (L-threo-3,4-dihydroxyphenylserine - NORTHERA; Chelsea Therapeutics, Charlotte, NC) was approved by the FDA for treatment of symptomatic NOH based on data collected in conditions of autonomic dysfunction. Droxidopa is a NE precursor that is stored in neuronal and non-neuronal tissue and has been shown to increase standing BP and reduce symptoms of orthostatic intolerance in individuals with symptomatic NOH. [13-15] We recently reported preliminary evidence of a mean increase in seated BP in individuals with SCI following oral administration of 400 mg of droxidopa; however, this dose was effective in only 5 of the 10 subjects tested and the BP effect waned over a 4-hour observation. [16] Because of its unique pharmokinetic profile, [17] droxidopa is a highly promising agent to treat hypotension in persons with SCI. As such; there exists a pressing imperative to determine the clinical value and safety of droxidopa in hypotensive individuals with SCI.

B. State the purpose of the study:

Primary Aim 1.1: Dose optimization, open-label trial to determine the proportion of subjects with SCI with a normotensive response to droxidopa (Efficacy #1). Normotension will be defined as an average systolic BP (SBP) recorded 60-120 minutes after dose administration of 111-139 mmHg in males and 101-139 mmHg in females or a maximum dose of 800 mg is reached without adequate SBP response.

Primary Aim 1.2: Dose optimization, open-label trial to determine the proportion of subjects with SCI with a hypertensive response to droxidopa (Safety #1). Hypertension will be defined as a sustained elevation (≥ 30 consecutive minutes)

in seated SBP ≥ 140/100 mmHg or intolerable side effects considered related to study medication.
Secondary Aims: To determine the effect of the individualized optimal dose of droxidopa, compared to placebo, on (1) supine BP (Safety #2), (2) SBP during a head-up tilt (HUT) maneuver to 70° (Efficacy #2) and change in cerebral blood flow velocity (CBFv) from supine to HUT (Efficacy #3).

C. Background of Study Population - Clinical Information:
   a. Describe the general population from which you plan to recruit subjects for this study (i.e., Demographics of potential subjects):
   All eligible participants, including women and minorities, will be included in this investigation if they demonstrate an understanding of the study procedures, meet entrance criteria, and sign the informed consent. Individuals will be recruited from prior study participation and referral from primary physicians.

   b. Describe the medical condition in this population:
   Subjects have experienced a spinal cord injury, experienced muscle paralysis below the level of injury, and have a variety of secondary medical consequences such as cardiovascular disease, pressure ulcers, osteoporosis, and diabetes. In addition, it is not uncommon for them to have received an initial dual diagnosis of traumatic brain injury and SCI.

   c. How does this condition affect this population (symptoms)? **Depending on the level of injury subjects may have blood pressure dysregulation, elevated resting heart rate, reduced blood flow to the brain, and impaired cognitive function in addition to decreased levels of upper and/or lower body sensory and motor function.**

   d. Does this population have an understanding or knowledge of the medical condition being studied? **Many of the subjects who have been injured longer do have an understanding of their injury and the problems associated with it. Subjects who are acutely injured may not have been provided with a vast amount of knowledge on their injury but they will not be recruited for this study.**

   e. What is the traditional treatment provided for this condition?
   Traditional treatments address the secondary medical consequences of SCI via prevention and specific organ system therapies. Some individuals undergo experimental therapies in an effort to regain function.

   f. Explain how special needs that may arise with this population due to this medical condition are addressed (e.g. Additional care provided, supportive therapy, physiotherapy, behavioral therapy):
   We accommodate subjects as best as possible by providing physical assistance for transferring, preparing for the study, and completing study-related paperwork. In addition, all our resources (i.e., bathroom, desks and doors) are wheelchair accessible.

g. Describe how research subjects will be referred for appropriate care while they are enrolled in the study? **If, and when necessary, all participants will be referred to the appropriate clinical personnel given the medical concern presented.**

h. Describe whether providers (all clinical staff) have experience in providing care to subjects: **There are several physicians at the site that have been board certified for a number of years and have excellent experience.**

i. Does the James J. Peters VAMC have the appropriate medical or psychosocial resources required for any emergency needs for research subjects? **The JJPVAMC is an SCI center and cares for more than 300 veterans with SCI as both In-patients and outpatients; medical resources are available if emergently required.**

4. Selection of subjects:

a. Indicate number of subjects to be enrolled at this site **(Total # of subjects approved by IRB)**:

A total of 75 subjects will be screened (25 at JJPVAMC; 25 at ISMMS; 25 at KF). Of those 75 screened, 60 eligible subjects will be enrolled for study 1 (20 at JJPVAM; 20 at ISMMS; 20 at KF). From those 60 who complete study 1, A total of 30 will enrolled for study 2 between all sites.

b. Indicate total number of subjects to be enrolled, if multisite study:
A total of 75 subject will be screened. (25 at JJPVAMC; 25 at ISMMS; 25 at KF)
A total of 60 subjects will be enrolled for study 1. (20 at JJPVAM; 20 at ISMMS; 20 at KF)
A total of 30 subject will be enrolled for study 2. (between KF, ISSMS and JJPVAMC)

c. Are veterans being enrolled at this site?

YES	**X**	**NO**	

d. Are non-veterans being enrolled at this site?

YES	**X**	**NO**	

If no, proceed to question 4.f.
Justify why non-veterans will be enrolled at this site: **Non-veterans are being enrolled to meet the study's enrollment number and to broaden the population pool.**
Of all subjects to be enrolled at this site, what percentage will be non-veterans? **This number cannot be determined given the unknown demographics of patients at the site. However it is likely that a greater percentage will be non-veterans as the ISMMS is not a veteran care institution.**

e. Describe the setting in which the research will be conducted (e.g., research office, clinic, lab, inpatient unit, outpatient unit):

The study will take place at James J. Peter VA Medical Center in the Spinal Cord Injury Research Department in room 7A-13. All necessary equipment needed for the study is present in that department.
ISMMS: The research will be performed at Mount Sinai School of Medicine in the Klingstein Clinical Center (KCC) building on floor KCC2 in the Rehabilitation in-patient ward. All necessary equipment needed for the study is present in that department.
KF: The research will be performed at Kessler Foundation at the Kessler Institute for Rehabilitation, 1199 Pleasant Valley Way, West Orange New Jersey in the main building, Room L050. All necessary equipment needed for the study is present in that department.

