Title: SGB CA Study

PROTOCOL TITLE:

Effects of Stellate Ganglion Block on Vasomotor Symptoms in Women Receiving Anti-Estrogen Therapy for Breast Cancer

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1.0 Objectives

1.1 Research Aims:

Vasomotor symptoms (VMS) affect up to 65% of breast cancer survivors and negatively impact their quality of life. VMS in African American and Latino women are significantly more severe as compared to Caucasian women. Symptom management should be a priority in Women's Health research. Few effective treatments for VMS are available. Stellate ganglion blockade (SGB) with local anesthetic, previously performed for chronic pain indications, has shown promise as a treatment for women with VMS in previous clinical trials, but has not been investigated in women with breast cancer receiving anti-estrogen therapy in a randomized, sham-control study.

We aim to evaluate the benefit of SGB in symptomatic women with breast cancer seeking relief from moderate to very severe VMS that are adversely affecting health and wellbeing.

Scope: Women with breast cancer on Tamoxifen, aromatase inhibitors or SERMs with moderate to very severe VMS will be enrolled as participants in this study.

Hypotheses:

The frequency and intensity of subjective and objective VMS will be significantly lower in women randomized to active SGB as compared to sham controls. Mood, memory, cognition, sleep, and quality of life will all be improved in the treatment group as compared to the sham-control group.

Specific Goals and Objectives:

Goal 1: To determine the effect of stellate ganglion blockade (SGB) for reducing subjective and objective VMS in women with breast cancer on tamoxifen, AIs, or SERMs

Goal 2: To evaluate the effect of SGB on mood, memory, cognition, sleep and quality of life in women with breast cancer on tamoxifen, AIs, or SERMs.

Goal 3: Using the results of this pilot study, we plan to submit an R01 grant to the National Cancer Institute for a larger scale study.

2.0 Background

VMS (hot flashes and night sweats) are common in women with breast cancer in those treated with tamoxifen, aromatase inhibitors, selective estrogen receptor modulators (SERMs) and other chemotherapy[1-6]. To many of these women, these symptoms are severe and intolerable, with a significant decrease in quality of life[4]. VMS are also more common in African American and Latino women[3]. Most importantly, VMS may be a factor in premature discontinuation of anti-estrogens therapy for women with breast cancer.

2.1 Describe any relevant preliminary data.

Uncontrolled studies have demonstrated improvements in the frequency and intensity of VMS following stellate ganglion blockade (SGB) with local anesthetic, with effects ranging from 45-90% reduction for 6 weeks to several months[8-10]. These same studies showed improvements in sleep quality as well.

The stellate ganglion is a neural structure in the anterior cervical spine region and is part of the sympathetic nervous system. It has been injected safely in the practice of pain management for more than 50 years in cases of post herpetic neuralgia (shingles), complex regional pain syndrome (CRPS) and other painful neuropathies. Prior studies have confirmed connections between the stellate ganglion and the insular cortex and hypothalamus via third order neurons.

2.2 Describe the relevant prior experience and gaps in current knowledge

We recently published a prospective, randomized, sham controlled study of SGB in women with natural or surgical menopause, in which we found a 52% decrease in moderate to very severe VMS in women who underwent a single SGB with bupivacaine, a local anesthetic, as compared to a 4% decrease in women in the sham control group who underwent an injection of saline[11]. We also identified statistically significant improvements in objective hot flashes, measures of verbal learning and trends toward improved depression in the SGB treatment group, whereas such beneficial effects were not seen in the sham control group.

Only one controlled study of SGB in women with breast cancer has been published to our knowledge[14]. Patients with at least one month of VMS underwent either an image-guided stellate ganglion injection at the C7 level with 0.5% bupivacaine 10mL, or were prescribed pregabalin, a membrane stabilizer found to diminish vasomotor symptom in some patients, at 75 mg twice daily, and were followed for 3 months. Participants recorded the intensity and frequency of hot flashes in a diary. Both treatment groups were observed to have considerable reductions in frequency and intensity of VMS, but there was no control group in the study design and the randomization method was not described[14]. As it is well known that the placebo effect in hot flash studies can be dramatically high, more than 60% in some reports[15], it is important to use a study design that evaluates the placebo effect of any treatment.

Our prior work demonstrated a significant treatment effect with SGB for VMS. In addition to the fact that VMS are typically more severe and bothersome in breast cancer patients, VMS symptoms can be a factor in patients stopping breast cancer treatment. We feel it is important to study the effects of SGB in this patient population using a randomized sham-control study design.

2.3 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge

Very few effective treatments are available for VMS, and racial and socioeconomic disparities significantly decrease access to treatments that are available. Although hormone therapy (HT) remains a highly effective treatment for VMS in some menopausal women, HT is contraindicated in breast cancer patients, breast cancer survivors, and those at risk of breast cancer or other hormone sensitive malignancies.

Non pharmacologic treatments like botanicals, acupuncture, yoga, and lifestyle interventions have shown little to no improvements in VMS symptoms in clinical trials. Although Brisdalle (Paroxetine, an anti-depressant) was recently approved by the FDA in 2013 for the treatment of VMS in menopausal women, fairly low efficacy of this therapy as compared to placebo is seen and intolerable side effects are attributed to this class of drugs (weight gain, decreased libido and anorgasmia).

The exact mechanism of SBG is not fully understood. Treatment with SGB is based on the interruption of the sympathetic nervous system, changes in blood flow and modulation of norepinephrine (NE) levels or nerve growth factor (NGF) in the thermoregulatory regions of the brain. As well, remodeling or modulation of neural receptor systems or feedback systems involving the stellate ganglion and the insular cortex, the thermoregulation and homeostatic control centers in the brain1[15, 16] are likely being affected.

In this study, we aim to assess the effects of SGB on subjective and objective VMS, mood, memory, cognition, sleep and quality of life in women with breast cancer using tamoxifen, aromatase inhibitors or SERMS in a prospective, randomized, sham-control study, with a six month follow up.

3.0 Inclusion and Exclusion Criteria

3.1 Describe how individuals will be screened for eligibility.

Patient entry, exclusion and dropout criteria:

a. <u>General inclusion criteria include</u>

1. aged 30 to 75 years
2. 28 or more reported moderate-to-very severe hot flashes per week
3. a minimum of two weeks of VMS diary recording prior to SGB
4. current use of tamoxifen, aromatase inhibitors, or SERMs for a breast cancer indication for at last six months

5. willingness to undergo fluoroscopy-guided SGB or sham treatment.
6. if participant is on an SSRI or SNRI, they must be on a \ stable dose of SNRI or SSRI for previous six month
7. approval of treating psychiatrist or psychologist to participate in study if Depression and Anxiety Scale Score (DASS) score is ≥ 21 for depression or ≥15 for anxiety

b. <u>General exclusion criteria include:</u>

1. conditions that preclude SGB or sham intervention (e.g., anatomic abnormalities of the anterior neck or cervical spine; goiter, cardiac/pulmonary compromise; acute illness/infection; coagulopathy or bleeding disorder; allergic reactions/contraindications to a local anesthetic or contrast dye);
2. use of treatments in the past two months that can affect VMS (e.g., use of oral or transdermal HT or contraceptives,
3. conditions or disorders that can affect performance on cognitive tests (e.g., dementia/mild cognitive impairment; stroke; traumatic brain injury; alcohol/substance use; inability to write, speak, or read in English, English as a second language
4. Mini-Mental State Exam (MMSE) ≥ 28
5. conditions that can affect sleep quality (e.g., use of sleep agents; shift work; etc.)

3.2 Describe the criteria that define who will be included or excluded in your final study sample.

After participants have reviewed and signed the consent form in person, they will be interviewed to determine candidacy for the study. They will be asked to provide information about themselves and their medical history. Before the intervention procedure, they will be asked to maintain a diary of VMS. Participants will be instructed to record the frequency and severity of each hot flash or night sweat using the following definitions: “mild” (< 5 minutes, warm, red face, uncomfortable), “moderate” (< 15 minutes, warmth involving neck, ears, head, whole body, with perspiration, clammy skin, dry mouth, tense muscles, tachycardia, irritation, agitation, embarrassment), “severe” (< 20 minutes, warmth described as a raging furnace or burning up, weak, faint, headache, chest heaviness, extreme perspiration, prickling sensation over skin, heart irregularities, anxious, panic attacks) or “very severe” (< 45 minutes, boiling eruption, rolling perspiration, inability to breathe, faint/dizzy, leg/foot cramps, heart irregularities, difficulty functioning, distressed, nausea). They will be asked to do this for a minimum of <u>two weeks</u> prior to the procedure in order to determine eligibility for the study. VMS eligibility will be re-assessed 24 hours before the SGB. A participant will not be permitted to proceed with the initial procedure if they do not have the completed written

baseline diary for a confirmatory VMS frequency and severity count at the time of the procedure.
To screen for depression, we will use the Depression Anxiety and Stress Scale (DASS). Women excluded on the basis of their DASS (≥ 21 for depression and ≥15 for anxiety) scores will be referred to a mental health provider.

To screen for dementia, we will administer the Mini-Mental State Exam (MMSE). Women with an abnormal or low MMSE score (MMSE ≥ 28) will be referred to a health provider.

3.3 Indicate specifically whether you will include or exclude each of the following special populations:

*The following special populations **will not** be included in this research:*

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

4.0 Study-Wide Number of Subjects-NA

5.0 Study-Wide Recruitment Methods-NA

6.0 Multi-Site Research-NA

7.0 Study Timelines

7.1The duration of an individual subject's participation in the study

Subjects will participate in this research study for at least seven months. They have the option of recording hot flashes on a paper diary for an additional six months after the study ends. If they elect to do this, their participation will last at least thirteen months.

7.2 The duration anticipated to enroll all study subjects

We expect to complete enrollment within twelve months.

7.3 The estimated date for the investigators to complete this study

We expect to complete the study in approximately 1.5 to 2.0 years.

8.0 Study Endpoints

8.1 Describe the primary and secondary study endpoints.

Primary Outcome/Endpoint: reduction in frequency and intensity of VMS subjective hot flashes that have been recorded on a paper diary for the duration of the study.

Secondary outcomes/endpoint: Changes in the following measures from baseline, 3 months, 6 months**:**
Objective hot flashes as measured over a 24-hour period with a validated skin conductance monitor
Memory: Mini-Mental State Exam (MMSE)
Mood: Depression Anxiety and Stress Scale (DASS) and Center for Epidemiological Studies-Depression (CES-D)
Cognition: Neurocognitive testing: California Verbal Learning Test (CVLT),List A, List B, List A Short-Delay Free Recall, List A Short-Delay Cued, Recall, List A Long Delay Free Recall, Long Delay Cued Recall, Card Rotation Tests, Digit Span (Forward and Backward), Benton Visual Retention Test,(BVRT), Finding As, Brief Test of Attention (BTA) Numbers, Brief Test of Attention (BTA) Letters, Logical Memory Subtest of Wechsler Memory Scale, Revised (WMS-R/LM-R), Letter, Semantic and Phonemic Fluency) Baseline and 3 months only.
QOL: Functional Assessment of Cancer Therapy-Breast (FACT-B McCoy Female Sexuality Questionnaire (MFSQ)),
Sleep: Pittsburg Sleep Quality Inventory (PSQI), Actigraphy changes in sleep Quality

8.2 Describe any primary or secondary safety endpoints

Before the procedure, a medication line will be inserted into a vein in the subject's arm. An oxygen monitor and blood pressure cuff will also be placed. Subjects will be positioned on their back for this procedure. Their neck will be swabbed with disinfectant to clean the skin, and sterile equipment and technique will be used for the entire of the procedure.

After the study procedure is completed, subjects will stay in the office for half an hour for observation. Blood pressure will be checked. All subjects will have a peripheral intravenous catheter (a plastic tube to take blood and give medicines without having to stick the vein multiple times) placed in their arm prior to the procedure, and temperature monitoring of the arm and hand, evaluation for temporary drooping of the right eyelid, redness in the eye, congestion in the nose, and sweating on the right side of the face will be performed. These confirmatory signs of proper SGB placement will not be recorded as AEs.

The study team will meet and review all adverse events after five subjects have been randomized and received the SGB procedure or sham. Per NU IRB protocol, all UPIRSO's or PRNCs will be reported a soon as the PI becomes aware of it. As the PI is the injectionist, the likelihood of missing a UPIRSO is highly unlikely. If no SAEs/UPIRSO's are observed, the team will meet again after 10 subjects have been randomized. No UPIRSOs or SAEs have occurred in previous studies.