f. What is the expected length of time a study subject will participate? (i.e., number of days, weeks, months, years) **Qualified subjects will come in for 10 visits, including the screening visit for study 1. They will then come in for an addition 2 visits for study 2 if they qualify. The approximate maximum length of time they would be participating in the study would be 11 weeks if they come in once a week.**

5. Indicate the characteristics of study population (with the letter x in the appropriate column):

a. Gender:

	YES	NO
Male	X	
Female	X	

b. Age range: from to [max age is 89 years]

c. Racial and Ethnic/Minority Groups:

	YES	NO
Caucasian	X	
Alaskan Native	X	
American Indian	X	
Hispanic	X	
Black	X	
Asian/Pacific Islander	X	

Other: (Specify)

d. Justify any exclusion of specific gender, age, and racial or ethnic groups:
N/A

6. State inclusion criteria for enrollment in study:
Study 1:
1) Male or Female, age 18 to 89 with traumatic SCI.
2) SCI Subjects (n=40):
   a) Any level of injury;
   b) Any AIS grade of SCI;

c) Non-ventilator dependent
d) Primarily wheelchair dependent for mobility;
e) Duration of injury < 1 year

3) Low Blood Pressure:

Systolic BP less than 110 mmHg and/or diastolic BP less than 70 mmHg for males;
Systolic BP less than 100 mmHg and/or diastolic BP less than 70 mmHg for females;

4) Primary Language is English.

Able to provide informed consent

Study 2:

5) Male or Female, age 18 to 89 with traumatic SCI.
6) SCI Subjects (n=40):
   a) Any level of injury;
   b) Any AIS grade of SCI;
   c) Non-ventilator dependent
   d) Primarily wheelchair dependent for mobility;
   e) Duration of injury < 1 year
7) Low Blood Pressure:

Systolic BP less than 110 mmHg and/or diastolic BP less than 70 mmHg for males;
Systolic BP less than 100 mmHg and/or diastolic BP less than 70 mmHg for females;

8) Primary Language is English.

Able to provide informed consent

9) Showed a normotensive blood pressure in response to Droxidopa during study 1.

7. State exclusion criteria for enrollment in study:

Study 1 and Study 2:

- Current illness or infection
- Individuals with frequent or severe autonomic dysreflexia
    a. More than 3 symptomatic events per week
    b. BP ≥140/90 mmHg
    c. Significant adverse subjective symptoms reporting
- Hypertension
- Any neurological condition other than SCI (Alzheimer's disease, dementia, stroke, multiple sclerosis, Parkinson's disease, etc.)
- History of epilepsy or other seizure disorder
- History of traumatic brain injury (TBI)
- Liver or kidney disease
- Bladder problems including blockage of the urine and/or weak urine stream.
- Diagnosis of a psychiatric disorder such as schizophrenia or bipolar disorder
- Known artery disease, heart failure, AV block, and irregular heartbeat
- Any allergies to droxidopa, asprin, polyethylene oxide, polyethylene glycol, hydroxypropyl cellulose, butylated hydroxytoluene, magnesium stearate, hypromellose, yellow ferric oxide, and red ferric oxide
- Major surgery in the last 30 days
- Illicit drug abuse in the past 6 months
- Pregnant
- Your prescription medications will be reviewed by the study investigators and research staff. If you are currently taking medications to treat any of the following please make the investigators aware:

d. Depression, Schizophrenia, ADHA
e. Pain (opioids)
f. Infection or illness (antibiotics)
g. Erectile dysfunction (Viagra, Cialis, etc.)
h. Overactive bladder
i. High or low blood pressure
j. Migraine headaches
k. Malaria
l. Ashtma

8. Will vulnerable subjects be enrolled in this study?

YES		**NO**	

	YES	**NO**
Individuals with lack of decision-making mental capacity		X
Economically/socially disadvantaged persons	X	
Educationally disadvantaged persons	X	
Pregnant women, for minimal risk only		X

Fetuses Requires Medical Center Director authorization. See IRB SOP.
Children Requires Medical Center Director authorization. See IRB SOP.
Prisoners Requires CRADO authorization. See IRB SOP.

If Yes for any answer, provide a means by which vulnerability is determined: **We will not be determining vulnerability; however, it is possible that an economically or socially disadvantaged individual may consent to participate in this study.**

9. Are prospective subjects likely to feel vulnerable to coercion or undue influence to enter the study?

YES		**NO**	**X**

a. Are there any payments to subjects?

YES	**X**	**NO**	

b. If No, proceed to question 9.c.
How much are the payments? **$25 for the screening session and $50 for the testing sessions for study 1 and study 2**

Provide a schedule (timing) of payments.
Study 1- up to $425.00
Visit 1 (1 hours)-$25.00
Visit 2 (5 hours)-$50.00

Visit 3 (5 hours)-$50.00
Visit 4 (5 hours)-$50.00
Visit 5 (5 hours)-$50.00
Visit 6 (5 hours)-$50.00
Visit 7 (5 hours)-$50.00
Visit 8 (5 hours)-$50.00
Visit 9 (5 hours)-$50.00

Study 2- up to $100.00
Visit 10 (5 hours)-$50.00
Visit 11 (5 hours)-$50.00

In your opinion, will such payments have any influence on a person's decision to participate?

YES		**NO**	**X**

Why or why not?
The subject stipend that is offered is not coercive and should not have any influence on the subject's decision to participate for the following reasons:

- **Payment for participation will not be discussed during the recruitment process unless a question is specifically asked by the participant.**
- **The stipend offered is as compensation for participants' time and travel; and is reasonable given the duration of testing.**

c. What special safety precautions are utilized to minimize risk of coercion to protect the rights and welfare of these subjects [e.g., avoid financial incentives, consult with patient advocates or representatives]? **Participants will be given many opportunities to ask questions and to review the consent with their primary care physicians.**

10. As PI, do you have access to sufficient population that will allow recruitment of the necessary number of subjects?

YES	**X**	**NO**	

11. Indicate how potential subjects will be recruited:
Potential participants will be recruited via primary care referral from a KF, ISMMS or JJP VAMC care provider or from prior enrollment in a research study. All subjects will be recruited in accordance with HIPAA and local IRB guidelines by the co-investigator by telephone or on the day of their regularly scheduled appointment.