9.0 Procedures Involved

9.1 Describe and explain the study design.

We aim to conduct a randomized, single-site, sham-control clinical trial of SGB on VMS in 36 women with breast cancer on anti-estrogen therapy (18 per group). We will need to screen and enroll approximately 50 women to randomize 36 women. Some women may not qualify due to insufficient number of hot flashes or there may be some withdrawals. The primary entry criterion will be 28 or more moderate to very severe hot flashes per week. VMS will be measured by self-report on a written daily dairy over a 6-month period. Secondary outcomes include changes in mood, sleep, quality of life, memory performance with neurocognitive testing, and objective hot flashes measured by ambulatory monitoring (skin-conductance temperature monitoring) for 24 hours at baseline, three months and six months.

Randomization and Masking Procedures A computer-generated 1:1 block randomization scheme will be used to assign participants to receive either a SGB with bupivacaine or a sham injection with saline. Randomization will be performed by the injectionist immediately before the injection procedure by opening an opaque envelope to reveal the participant number and group assignment printed on an index card. Randomization assignment will be kept under lock and key. Participants and all other study personnel, including those who will perform follow-up evaluations, will be blinded to group assignment. The injectionist will not have access to the written VMS diaries until the conclusion of the study.

9.2 Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

Screening Visit 1

Recording of Hot Flashes

After the participant has reviewed and signed the consent form, they will be interviewed to determine if they are a candidate for the study. We will ask them to provide information about themselves and their medical history. A member of the study team will administer the Depression Anxiety and Stress Scale (DASS) to ensure that participants are not suffering from extreme anxiety or depression. If they are found to have any of these conditions and meet the exclusion criterion, they will not qualify for our study and will be referred to a mental health provider.

Before having the SGB procedure participants will be asked to maintain a daily paper diary of their hot flashes, recording the number and severity using a scale that will be provided to them. They will be asked to do this a minimum of two weeks prior to the SGB procedure in order to determine if they are eligible for the study. They will also record any comments about the hot flashes they experience each day.

At the end of two weeks, a member of the study team will telephone to ask how many hot flashes they are experiencing in a week. If they qualify based on the total number of hot flashes, they will be scheduled to return to the research office for placement of the hot

flash monitor, actigraph watch, questionnaire completion and cognitive testing procedures which are described separately.

The study procedure with Dr. David Walega in the Department of Anesthesiology will be scheduled to occur at a separate visit.

Visit 2 (2 to 3 weeks after visit 1)

There are four types of research evaluations that they will be asked to complete: questionnaires, hot flash monitoring, actigraph watch monitoring and tests of mental abilities (cognitive testing). They will be asked to complete these four tasks at three time points: before the procedure, three months after the procedure, and six months after the procedure. Below we describe each of these types of research evaluations.

Cognitive Testing

They will be asked to complete some memory functioning tests that will assist us in the evaluation of the results of the study procedure. At each session, they will meet one-on-one with a research assistant who is trained in giving tests of different mental abilities. That assistant will instruct the participant on how to complete tasks that measure different mental abilities, such as memory, concentration, and language. Assessment of cognitive function has certain exclusion criteria. If they are found to be ineligible to participate in this portion of the study, they may still participate in the hot flash portion of the study.

Questionnaires

They will also complete questionnaires about mood and everyday functioning. They may refuse to answer any question that they don't wish to answer. If they become uncomfortable at any time and wish to stop, the tests will be stopped. These forms are:

- Depression Scale (CES-D)
- Depression Anxiety and Stress Scale (DASS)
- Mini-Mental State Exam (MMSE)
- McCoy Female Sexuality Questionnaire (MFSQ)
- Modified Pittsburgh Sleep Quality Index (PSQI)
- Functional Assessment of Cancer Therapy (FACT-B)
- Pain Intensity and Interference Scale (PEG)

Hot Flash Monitoring

A research assistant will attach a hot flash monitor to the participant after they have completed the above mentioned. The hot flash monitor will be returned 24-hours later to the office via UPS or, at their convenience, a research assistant can meet them to disconnect and collect the hot flash monitor at their doctor's office or back at the study site.

The hot flash monitor we are using in this study is a small, lightweight, portable recorder that measures how many hot flashes you have each day. The monitor includes some wires and adhesive pads. The adhesive pads are attached to the skin on the chest just below the collarbones. Inside each adhesive pad is a small device that measures hot flashes. Wires send signals from the device to the monitor. Occasionally, the device may malfunction if the adhesive loosens or for other unknown reasons. Should this occur, they may be asked to wear the monitor for an additional 24 hours in order to collect missing objective hot flash data. The monitor measures 1 x 4 x 6 inches and weighs 8 ounces. The monitor is carried in a bag that is worn around the waist like a fanny pack. They will be given verbal instructions and handouts describing how to use the monitor.

Actigraph Watch

The research assistant will also instruct the participant on how to wear an Actigraph. An Actigraph is worn just like a watch and monitors sleep and wake habits. It should be removed for bathing, showering or swimming. They will be given verbal instructions and handouts describing how to use the actigraph watch. They will be given a prepaid return mailing box so that they can return the hot flash monitor and the Actigraph to us via UPS.
Visit 3 (4-5 weeks after visit 1)

Stellate Ganglion Injection Procedure

Participants will be interviewed to assess health status and a brief physical exam will be performed by Dr. Walega. If they are determined to be a candidate for the procedure by Dr. Walega, will randomize the participant into one of two groups: one group will receive the study procedure (stellate ganglion injection with local anesthetic or numbing medication) and the other will receive a sham procedure involving a saline injection in the superficial tissues of the right side of the neck in the region just below the skin layer.

Assignment to groups will be done by randomization similar to flipping a coin. They will have a 50% chance of going into either of the two groups. The study will be single blinded. Participants will not know which group they are in and only Dr. Walega will know whether they have received the stellate ganglion injection with numbing medication or the sham injection with saline. Since it is unknown how long the effects of the injection on hot flashes lasts, participants will have the option of receiving a second injection after the three month procedures if they notice an increase in the severity or frequency of their hot flashes. They will receive the same injection (bupivicaine or sham) that they got at the beginning of the study.