12. Description of the Consent Process:
a. Describe the enrollment procedures for participation in the study:
Participants contact or are referred to a Co-investigator at KF, ISMMS and JJP VAMC and will provide information relative to the inclusion criteria. If the participant displays interest in participating, the co-investigator will thoroughly review the consent documents, and after the consent process is complete a testing date is scheduled.

b. Indicate when and where consent will be obtained:

The informed consent process will be conducted in the privacy of the research laboratory at a time that is convenient for the participant and research staff, prior to initiation of study procedures.

c. Who will conduct the consent interview?
Research staff members associated with the research protocol as listed on the assurance page will conduct the consent interview.

d. Will a legally authorized representative provide consent or permission for a subject, as appropriate?

YES	**X**	**NO**	

e. What is the waiting period between informing the prospective subject about the study and obtaining consent?
There is no defined waiting time between completion of the informed consent process and initiating study procedures. However, the informed consent process will be completed prior to initiating study procedures.

Time devoted to consent discussion? **The participant will be given adequate time to read the consent and ask questions. As long as necessary.**
Time allowed for a decision? **Subjects will be reminded that they may take the consent home and review it with their family and/or primary care physician. As long as necessary.**

f. How will you insure that the language used by those obtaining consent will not include exculpatory language which would waive or appear to waive any of the subject's legal rights? **The IRB approved consent will be read verbatim to the participant or translator. Participants will be asked to reiterate the study procedures and goals, any uncertainty will be clarified by study team members.**

g. How will you insure that the information being communicated to the subject or the representative during the consent process will not include exculpatory language through which the subject or the legally authorized representative releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence?
The consent form has information on the rights of the participant and the responsibilities of the investigator, the institution and/or its agents toward the participant as a consequence of his/her participation in the study. This consent form will be discussed with the participant in detail, and will clearly state the above-mentioned participant's rights and the investigator's/institution's or its agent's responsibilities in non-exculpatory language. Investigators and coordinators will have completed all mandatory training.

h. How will you know that the language is understandable to the prospective subject or the legally authorized representative?
Eligible participants will be given a copy of the consent to read through at home at their own leisure. After about one (1) week the investigator, or a representative, will call the participant to go over the details of the consent and ask if there are any questions prior to scheduling a study visit. Before signing the consent, potential participants or their surrogate will be asked to concisely reiterate what they understand about the study, its objectives, and the consent form in their own words in a clear, concise and accurate manner. Only after the investigator/representative has received signed informed consent, will studies be performed with any subject.

i. Indicate how you will determine whether the subjects (or their surrogates) understand the content of the information that is provided in the consent document:
Through open dialog with the study participant or his/her surrogate the investigator/representative will gain an understanding of the potential participant's ability to objectively discern the study procedures and his/her role in participating. The coordinator will emphasize the voluntary nature of participation in the study. Participants or their surrogate will be asked to reiterate what they understand the implications of their decision to, or not to, participate in the study are. If the participants or their surrogate demonstrate inability to communicate a decision, they will not be enrolled in the study and the consent process will cease.

j. How will you insure that the consent process will minimize the possibility of coercion or undue influence?
The relationship between study investigators and study participants is and will remain exclusively for the purposes of research. We maintain open dialog with the study participant or his/her surrogate at all times and as such we have an understanding of the potential subject's ability to objectively discern the study procedures and his/her role in participating. Reimbursement is allocated for the time investment in the research process for study participants and is not excessive. Participants will be afforded the opportunity to ask as many questions as they desire, speak to other individuals regarding their participation and schedule testing at their leisure.

13. Summarize what actually will be done to the subjects during their participation in the study:

a. Provide a clear description of what is being done for research purposes and what is being done as part of "usual care":
All procedures are being performed for research purposes.

b. Provide a detailed **list of tests and procedures** that will be performed for research purposes (e.g., blood tests, urine tests, cultures, interviews, questionnaires, surgical procedures, cardiac catheterization, pulmonary function tests, X-rays, scans, etc) during the course of the study. **List must indicate tests and procedures only for subjects who sign a VA consent form, regardless of where tests and procedures take place**:

Test /Procedure:	Where:	Performed by Whom: (Insert Name or TBD if not yet known)	When:	# of times:
Heart Rate and Breathing Rate	**KF:L050/JJP VAMC: 7A13/ISMMS: KCC2**	**Matt Maher Jaclyn Wecht Andrew Delgado Kristell Taylor Meghana Noonavath Daniel Vaccaro**	**All visits**	**Continuous**
Brachial Blood Pressure	**KF:L050/JJP VAMC: 7A13/ ISMMS: KCC2**	**Matt Maher Jaclyn Wecht Andrew Delgado Kristell Taylor Meghana Noonavath Daniel Vaccaro**	**All visits**	**1x/minute**
Finger Blood Pressure	**KF:L050/JJP VAMC: 7A13/ ISMMS: KCC2**	**Matt Maher Jaclyn Wecht Andrew Delgado Kristell Taylor Meghana Noonavath Daniel Vaccaro**	**All visits**	**Continuous**
Cerebral Blood Flow	**KF:L050/JJP VAMC: 7A13/ ISMMS: KCC2**	**Matt Maher Jaclyn Wecht Andrew Delgado Kristell Taylor Meghana Noonavath Daniel Vaccaro**	**2 visits**	**Continuous**
Orthostatic Hypotension (OH) questionnaire	**KF:L050/JJP VAMC: 7A13/ ISMMS: KCC2**	**Matt Maher Jaclyn Wecht Andrew Delgado Kristell Taylor Meghana Noonavath Daniel Vaccaro**	**All visits**	**Continuous**
Fatigue Survey	**KF:L050/JJP VAMC: 7A13/ ISMMS: KCC2**	**Matt Maher Jaclyn Wecht Andrew Delgado Kristell Taylor Meghana Noonavath Daniel Vaccaro**	**All visits**	**2x/visit**
Head-Up Tilt (HUT)	**KF:L050/JJP VAMC: 7A13/ ISMMS: KCC2**	**Matt Maher Jaclyn Wecht Andrew Delgado Kristell Taylor Meghana Noonavath Daniel Vaccaro**	**2 visits**	**1x/visit**
Plasma catecholamine collection (20mL)	**KF:L050/JJP VAMC: 7A13/ ISMMS: KCC2**	**Matt Maher Jaclyn Wecht Meghana Noonavath Daniel Vaccaro**	**2 visits**	**4x/visit**

c. If laboratory tests are part of this protocol, will some or all study-related tests be performed outside this medical center?

YES		**NO**		**N/A**	**X**

d. Provide a statement that defines who will be financially responsible for the costs associated with participation in the study (e.g., examinations, procedures, drugs, devices, etc.) and a statement that defines what will be provided without cost to the subjects:

Funds from the New York SCIRB program (Grant # DOH01-PART2-2017-00043) will be used for all expenses associated with the study (see attached Budget).

e. VHA Health Record (If yes to (i) below or if clinical resources are to be used, a VHA health record must be created in CPRS [VHA Handbook 1200.05 #29j).

(i) Will the research intervention possibly lead to physical or psychological adverse events?

YES	**X**	**NO**	

(ii) Do you have a process in place to include a copy of the signed informed consent and HIPAA authorization in the medical record for the type research described above for each subject?

YES	**X**	**NO**	

If yes, Please describe: **A copy of the signed informed consent and HIPAA authorization will be included in the medical record of each enrolled patient. A note will be entered into each enrolled subject's computerized medical record documenting the consent process and study progress/completion. In the case that a subject does not have a preexisting medical record; one will be created for research purposes.**

(iii) Did the IRB determine that CPRS flagging is required?

YES	**X**	**NO**	

14. Risks:

a. Identify study risk:

No Risk	
Minimal Risk	
Greater Than Minimal Risk	**X**

b. Describe the steps you could take to minimize risk to subjects, *without changing the science* of the study:

The scientific team has chosen the present design after consideration of a range of alternative procedures to gather the best quality of data possible while minimizing the risk of harm to the participants. All testing procedures will be performed by qualified and trained personnel, including the consenting process and data collection.

c. Could you use the data obtained from "usual care" so that tests are not repeated for research purposes (to minimize risk to subjects)?

YES		**NO**	**X**

d. Describe the steps you could take to minimize risk to subjects *by changing the science* of the study or study design:
Individual participant data will be reviewed in real time during clinical testing. If a problem arises in an individual subject or in a group of participants, the protocol will be modified in accordance. This information will be conveyed to the governing IRB within the appropriate time allotment depending on the severity of the adverse event.

15. Clinical Trials: If this study is a clinical trial (Part I, question 7) answer a-e, as applicable:

Has a description of this clinical trial been recorded on http://www.clinicaltrials.gov?

YES	**X**	**NO**	

a. Provide a list of investigational drugs that will be administered:
Droxidopa (trade name: Northera)

b. Is the investigational drug information record attached?

YES	**X**	**NO**	

If yes, please attach VA Form 10-9012. (Investigational Drug Informational Record) if not a marketed drug.
If a marketed drug, provide authorized prescribers: **William A Bauman, MD.**

c. Is an investigational drug used in research for new or different purposes compared to that which the FDA approved?

YES		**NO**	**X**

Is there an IND number for this drug?

YES	**X**	**NO**	

IND number or other status (submit validation or correspondence): **137213**
If there is no IND number, is there an FDA exemption? (If yes, please submit FDA correspondence.)? **See attached FDA IND letter.**

YES	**X**	**NO**	

d. Will investigational devices be used:
No.

Is there an IDE issued by the FDA? **N/A**

YES		**NO**	

IDE number or other status (submit validation or correspondence):
Is there an abbreviated IDE?

YES		**NO**	

If there is no IDE number, is there an FDA exemption? (If yes, please submit correspondence with FDA.)?

YES		**NO**	

How would you determine the risk-benefit analysis for investigational devices?

e. Risks for Investigational Drugs/Device:

For investigational drugs, what are the possible risks associated with the study drug relative to possible interactions with medications likely to be used by subjects? **Following droxidopa, administration BP may elevate above the normal range (>140/90 mmHg). In addition, symptoms of autonomic dysreflexia (AD) may become frequent or worsen while taking the study medication. Clinical staff will assist the subject to an upright seated position, loosen any tight clothing or braces that the subject is wearing and may check and empty your bladder and bowel. If BP remains high for more than 30 minutes the subject will be provided with a medication to lower their pressure. The medication of choice will be a nitropaste (Nitroglycerin Ointment, 2%) that will be placed one inch on the subjects forehead.**
Droxidopa risks (≤8% likely) include: slow or fast heartbeat, pounding in the ears, low back or side pain, and nervousness.
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.
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.

What will your approach be to such risks? **Study personnel and clinical staff will monitor BP daily during the study participation period.**
Will such subjects be excluded from the study? **No.**

Have you reviewed scientific literature or relevant FDA and Sponsor Advisories alerts or warnings relevant to this medication/device?

YES	**X**	**NO**	

If there was any new information, what were the possible risks to subjects based on this information? **Not that we are aware of.**
If there was any new information, how were potential benefits for subjects affected by this information? **Not that we are aware of.**

If new information is received from the FDA or Sponsor that may affect the conduct of this study, would you be willing to change the study design or study procedures?

YES	**X**	**NO**	

How will you inform subjects of any relevant information from the FDA or Sponsor Advisories? **If relevant information regarding droxidopa, is published, all participants enrolled in the study will be notified, in person, by either the PI or study coordinator.**

What advice will you provide to subjects if there are questions on continuing participation in the study? **The study team will provide participants with the necessary information in order to make an informed decision, should more risk arise through FDA information. Participants can speak with the study team about any questions they may have on continuing involvement in the study.**

16. Research Safety:

a. Describe your Data Safety Monitoring Plan for subjects (3-4 sentences):
During testing, an investigator/research staff member will be present with the participant at all times. Participants will be asked frequently about symptoms during the study.
Participants will be informed of how they may feel and that if they are uncomfortable, to inform the investigator as soon as possible.

b. What information will you be collecting for AEs/SAEs and what is your plan for reporting these to the IRB?
All AEs and SAEs will be reported to the IRB either via the AE/SAE form or as part of the AE log on the annual continuing review application in accordance to local IRB policy.

How will you monitor adverse events? **Study investigators will meet on a weekly basis to monitor and evaluate all adverse events, and to determine if changes to the study protocol need to be made, based on this information.**

c. Provide a plan for periodic review of safety of research subjects and data:
Safety information will be collected in the 1) case report forms, 2) study visit documents, and 3) via telephone follow-up calls. All data will be monitored. Data will be collected during scheduled study visits (weekly). Cumulative data will be reviewed on a monthly basis.

d. Describe how you will determine whether the study should be continued in light of emerging information:
If the current risk/benefit ratio shifts at any time during the study, the research protocol will be modified or discontinued immediately.

e. Is there a Data Monitoring Committee (DMC) or a Data Safety Monitoring Board (DSMB)?