Before the procedure, a medication line will be inserted into a vein in the arm. An oxygen monitor and blood pressure cuff will also be placed. They will be positioned on their back for this procedure**.** Their neck will be swabbed with disinfectant to clean the skin, and sterile equipment and technique will be used for the entire of the procedure.
With the use of a low dose x-ray machine (fluoroscopy machine) to help guide the injection, a bone in the right side of the neck (C6) will be identified and local anesthesia or numbing medicine (1% lidocaine) will be injected to the skin overlying the bone.

For subjects receiving the stellate ganglion injection, a small needle will be placed through the numbed skin on the front of the right side of the neck to make contact with the tissues over the C6 (neck) bone. The correct position of this needle will be confirmed by injecting a small amount of dye that can be seen by Dr. Walega under x-ray. Then 10 cc or about 2 teaspoons of 0.5% bupivicaine (numbing medicine) will be injected and the needle will be removed.
In participants put in the sham injection group, the needle will be placed in the superficial tissues overlying the front right neck (C6 bone), just underneath the skin. 5 cc of saline fluid will be injected and the needle will be removed. This procedure will take a few minutes. After it is completed, they will stay in the office for about half an hour for observation. Their blood pressure will be checked.

As above, all subjects will have a peripheral intravenous catheter (a plastic tube to take blood and give medicines without having to stick the vein multiple times) placed in their arm prior to the procedure, and temperature monitoring of the arm and hand, evaluation for temporary drooping of the right eyelid, redness in the eye, congestion in the nose, and sweating on the right side of the face will be performed.

Visit 4 (3 months after study procedure)
They will be asked to return to the clinical site 3 months following the injection procedure. At this visit, the same procedures listed in visit 2 will be performed.

Visit 5 (6 months after study procedure)
They will be asked to return to the clinical site 6 months following the injection procedure. At this visit, the same procedures except for cognition testing listed in visit 2 will be performed.

Participants will continue to complete their hot flash diary for the duration of the study.
Their part in this study will last for approximately seven months and will involve five visits.

Additional Follow Up (6-12 months after study procedure)
Participants will be asked if they have any interest in maintaining a paper diary for an additional six months to assess longer term effects of the treatment. If they agree, a member of the research staff will call once a month for the next six months and to remind them to complete their hot flash diary and record long term effects, if any.
If they choose to continue to record their hot flashes, their participation may increase to thirteen months and they will have 6 visits.

9.3 Describe:

- ***Procedures performed to lessen the probability or magnitude of risks.***

At the time of the injection procedure, an angiocatheter will be placed in the left hand/arm for peripheral intravenous access as a safety precaution and a temperature monitor will be placed on the right dorsal hand. Participants will be positioned supine in cervical extension. The anterior neck will be prepped with chlorhexidine and draped in

the standard sterile manner. For active SGB, a right-sided SGB will be performed. Using fluoroscopic guidance, the C6 vertebra will be identified and the skin overlying the tubercle will be anesthetized using 2 mL of 1% lidocaine. Using digital pressure to laterally retract the carotid artery, a 22 g 1.5-inch needle will be placed to make contact with the anterolateral portion of the C6 vertebra and then retracted 1-2 mm and secured; contrast material (iopamidol 1-2 mL) will be injected with fluoroscopic guidance to confirm contrast dye spread in the prevertebral fascial plane and to rule out intravascular or intrathecal dye spread. 0.5% bupivacaine (10 mL) will be injected and the needle will be removed. Generally, any woman can safely have this injection unless she has an allergy to local anesthetic, contrast material, or has anatomic abnormalities of the anterior neck, all of which are rare. Drug interactions are a concern with other non-hormonal treatments for VMS, but not with SGB. The dose of local anesthetic needed to block the stellate ganglion does not cause toxic plasma levels of local anesthetic in the bloodstream and does not significantly interact with medications used for hypertension, asthma, depression, or seizures.

For sham injection, the same positioning, monitoring, sterile preparation and technique will be used with identical visual, auditory and tactile cues, except the needle will be placed in the superficial tissues overlying the C6 tubercle. With fluoroscopic guidance, contrast material (iopamidol 1-2 mL) will be injected to confirm contrast dye spread in the subcutaneous tissues, not in the prevertebral fascial plane of the stellate ganglion. Preservative-free saline (5 mL) will be injected and the needle will then be removed. Participants will be transferred to a recovery area and monitored in a reclining position for at least 20 minutes to assess potential adverse effects of the injection. Vital signs will be measured every 5 minutes during the recovery phase. Presence of a Horner's sign (miosis, ptosis, anhydrosis) will be recorded and will validate successful SGB. Pre- and post-injection temperatures of the right hand will be measured and recorded. The research team will not have access to the injectionist's procedure notes in order to maintain the blind. Miosis, ptosis, and anhydrosis will not be considered adverse events as they are confirmatory for adequate SGB placement.

- ***All drugs and devices used in the research and the purpose of their use, and their regulatory approval status.***

The study will use approved drugs (0.5% Bupivacaine, 1% Lidocaine and sterile saline) for unapproved uses (reduction in VMS). The package inserts have been uploaded into the "Supporting Documents" section of the IRB application.

- ***The source records, including medical or educational records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)***

Copies of all surveys, diaries, subject instructions, cognition testing battery and data collection forms have been uploaded under the" Supporting Documents" section of the IRB application.

9.4 What data will be collected, including long-term follow-up.

Baseline data for subjective VMS frequency and severity will be recorded by

participants in a written diary. Additional data for depression, sleep, fatigue, sexual health, quality of life, and cognitive function will be recorded, along with sociodemographic information related to the study participants in a case report form (see Participant Booklet in "Supporting Documents" section of IRB). The research chart and Case Report Form (CRF) will be maintained in the research office of Dr. Walega.

9.5 For HUD uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures. **N/A**

10.0 Data and Specimen Banking-N/A

10.1 If data or specimens will be banked for future use, describe where the specimens will be stored, how long they will be stored, when they will be destroyed (if ever), how the specimens will be accessed, and who will have access to the specimens.
10.2 List the data to be stored or associated with each specimen.
10.3 Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens, including whether those data will be identifiable to others.