DMC		**DSMB**		**NO**	**X**

If no, proceed to question 17.

Describe your DMC or DSMB, including frequency of reporting:
Describe how the DMC or DSMB will communicate with the IRB:

17. Data Analysis and Sample Size:

a. Describe the analysis that will be performed on the data:
<u>Primary Aim 1.1:</u> Dose optimization, open-label trial to determine the proportion of subjects with SCI with a normotensive response to droxidopa (Efficacy #1). Normotension will be defined as an average systolic BP (SBP) recorded 60-120 minutes after dose administration of between 111-139 mmHg in males and 101-139 mmHg in females.
•Hypothesis 1.1 – Seated SBP will be normalized in 60% of the study sample following administration of droxidopa.
- **This hypothesis will be tested by constructing a 95% confidence interval about the sample proportion of cases in which BP is normalized with**

droxidopa. The inclusion of the 60% value in the confidence interval will be taken as evidence in support of the hypothesis. Further, the point estimate and confidence interval will provide the first reported estimate of the BP normalizing effect of droxidopa in the population with SCI.

Primary Aim 1.2: Dose optimization, open-label trial to determine the proportion of subjects with SCI with a hypertensive response to droxidopa (Safety #1). Hypertension will be defined as a sustained elevation in seated SBP ≥ 140/100 mmHg or intolerable side effects considered related to study medication

•Hypothesis 1.2 – Less than 10% of the study sample will exhibit hypertension or intolerable side effects related to administration of droxidopa.

- **This hypothesis will be tested by constructing a 95% confidence interval about the proportion of cases in which either seated BP ≥ 140/100 or intolerable side effects occur. If the 95% CI excludes values ≥ 10%, this will be taken as evidence in support of the hypothesis. Further, the point estimate and confidence interval will provide the first reported estimate of the expected side effects of droxidopa treatment in the population with SCI.**

Secondary Aims: To determine the effect of the individualized optimal dose of droxidopa, compared to placebo, on (1) supine BP (Safety #2), (2) SBP during a head-up tilt (HUT) maneuver to 70° (Efficacy #2) and change in cerebral blood flow velocity (CBFv) from supine to HUT (Efficacy #3). The following hypotheses will be tested in hypotensive individuals with SCI:

•Hypothesis 2.1A – Average supine SBP will be significantly increased following droxidopa administration compared to placebo.

- **This hypothesis will be tested using a repeated measures analysis of covariance where the pre-droxidopa or placebo SBP will be used as the covariate and the adjusted post-test scores will serve as the dependent variable. In addition, the covariate adjusted point estimate and 95% confidence interval of the difference between drug conditions will provide the first reported estimate of the supine SBP response to droxidopa versus placebo in the SCI population.**

•Hypothesis 2.1B – The proportion of supine BP observations ≥140/100 mmHg following droxidopa administration will not differ significantly from the proportion observed during the placebo trial.

- **This hypothesis will be tested by performing separate (one each for systolic and diastolic pressure) tests of the differences between dependent proportions, from which the 95% confidence intervals will be calculated. The presence of zero in a confidence interval will indicate a lack of statistical difference in incidence of hypertensive events between the droxidopa and placebo conditions.**

•Hypothesis 2.2 – Average SBP during 70° HUT will be significantly increased following droxidopa administration compared to placebo.

- **This hypothesis will be tested by performing a dependent t-test between the mean SBP during 70° HUT comparing droxidopa to placebo. Further, the point estimate and resulting 95% confidence interval will provide an estimate of the SBP response to HUT of droxidopa versus placebo in the SCI population.**

<u>Hypothesis 2.3</u> – The change in CBFv from supine to HUT will be significantly attenuated following droxidopa administration compared to placebo.

- **This hypothesis will be tested using a repeated measures analysis of covariance where the pre-HUT CBFv will be used as the covariate and the adjusted post-HUT CBFv scores will serve as the dependent variable. In addition, the covariate adjusted point estimate and 95% confidence interval of the differences between drug conditions (droxidopa vs. placebo) will provide the first reported estimate describing the effect of droxidopa on the CBFv response to HUT.**

<u>Hypothesis 2.4</u> – Plasma renin and serum aldosterone concentrations will be reduced and plasma norepinephrine concentrations will be increased during HUT following administration of droxidopa compared to placebo.

- **These hypotheses will be tested using a repeated measures analysis of covariance where the pre-HUT concentrations will be used as the covariate and the adjusted post-HUT concentrations will serve as the dependent variable. In addition, the covariate adjusted point estimate and 95% confidence interval of the differences between drug conditions (droxidopa vs. placebo) will provide the first reported estimate describing the effect of droxidopa on these vasoactive substances in response to HUT.**

b. Provide power analysis or describe how sample size was determined:
This is a pilot trial to determine the dose efficacy and safety of droxidopa to increase systemic BP and improve orthostatic BP and CBFv responses compared to placebo in hypotensive individuals with SCI.
Because this is a pilot trial, the following statistical analyses are not powered for a specific effect size; however, the results will be used to power a subsequent large scale clinical trial to identify the utility and safety of droxidopa for treatment of asymptomatic hypotension in persons with SCI.

18. Community-based Participatory Research

Is this research based on Community-based participation?

YES		**NO**	**X**

If Yes, answer questions (a-h). If No, proceed to Question 19.

a. Describe the community that will be involved in this research:

b. What is the role of the community in this research?

c. Does this research include a community organization that is engaged in research?

YES		**NO**	

If Yes, does that organization have a Federal Wide Assurance (FWA)?

YES		**NO**	

d. Describe any part of this community-based research that an outside IRB will review:

e. Describe the risks to the community as a result of this research:

f. Do you have a plan for disclosure of individual results to research participants?

YES		**NO**	

If Yes, please describe:

g. Describe who will have access to study data if multiple groups are involved:

h. Is there an agreement for this research (e.g. CRADA, subcontract) or a data ownership agreement?

YES		**NO**	

If Yes, please provide details:

19. Advertisements:

a. Are you submitting advertisements for IRB review?

YES		**NO**	**X**

If yes, attach previously stamped ads.

20. Privacy:

a. Explain the plan to protect Privacy and the Privacy Interests of subjects: (1)Environment/Sharing of information (Time and place for study activities (e.g., potentially stigmatizing locations, such as a clearly identified pregnancy counseling center), nature of the information given, who receives and can use the information and whether information sought is of legitimate interest to the researcher): **Study**

procedures and data collection will be performed at Kessler Foundation at the Kessler Institute for Rehabilitation, West Orange, New Jersey, Mount Sinai School of Medicine in Manhattan, New York and at the James J Peters VAMC. Participants enrolled in this study have regular occurring appointments at these facilities and are used to the environment within them. Information will be given either in the SCI research lab at a scheduled time convenient to the research staff and the participant. Patients may have to provide information regarding personal medical history and will be reassured that all information will be kept according to HIPAA regulations.

(2)Subject's expectation of privacy, comfort in the research setting, comfort with research procedures: **Participants that we are recruiting are aware of the location. Every attempt will be made to assist participants to reduce any discomfort with the research setting and or procedures.**

b. Data Use (**Please also submit a completed Research Data Inventory Form**):
Is data shared with external parties?

YES	**X**	**NO**	

If Yes, answer the following. If No, proceed to question 20.c.
Is there a Memo of Understanding with the external facility?

PENDING		**EXECUTED**		**NO**	**X**

Is there a Data Use Agreement?

PENDING		**EXECUTED**	**X**	**NO**	

Indicate any other data agreements:

PENDING		**EXECUTED**		**N/A**	**X**

c. Signature and Date:
Are subjects incompetent or do they lack decision making capacity?

YES		**NO**	**X**

If Yes, is there a signature line on the HIPAA authorization for the person legally authorized in writing by the individual or the individual's legal guardian?

YES		**NO**	

d. HIPAA Waiver:
Is a HIPAA waiver being requested?

YES	**X**	**NO**	

***** Please note that a HIPAA Waiver is <u>ONLY</u> being requested for individuals who lack upper limb function, incapable of writing/signing their name and that their assent will be witnessed. See attached approval***
If No, proceed to 20e.

(a) Is there a written plan to destroy identifiers at the earliest opportunity consistent with conduct of the research?

YES	**X**	**NO**	

Records Retention Schedule Number DAA-0015-2015-004-0032 Item 7.6. "Records are to be destroyed 6 years after cutoff, may retain longer if required by other federal regulations."

e. Specimens:
Are you collecting specimens (Blood, saliva, tissue, etc.) in this study?

YES	**X**	**NO**	

Will you send specimens off site for analyses? (Material Transfer Agreement may be required)

YES		**NO**	**X**

If yes, please indicate how transporting specimens, who will transport and list name of institution, address and contact information for person(s) in charge of receiving, storing and processing of specimens at external site. Please also indicate how long specimens will be stored (for specimen storing), if all specimens will be used up or whether or not unused specimens will be destroyed, when they be destroyed, remaining specimens shipped back to PI at a later date, keep specimens stored indefinitely, whether or not specimens will be shared with other researchers (for specimen banking), for future analyses, etc.

If NOT sending specimens off site, please list procedure for storage, handling, by whom, destroying, length of time storing and whether or not specimens will be used for future research. **VA staff will draw blood from a vein in the arm or hand four times for both of the Study 2 visits. One sample will be taken in the supine position after baseline hemodynamic data collection, 2 samples will be collected when tilted to 70º and one sample will be taken in the seated position. A total of 80 ml BP Vacutainers will be collected during both of the visits for study 2 (4 green EDTA). A small needle will be inserted into the vein to collect blood. Once the blood has been collected, the needle will be removed and the puncture site will be covered. Samples will be immediately spun, down plasma separated and stored at -80 º C for subsequent high-performance liquid chromatography (HPLC) analysis of plasma renin, serum aldosterone and plasma norepinephrine concentrations which will be performed at the at JJPVAMC 1F-11 research lab.**

Does the study documentation state when specimens will be labeled with identifiable or de-identified information?

YES	**X**	**NO**	

f. De-Identification of Data:
Does the protocol indicate whether or not data will be de-identified?

YES	**X**	**NO**	

Data is coded, but a link between the coded data and subject PHI will be generated using subject ID. The link between PHI and coded data will be kept secure and separate from the coded data behind locked doors in locked cabinets. Access to the link will be limited to VA staff affiliated with the study at Kessler and Mount Sinai.

If so, please indicate all that apply. If no, proceed to question 20.g.

De-identified information is provided to PI (who has access to IIHI) by his/her research team per a HIPAA authorization or waiver of authorization.	X
De-identified information is provided by PI (who has access to IIHI) to his/her research team per a HIPAA authorization or waiver of authorization.	X
De-identified information is to be sent to non-VA research team member, such as a statistician.	

De-identified information will be disclosed to a non-VA party. If so, please identify: **Dr. Miguel Escalon, Mount Sinai School of Medicine; See attached DUA**	X

g. VA sensitive data:

(a) Is VASI shared with parties external to JJP?

YES	**X**	**NO**	

If Yes, is a Data Use Agreement (DUA) in place for this activity? (NOTE: See the Privacy Officer regarding DUA's.)

YES	**X**	**NO**	

(b) Have all research staff who will transport, transmit, download, and/or store VA sensitive information (all formats and media, see VHA Handbook 1200.12, Definitions) outside of the VA protected environment obtained written approval from their immediate supervisor and JJP ISO (see the ISO for form "Authorization to Transport and Utilize VA Sensitive Information Outside Protected Environments"?

YES	**X**	**NO**	

If yes, please name individuals who have received authorization: **Jill M. Wecht EdD, and Matthew Maher MS, see attached approvals.**

(c) Collected or stored in hard copy outside of the James J Peters VAMC:

YES	**X**	**NO**	

If Yes, how will it be protected? **PHI information and consent forms will be stored temporarily in a locked cabinet at the Mount Sinai School of Medicine, KCC Floor 2. VA consents form will be hand delivered to the VA in a locked briefcase at approximately monthly intervals, and are stored behind locked doors in a locked file cabinet at the VA. Case report forms and data collected will be kept in a separate locked cabinet Mount Sinai School of Medicine will be hand delivered back to JJPVAMC by the VA staff from JJPVAMC and stored in a locked file cabinet behind locked doors in the JJP VAMC Rm. 7A-13. PHI information and consent forms will be stored temporarily in a locked cabinet at the Kessler Institute of Rehabilitation, Main Building, Room L2100. Case report forms and data collected will be kept in a separate locked cabinet at the Kessler Institute of Rehabilitation, Main Building, Room L2100. VA consents form will be hand delivered to the VA in a locked briefcase at approximately monthly intervals, and are stored behind locked doors in a locked file cabinet at the VA.**

Please note that while the study is also being conducted at KF and ISSMS, the study itself is a VA funded study and is being done by VA employees offsite. Electronic data are collected with VA IRM issued laptops and hard copies are temporarily stored at ISSMS in locked file cabinets behind locked doors in KCC 2 and at KF in locked file cabinets behind locked doors in L2100. Electronic data and hard copies will be hand delivered in a locked briefcase back to JJPVAMC by the VA staff from JJPVAMC and stored in a locked file cabinet behind locked doors in the JJP VAMC Rm. 7A-13.