11.0 Data and Specimen Management

11.1 *Describe the data analysis plan, including any statistical procedures.*

Subjective VMS: As described in the determination of eligibility based on VMS entry criteria section for six months following the intervention, intensity of daytime VMS will be calculated as follows: Intensity = Frequency*Severity = [(frequency of mild*1)+ (frequency of moderate*2) + (frequency of severe*3) + (frequency of very severe*4)] and used as a secondary endpoint. Frequency of night sweats will also be recorded daily via self-report the following morning. Baseline VMS frequency will be calculated as the mean of the daily count totals on diaries during the first two screening weeks. VMS frequency at Months 1 to 6 will be calculated as the mean of the daily count totals reported for the 30 days before each visit.

Objective VMS: At baseline, and the 3- and 6-month post-intervention visits, participants will complete a second measure VMS objectively using the ambulatory sternal skin conductance monitor (Biolog Model 3991 x/2-HFI). Raw objective hot flash data will be analyzed by a combination of automated computer software and two trained data coders. According to standard procedures, once an objective hot flash will be coded, no other VMS will be coded for the next 15 minutes. Data will be independently double-scored and double-entered into the database by coders blinded to treatment assignment. Participant sensitivity to objective HF will be calculated by dividing the total number of true positive hot flashes (i.e., objectively determined hot flashes that were subjectively detected) by the sum of the total number of objectively measured hot flashes (i.e., true positives and false negatives). Primary outcome measures will be total objective and subjective hot flashes in a 24-h period, during waking hours, and during sleeping hours.

Baseline characteristics: (e.g., sociodemographic variables, primary and secondary outcomes) will be compared between treatment groups using t-tests or chi-square tests for categorical variables. Multiple types of measurement outcomes (frequencies, counts, continuous and incidence outcomes) will be collected in this study. We will conduct intent-to-treat (ITT) analyses for all primary and secondary outcomes using a series of generalized mixed-effects regressions as described below. All statistical tests will be two-sided with significance set at $p \leq .05$. SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC, USA) will be used for statistical analyses. In preliminary analysis, the distributional aspects of the variables under consideration will be examined through descriptive statistics. These statistics will include measures of location (mean, median, quartiles) and measures of dispersion (range, standard deviation, variance) for continuous variables and frequencies of the levels of categorical variables. These measures will also assist with a data cleaning/screening procedure to eliminate any possible copying, handling, recording or measurement errors.

In addition to the features described above, the dependence of outcome measures will need to be properly accounted for in the data analysis as measures will be made at multiple times for the same participant. Consequently, these observations tend to be correlated and require statistical techniques that can properly account for the correlation in order to draw valid inference. Our general approach for analyzing these multiple types of data in this trial will be the Generalized Linear Mixed-Effect Models (GLMM). These models can accommodate a wide range of outcomes including normal, binary, ordinal, and Poisson outcomes, while taking into account correlations from within-subject observations. To study the changes in outcomes over time and to evaluate group differences in these changes, we will construct GLMM models. The main independent variables in statistical model specifications typically include the group indicator, dummy variables for time, and the interactions between them, after controlling for observed and relevant covariates. By properly constructing GLMMs, a wide range of scientific hypotheses can be tested, including cross-sectional differences among groups, the effect of treatment over time and differences between groups over time.

Data will be analyzed using the PROC MIXED, PROC GLIMMIX and PROC NLMIXED in SAS statistical software version 9.2. For the correlation between changes in objective VMS and changes in memory performance, we propose to examine the correlation between frequency of total objective VMS and verbal learning by conducting Pearson correlations to examine associations between changes in cognitive performance and changes in VMS. We will conduct partial correlations to examine whether these associations remained significant after controlling for changes in sleep quality (PSQI and actigraphy-based measures).

11.2 Provide a power analysis, if necessary.

A sample size of 18 in each treatment group will provide at least 80% power to test the two-way interaction between Treatment and Time with a significance level set at 0.05.

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We will need to screen and enroll approximately 50 women to randomize 36 women. Some women may not qualify due to insufficient number of hot flashes or there may be some withdrawals.

11.3 Describe the steps that will be taken to secure the data to maintain confidentiality (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission

Research files and case report forms will be stored in the research offices of Dr. Walega and will be kept in locked offices with access only to the research team. Wherever possible, subject data will be stored using only the study ID. Measures will be taken to protect all personal information and data, including keeping all data sheets under lock and key and entering data into a database that requires login identification and a password made available only to immediate study personnel. The entire study team has taken the CITI training and is familiar with confidentiality requirements and procedures.

Downloaded data from the Biolog hot flash monitor and the actigraph watch will be processed, stored, and analyzed in password-protected network at the University of Illinois in Chicago of Dr. Pauline Maki. Data related to cognitive assessments will be stored and analyzed at the University of Illinois at Chicago in Dr. Maki's lab.

11.4 Describe any procedures that will be used for quality control of collected data

A computer-generated 1:1 block randomization scheme will be used to assign participants to receive either a SGB with bupivacaine or a sham injection with saline. Randomization will be performed by Dr. Walega immediately before the injection procedure by opening an opaque envelope to reveal the participant number and group assignment printed on an index card. Randomization assignment will be kept under lock and key. Participants and all other study personnel, including those who will perform follow-up evaluations, will be blinded to group assignment. To ensure that Dr. Walega's knowledge of randomization assignments does not influence study results, he will have no additional follow up or interaction with study participants, unless an adverse event occurs that requires his immediate attention. The study team will be briefed on the types of adverse events that require his attention. Dr. Walega will not be involved in the collection of any primary or secondary data outcome.

11.5 Describe how data and specimens will be handled study-wide: see Section 11.0 Data and Specimen Management

11.6 What information will be included in that data or associated with the specimens?

See Section 11.0 Data and Specimen Management

- ***Where and how data or specimens will be stored?***

See Section 11.0 Data and Specimen Management

- ***How long the data or specimens will be stored?***

Data will be stored indefinitely.

- ***Who (role on the study) will have access to the data or specimens?***

See Section 11.0 Data and Specimen Management

- ***Who (role on the study) is responsible for receipt or transmission of the data or specimens?***

Dr. Walega at NU and Dr. Maki at UIC are responsible for the receipt or transmission of data. They may designate a member of the research team to transmit data in accordance with NU/UIC IT security policies.

- ***How data and specimens will be transported?***

See Section 11.0 Data and Specimen Management

Provisions to Monitor the Data to Ensure the Safety of Subjects

11.5 Describe:

- ***The plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.***

The study team will meet and review all adverse events after five subjects have been randomized and received the SGB procedure or sham. Per NU IRB protocol, all UPIRSO's or PRNCs will be reported a soon as the PI becomes aware of it. As the PI is the injectionist, the likelihood of missing a UPIRSO is highly unlikely. If no SAEs/UPIRSO's are observed, the team will meet again after 10 subjects have been randomized. No UPIRSOs or SAEs have occurred in previous studies.

- ***What data are reviewed, including safety data, untoward events, and efficacy data?***

Participants who undergo the SGB with bupivacaine will experience a temporary sympathetic block of the right upper extremity and right face. Efficacy of the SGB will be confirmed by the presence of Horner's syndrome (miosis, abnormal contraction of the pupil; ptosis, drooping upper eyelid; and anhydrosis ,absence of facial sweat) and a temperature increase of the affected extremity, the latter the result of regional venodilation. The temperature of the right upper extremity will be monitored prior to and 30 minutes following the injection to confirm, along with a Horner's syndrome, successful SGB. These events are expected and confirm correct SGB placement. Events outside of those expected are what will be reviewed as stated above. The study team will be trained on the types of study related SAEs or AEs that should immediately be reported to the PI/IRB since they will not have access to the procedures records to maintain the blind.

- ***How the safety information will be collected***

Safety data will be collected with case report forms, at study visits, and by telephone calls with participant.

- ***The frequency of data collection, including when safety data collection starts.***

Safety data is collected as soon as the participant agrees to participate and signs the informed consent document.

- ***Who will review the data?***

The PI will review the data with the study coordinator.

- ***The frequency or periodicity of review of cumulative data.***

Efficacy data will be reviewed at the conclusion of the study. Safety data will be reviewed after 5 are randomized, then after 10 are randomized. Thereafter, safety data will be reviewed every 6 months provided that no UPIRSOs are observed in those that have received the study procedure.

- ***The statistical tests for analyzing the safety data to determine whether harm is occurring.***

No statistical test will be used to determine whether harm is occurring. There is a preponderance of safety information on the SGB procedure that is familiar to the PI as this is his area of expertise. If the PI determines that unexpected SAEs and AEs are occurring in the SGB which is higher than seen in clinical practice, he will immediately cease enrollment and notify the IRB.

- ***Any conditions that trigger an immediate suspension of the research.***

A participant study related death will trigger an immediate suspension of the research.

12.0 Withdrawal of Subjects*

12.1 Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent, including stopping participation for safety reasons.

The PI can remove subjects from the research study without their approval. Possible reasons for removal include the following: if it appears to be medically harmful to the subject, or if they fail to follow directions for participating in the study, such as taking excluded medication (aspirin, anti-coagulants) prior to the SGB procedure, if it is later discovered that they did not meet the study eligibility requirements, at the discretion of the study doctor or, if the study is canceled.

12.2 Describe any procedures for orderly termination.

A subject who withdraws will be schedule to return to the research office. At this time, written diaries will be collected and AEs will be assessed, if any. Prior to scheduling the appointment, the subject will be asked if she would like to see the PI. If yes, this will be done on the same visit. If a subject does not wish to return, she will be asked to mail or fax any written diaries. Final payment will be mailed to the subject if compensation has not already been paid out.

12.3 Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

Subjects only have the option of not participating in the cognition study. All other procedures are required as part of the study. The subject has the option to withdraw if she does not want to participate in the hot flash monitoring, actigraph monitoring and most importantly, maintaining a written diary for the duration of the study.

13.0 Risks to Subjects*

13.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, describe the probability, magnitude, duration, and

reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

There are risks associated with participation in this study. Below is a description of the risks:

Stellate Ganglion Block with local anesthetic

Stellate ganglion injection carries the potential very rare risk of infection at the injection site, bleeding or blood clot formation at the injection site, seizures (sudden, uncontrolled muscle spasms and loss of consciousness) and nerve injury which may present as temporary parasthesia (numbness) and/or weakness. All of these rare risks are minimized with the use of fluoroscopic guidance (visualization with a type of x-ray). Other complications related to the stellate ganglion injection that can occur are puncture of the lung on the right during placement of the needle on the right neck, or an allergic reaction to the medications being injected into the subject. Temporary voice hoarseness, temporary mild shortness of breath, temporary difficulty swallowing, and temporary changes in your blood pressure may occur after the stellate ganglion injection from the numbing medicine. Possible reactions from the numbing medicine used in this study last 6-8 hours. Minor soreness at the injection site could last 1-2 days.

Tissue injection of saline (sham) below the surface of the skin

Needle placement carries the potential very rare risk of infection at the injection site, bleeding or blood clot formation at the injection site, temporary swelling of the right side of the neck from the injected liquid and an allergic reaction to the medications being injected into you. Minor soreness at the injection site could last 1-2 days.

Risk of Radiation from the x-ray

The cumulative radiation exposure from these tests is considered small and is not likely to adversely affect the subject or their disease.

The contact with radiation in this study is thought to be small. However, the effects of radiation add up over a lifetime. It is possible that having several of these X-rays may add to the subject's risk of injury or disease. When deciding to enter this study, subjects will be asked to consider past and future contact with radiation. Examples of contact with radiation include x-rays or CT scans taken for any reason or radiation therapy for cancer treatment.

Risks from the hot flash monitor

The hot flash monitor does not involve significant risk. Wearing the monitor can be a minor inconvenience. The monitor poses no risk of electric shock. Potential side effects of the monitor include (1) allergy to the paper or adhesive on the disposable electrodes (minor, 1%), (2) itching at the site of electrode attachment (minor, 4%) and (3) discoloration of the skin from the electrode gel.

Risks with the Actigraph watch

The Actigraph watch does not involve significant risk. Wearing the watch can be a minor inconvenience, and the band may cause slight irritation.

Questionnaires

Being in this study may make the subject feel emotionally uncomfortable. They might feel anxious, or experience emotional reactions to some of the questions that will be asked

Cognitive Testing

Subjects may find some of the cognitive tests to be challenging, frustrating, or boring.

Confidentiality Risks

There is a risk of loss of confidentiality. Certain measures are taken to protect all personal information and data, including keeping all data sheets under lock and key and entering data into a non-network database that requires a login id and password made available only to immediate study personnel.

13.2 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.
Currently, there are no unforeseeable risks to the study procedures.