(d) Stored on non-VA computers or non-VA electronic media outside or inside the James J Peters VAMC:

YES		**NO**	**X**

If YES TO ANY OF THE FOUR PRECEDING QUESTIONS, answer i-ii below:

i. Are VA sensitive data in hard copy shared with parties specified in the consent form?

YES		NO	X

Are documents sent with a chain of custody (registered mail, FEDEX, UPS) or hand carried?

YES	X	NO	

If Yes, please specify: **Hand carried**

ii. Is VA sensitive data sharing/transmission with parties specified in the consent form FIPS 140-2 compliant using encryption provided by VA (IRM)?

Transferred using data storage media (e.g., CD, USB flash "thumb" drive):

YES	X	NO	

If Yes, please specify type of media: **IRM issued computer with encrypted USB flash thumb drive**

Transferred using electronic data transfer (e.g., email with PKI):

YES	X	NO	

If Yes, please specify type of electronic data transfer: **Electronic data (coded) is transferred by email with PKI or by encrypted USB flash thumb drive to VA intranet on the S-drive for Dr. Wecht's research team to analyze.**

h. Protection of Media Stored at Alternate Site:

Will VA Sensitive Information be removed from the VA Protected Environment?

YES		NO	X

Does the study team plan to store VA sensitive information outside the VA protected environment?

YES		NO	X

If Yes, by what method it will be protected? **At Mount Sinai School of Medicine, New York, NY, VA sensitive information (PHI information and consents) will be completed at ISSMS. PHI information including consent forms are hand delivered in a locked briefcase to JJPVAMC, by VA staff and will be stored in a locked file cabinet behind locked doors in the JJP VAMC Rm. 7A-13. At Kessler Foundation at Kessler Institute for Rehabilitation in West Orange, NJ, VA sensitive information (PHI information and consents) will be completed at Kessler Institute. Before the PHI information including consent, form are hand delivered to JJPVAMC, the VA consent forms will be stored at Kessler Institute in a locked room (L2100) in a locked cabinet.**

i. Data Repositories:

Is any data collected for this study to be shared with any other research study?

YES		NO	X

Does this study use data that is collected under a separate research study?

YES		NO	X

If Yes, provide Protocol #: MIRB #: or non-VA entity.

NOTE: If Yes for either question, please complete items a-d below for Data Research Repositories. See R&D Committee Procedures Manual, IRB SOP, and VHA Handbook 1200.12 regarding compliance with VA Research Data Repository requirements.

(a)If the repository received data, what were the sources of data being added to the research repository and the protocol(s) under which they were collected?

(b)If the repository shared data, what were the type of data released to others for use, the protocol(s) under which they were used, and the planned disposition of the data once the protocol is terminated?

(c) Were there any events involving risk to subjects or others, such as a breach of privacy or confidentiality?

(d) Were there any findings linking a negative impact on the health status of individuals in the data repository with identified causal factors, including whether there may be a clinical intervention?

21. Information Security:

a. Software:
Will specially obtained software be used?

YES		**NO**	**X**

If Yes, please identify:
Source of the software
Will a license be required?
How will a license be funded?
What data will be stored in temporary files on computer hard drives?

b. Web applications: (used for such purposes as recruiting subjects, completing questionnaires or processing data)

YES		**NO**	**X**

If Yes, please identify:
Web application's security features:

c. Incident Reporting:
Are procedures in place, in accordance with VA policy, for reporting incidents, i.e. theft or loss of data or storage media, unauthorized access of sensitive data or storage devices or non-compliance with security controls?

YES	**X**	**NO**	

If Yes, please describe the procedures, and briefly describe how they are conveyed to research staff. **All research staff handling data are HIPAA, GCP and HRPP trained and are aware that they must immediately report theft or loss of VA sensitive data or media containing VA sensitive data to the VA Information Security Officer (ISO) and Privacy Officer.**

DATA:
a. Data Flow:
Describe the data collection, data flow and/or data management process that will be used for the study: **Participant's PHI information and consent forms are stored separately from coded research data in a locked file cabinet behind locked doors. Access to the link will be restricted to VA staff listed on the assurance pages. Every subject has a data sheet with coded ID numbers, which is kept in a separate file cabinet from PHI. The key linking participants' names and IDs are kept in separate (from PHI) in locked cabinets behind locked doors and the keys are in the possession of VA employees along with the case report forms and data collection sheets.**

At the ISSMS hard copy data is temporarily stored in a locked file cabinet in the lab room in the Klingstein Clinical Center (KCC) building on floor KCC2. VA consents form will be hand delivered to the VA in a locked briefcase at approximately monthly intervals, and are stored behind locked doors in a locked file cabinet at the VA. Case report forms and data collected will be kept in a separate locked cabinet Mount Sinai School of Medicine will be hand delivered back to JJPVAMC by the VA staff from JJPVAMC and stored in a locked file cabinet behind locked doors in the JJP VAMC Rm. 7A-13.

At the JJ PVAMC hard copy data is stored in a locked file cabinet in room 7A-13D.
At Kessler hard copy data is stored in a locked file cabinet in the main building room L2100.

Coded electronic data is stored behind the VA firewall on the s-drive in password protected folders. Real-time data is collected on a VA issued password-protected laptop that is not connected to the internet by VA trained and certified staff. Once data collection is complete the raw data files are transferred to a VA IRM computer via a VA password protected thumb drive. VA research data will not be stored on any computer other than a VA issued laptop, VA issued thumb drive and on the VA network behind the VA firewall.

b. Data Security Plan:

Will Electronic Data be stored?