14.0 Potential Benefits to Subjects

14.1 Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.
Possible benefits include a reduction in the severity or frequency of hot flashes, an improvement in overall feeling of well-being and ability to perform the functions of daily living impacted by hot flashes. We do not know how long these benefits will last.

14.2 Indicate if there is no direct benefit. Do not include benefits to society or others.
Subjects who receive the sham procedure will have no direct benefit from participation.

15.0 Vulnerable Populations -N/A

16.0 Community-Based Participatory Research-N/A

Sharing of Results with Subjects

16.1 ***Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be***

shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.
Study results will not be shared with subjects as they are considered experimental and are not required or related to their on-going medical care.

17.0 Setting

17.1 Describe the sites or locations where your research team will conduct the research.
Northwestern Medicine, formerly the Northwestern Medical Faculty Foundation, maintains a dedicated Pain Medicine Center located in the Galter Pavilion at the Northwestern University Chicago campus. The stellate ganglion blockade or sham injection will take place at this facility.

Consenting, questionnaire completion and cognition testing will take place in the research office of Dr. Walega at 633 N St Clair, suite 1800 or 1876 N St Clair, Arkes Pavilion, Department of Anesthesia.

- ***Identify where your research team will identify and recruit potential subjects.***

IRB approved flyers, physician provider letters and internet notices will be utilized for the study. See "Supporting Documents" section. We expect that potential subjects will contact the research office as a result of the recruitment aids or will be referred to us by health providers.

18.0 Resources Available

18.1 Describe the qualifications (e.g., training, experience, and oversight) of you and your staff as required to perform their role. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research. You do not need to list individual names of your staff in this protocol.
Dr. Walega has the full and expressed support of his department Chair, Dr. Christine Stock, to successfully pursue this study. The Department of Anesthesiology and Northwestern University supported Dr. Walega's pursuit of a Master of Science in Clinical Investigation at Northwestern University through direct financial support. This is a rigorous program designed to enhance a clinician's ability to design and successfully execute clinical research studies and seek grant support for such studies. He successfully earned this degree while working full time as a Division Chief and a fellowship Program Director.

Dr. Shulman is a Professor of Obstetrics and Gynecology at Northwestern University, the Director of the Ovarian Cancer Early Detection and Prevention Program and Co-Director of Cancer Genetics Program at Northwestern. He will serve as Co-investigator for this study. His role as the Co-Director of the cancer genetics program allows him to interface with the team in facilitating recruitment for women with breast cancer with moderate to severe hot flashes.

Pauline M. Maki, PhD, is Professor of Psychiatry and Psychology at UIC and Director of the Women's Mental Health Research Program. She will oversee all research activities performed by UIC personnel, which center on the collection, scoring, management, and interpretation of secondary outcome measures: neurocognitive outcomes, objective hot flash monitoring, and actigraphy (sleep).

Ms. Banuvar is a Clinical Research Associate and has a long history of collaboration with Dr. Maki and Dr. Shulman and has worked on three projects related to vasomotor symptoms with her team. She will be responsible for data integrity and protocol maintenance. She will monitor the data and subject hot flash data collection of subjects. She will assist the PI in monitoring and reporting adverse events as well as correspondence with NU IRB.

18.2 Describe other resources available to conduct the research: For example, as appropriate:

At UIC under the supervision of Dr. Maki, all computers have access to a secure server which is accessed through a unique IT department provided log-in. All electronic data are stored on the secure server. Only delegated logins have the ability to view or edit the information stored in on this server. Currently two of the 10 computers are equipped with a Biolog Transfer box, Biolog DPS software (for downloading and convert Biolog data) and Biolog 3.7, the most recent version of the software used to score and edit the Biolog data. Eight computers are currently equipped with the Actiware software (version 5.7) which is used to configure, download and score Actiwatch data. The downloading platform can be moved between computers as needed.

- ***Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?***

Based on our experience with previous studies, we estimate we would need to screen 50 women to randomized 36 women. This is a small sample size. We do not anticipate problems in obtaining a complete sample size over the next year.

- ***Describe the time that you will devote to conducting and completing the research. (Note: This description is intended to provide the IRB with information relative to conduct of the study as relevant for the protection of research subjects, not for effort reporting.)***

We anticipate that the study team will contribute 2.5 days per week to the project.

- ***Describe your facilities. (Note: This description is intended to provide the IRB with information relative to conduct of the study as relevant for the protection of research subjects, not for Facilities and Administration considerations.)***

Already addressed in Section 17.0 and 18.0.

- ***Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.***
- ***Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.***

Prior to the inception of the study and after IRB approval has been obtained, the research team will meet to review the protocol. Safety endpoints will be reviewed and study logistics will be coordinated and agreed upon.

19.0 Prior Approvals

19.1 ***Describe any approvals that will be obtained prior to commencing the research***.
We will obtain radiation safety by means of the Radiation Dosimetry Form.

20.0 Recruitment Methods

20.1 Describe when, where, and how potential subjects will be recruited.
IRB approved flyers, physician provider letters and internet notices will be utilized for the study. See "Supporting Documents" section. We expect that potential subjects will contact the research office as a result of the recruitment aids or will be referred to us by health providers. Subjects will be asked to come to the research office for consenting if they are interested in the study.

20.2 Describe the source of subjects.
We expect that the majority of subjects will come from the practices of Northwestern Medicine providers.

20.3 Describe the methods that will be used to identify potential subjects.
IRB approved flyers, physician provider letters and internet notices will be utilized for the study. See "Supporting Documents" section.

20.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the eIRB+ application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video file. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video file.)
See "Supporting Documents" section.

20.5 Describe the amount, timing, and method of any payments to subjects. (E.g., Gift card, Clinker, check.)
The study will pay for parking in the hospital parking lot located on St. Clair St., between Superior and Huron Streets. Their parking ticket will be validated by the research staff and paid for up to six hours.

Subjects who agree to take part in this research study, will be paid $200.00 by check at study completion for time and effort. If they agree to collect hot flash data for an additional six months after completion of the study, they will be paid an additional $100.00 if they complete a written diary for each of the six months. They may choose to have the final check mailed to them, or they may come to the clinic to retrieve their check if that is more convenient.