YES	**X**	**NO**	

If Yes, please explain how it will be secured: **VA firewall on the s-drive in password protected folders. Real-time data is collected on the hard drive by a VA issued, password protected lap top computer that is not connected to the internet. The raw data is transferred to a VA IRM computer via a VA password protected thumb drive. A coded database will be sent to the PI at JJPVAMC by transferring the data via a VA password protected thumb drive to a VA IRM computer to the shared drive.**

Will Paper records be stored?

YES	**X**	**NO**	

If Yes, please explain how it will be secured: **Paper records of VA sensitive data are collected and used in the ISMMS Medicine in the Klingstein Clinical Center (KCC) building on floor KCC2 in the Rehabilitation in-patient ward, Kessler Foundation at Kessler Institute for Rehabilitation and stored in locked cabinets in locked rooms in the Main Building, Rooms L2100 and JJP VAMC (room 7A-13) will be stored in locked cabinets in locked rooms. Any code linking identities to data will be stored separately from the data, electronically behind restricted access computers or hard copy in a locked cabinet in a locked room inside ISMMS, KF and the JJP VAMC.**

c. Data on a Hard Drive:

Will VA research data be stored on a computer other than the VA network?

YES	**X**	**NO**	

If Yes, will it be encrypted?

YES	X	NO	

If Yes, will data that is stored outside the VA network be backed up regularly and securely stored on the VA network?

YES	X	NO	

d. Storage Location:
Identify share drive folder name where electronic data will be stored: **All de-identified data will be stored on the shared drive in "SCI Research\CardioAutonomic Program\WEC-17-42 Droxidopa"**

Identify location (facility, room number) where hard copy data will be stored: **JJPVAMC: 7A-13; ISMMS: temporarily stored Klingstein Clinical Center (KCC) building on floor KCC2; KF: Kessler Institute for Rehabilitation, Main Building, Rooms L2100.**

e. Data Transmission:
Will sensitive electronic information be transmitted? (Note: VA sensitive data or information may only be transmitted using VA-approved solutions such as FIPS 140-2 validated encryption)

YES	X	NO	

If Yes, please provide the method of transmission: **Encrypted email with PKI or IRM issued encrypted thumb drive.**

f. Data Backup:
Will original electronic VA research data stored on a mobile device be backed up regularly and stored securely within VA's protected environment?

YES	X	NO		N/A	

Will original electronic VA research data stored outside the VA protected environment be backed up regularly and stored securely within VA's protected environment?

YES	X	NO		N/A	

g. Shipping Data:
Will hard copy, electronic research data, or any encrypted media be sent via delivery service with a chain of custody?

YES	X	NO		N/A	

If Yes, please describe chain of custody: **For this multi-site study, being conducted at the JJP VAMC, KF at the Kessler Institute for Rehabilitation in West Orange, NJ, and the ISMMS Medicine in NY, VA sensitive information (PHI information and consents) will be completed at KF and ISMMS. VA PHI information including consent form are hand delivered to JJPVAMC in a locked briefcase once a month by a VA employee part of the research staff.**

Is sensitive electronic research data that must be sent via common carrier (e.g., USPS, UPS, Fedex) encrypted with FIPS 140-2 validated encryption?

YES		NO	X	N/A	

Sensitive electronic data is not sent via common carrier. Sensitive electronic data is only sent from a VA laptop computer with VA firewall and an encrypted via email with PKI or via a VA password protected thumb drive to a VA IRM computer to the shared drive.

h. Data Return (If no data is sent offsite, enter x here and proceed to i.):

What VA information will be returned to the VA? **For this multi-site study, being conducted at the JJP VAMC, KF at the Kessler Institute for Rehabilitation in West Orange, NJ and the ISMMS Medicine in NY, VA sensitive information (PHI information and consents) will be completed at KF and ISMMS Institute. VA PHI information including consent form are hand delivered to JJPVAMC in a locked briefcase once a month by a VA employee part of the research staff.**

Coded data is given to the PI at the JJP VAMC VAMC by transferring the data from a VA laptop computer with VA firewall and encryption via a VA password protected thumb drive to a VA IRM computer to the shared drive. Additionally, copies of the data recording sheets (which have no identifiers other than subject ID) will be hand delivered to the VA PI by a VA employee part of the research staff once a month.

How will the information be returned to the VA? **For this multi-site study, being conducted at the JJP VAMC, KF at the Kessler Institute for Rehabilitation in West Orange, NJ and the ISMMS Medicine in NY, VA sensitive information (PHI information and consents) will be completed at KF and ISMMS. VA PHI information including consent form are hand delivered to JJPVAMC in a locked briefcase once a month by a VA employee part of the research staff.**

Coded data is transferred to Dr. Wecht, the VA PI using VA email with encryption or the data are transferred from a VA thumb drive directly to the VA intranet s-drive behind the VA firewall. Additionally, copies of the data recording sheets (which have no identifiers other than subject ID) will be hand delivered to the VA PI by a VA employee part of the research staff once a month.

i. Termination of Data Access:
Will access to research study data be removed for study personnel when they are no longer part of the research team?

YES	**X**	**NO**	

j. Per CRADO memo "Creation of Research Data Inventory to resolve OIG report 11-01823-294" of January 15, 2015, please submit a "Research Data Inventory Tool" to accompany this application. This tool may be found on the Research intranet page under Other Forms.
Is a form being submitted with this application?

YES	**X**	**NO**	

EQUIPMENT:
a. Will any portable, mobile or wireless devices be used for research purposes?

YES	**X**	**NO**	

If No, proceed to Question m.
If Yes, are all these devices encrypted?

YES	**X**	**NO**	

How are these devices backed up? **Data on these devices are backed up on the VA IRM computer hard drive, VA, password protected computer without internet access and on the s-drive.**
Is the encryption FIPS 140-2 validated (required)?

YES	**X**	**NO**	

Has the investigator's immediate supervisor and the CIO authorized use of any such devices (contact the CIO for procedures)?

YES	**X**	**NO**	

b. Has all equipment owned by an affiliated institution, or purchased by such institution from grant funds, and used by the Investigator in this research project at JJP, been reported to the CIO (reporting to include: Type of equipment, Manufacturer, Model, Serial Number, PO Number, Vendor, Asset Value, Acquisition Date, Researcher's Service, and Location (Room Number)?

YES	**X**	**NO**	