Title: SGB CA Study

21.0 Local Number of Subjects

21.1 Indicate the total number of subjects to be accrued locally 36
21.2 If applicable, include a break-down of subjects by study location or procedure group 15 women will be in the SGB procedure group and 18 women will be in the sham group. All women will be recruited and followed at Northwestern.

21.3 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)
Thirty enrolled subjects are required to complete the study. We estimate that we would need to screen approximately sixty women to randomize thirty women.

22.0 Confidentiality-<u>Repetitive</u>

These issues have already been addressed in the Data and Specimen Management Section 11.3 to 11.4.

22.1 If this is a multicenter study, describe the local procedures for maintenance of confidentiality.

- ***Where and how data or specimens will be stored locally?***
- ***How long the data or specimens will be stored locally?***
- ***Who will have access to the data or specimens locally?***
- ***Who is responsible for receipt or transmission of the data or specimens locally?***
- ***How data and specimens will be transported locally?***
-

23.0 Provisions to Protect the Privacy Interests of Subjects

23.1 Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on with whom they interact or to whom they provide personal information.
Potential subjects do not have to authorize the use or disclosure of their health information; however, they will not be allowed to take part in this research study. They may also revoke authorization for use or disclosure of their health information in writing. Direct personal identifiers will not be used in the database. In addition, unless disclosure of the direct identifier is necessary for review by regulatory authorities or is required by law, access to direct identifiers will be strictly limited to research team delegates of the PI.

23.2 Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.
Subjects will be reassured that if there are questions in the surveys that they do not want to answer or if some of the questions make them uncomfortable, they do not have to

answer them. In addition, if they have questions or concerns about the study procedures the research team, including the PI, is available to them for the duration of the study . They will be told that they do not have to wait for study related clinic visits to be seen or assessed for any concern.

23.3 Indicate how the research team is permitted to access any sources of information about the subjects. (E.g., What permission does the research staff have to access medical records or other sensitive information?)

HIPAA Authorization will be obtained from all research subjects through the consent document. Subjects will give us the permission to use personal health information that includes health information in the medical records and information that can identify them. Personal health information may include the subject's name, address, phone number or social security number. Health information we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history
- Lab tests, or certain health information indicating or relating to a particular condition as well diaries and questionnaires
- Records about study medication or drugs
- Substance abuse information: current substance abuse is an exclusion to participation in the study
- Mental Health information: history of depression, psychosis and concomitant medication
- Dr. Pauline Maki from The University of Illinois at Chicago, Department of Psychiatry and her research assistants working directly under her supervision, may also receive, or use health information. The reason for sharing this data with these individuals is that UIC personnel may be involved in the collection of hot flash data, actigraph data. Questionnaire data and cognitive test results.

24.0 Compensation for Research-Related Injury

24.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research-related injury.

Subjects who need medical care because of taking part in this research study may seek medical treatment through the investigator or a treatment center of their choice. The care will be billed to the subject, or their insurance. The study has no program to pay for medical care for research-related injury.

24.2 ***Provide a copy of contract language, if any, relevant to compensation for research-related injury. N/A***

25.0 Economic Burden to Subjects

25.1 Describe any costs that subjects may be responsible for because of participation in the research.

There are no costs to the subject for participation in the research.

26.0 Consent Process

26.1 Indicate whether you will you be obtaining consent, and if so describe:

Written informed consent will be obtained from every subject.

- ***Where will the consent process take place***

Consent will take place in the research office of Dr. Walega and his team.

- ***Any waiting period available between informing the prospective subject and obtaining the consent.***

The waiting period available is solely at the discretion of the participant. If the subject learns of the study via a flyer or provider and telephones the research office, the subject will be asked to present to the research office in order for written informed consent to be obtained in person. Alternatively, if the subject learns of the study in a clinical setting, if the research team is available and if a private space is available, the team member can go to the subject to conduct the informed consent process and obtain written consent.

- ***Any process to ensure ongoing consent.***

The PI will again ask the subject prior to administration of the study procedure whether they have had any additional questions or concerns and whether they still wish to continue their participation.

- ***Whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, describe:***

"SOP: Informed Consent Process for Research (HRP-090)" will be followed for this study.

- ***The role of the individuals listed in the application as being involved in the consent process.***
- ***The time that will be devoted to the consent discussion.***

The discussion will take as long as is needed to insure that the subject has fully read the document and expresses understanding. For this study, we plan to allow 1 hour for the consent discussion but it may be extended if needed.

- ***Steps that will be taken to minimize the possibility of coercion or undue influence.***
- Although Dr. Walega will be overseeing the consent process, he will not be directly obtaining consent. It is unlikely that these study patients will be ones he may be treating in his Pain Clinic so there would likely be no concern for undue influence as the treating physician.
- **Steps that will be taken to ensure the subjects' understanding.**

Individuals involved in the consent process will dialogue with the subject to insure they understand what is required. They may be asked to summarize their understanding of the goals and procedures of the study. Care will be given to ensure they do not feel like they are being "tested".

Non-English Speaking Subject-NA

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)-N/A
Subjects who are not yet adults (infants, children, teenagers) -N/A.
Cognitively Impaired Adults-N/A
Adults Unable to Consent-N/A

27.0 Process to Document Consent in Writing

27.1 Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be documented in writing.
"SOP: Written Documentation of Consent (HRP-091)" will be followed for this study.

27.2 If you will document consent in writing, attach a consent document in your eIRB+ application.
Consent document is included in Supporting Documents Section.

28.0 Drugs or Devices

28.1 If the research involves drugs or devices, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.
Dr. Walega will be solely responsible for administering the drugs to be used in this study. They will be stored in the Pain Clinic as these drugs are typically used as part of the standard of care for SGB and other clinic procedures.

28.2 If the drug is investigational (has an IND) or the device has an IDE or a claim of an abbreviated IDE (non-significant risk device), include the following information: N/A

Literature

1.Carpenter JS, Johnson D, Wagner L, Andrykowski M. Hot flashes and related outcomes in breast cancer survivors and matched comparison women. Oncology Nursing Forum. 2002; 29(3): E16-25.
2.Gupta P, Sturdee DW, Palin SL, Majumder K, Fear R, Marshall T, et al. Menopausal symptoms in women treated for breast cancer: the prevalence and severity of symptoms and their perceived effects on quality of life. Climacteric. 2006; 9(1): 49-58.
3.Land SR, Wickerham DL, Costantino JP, Ritter MW, Vogel VG, Lee M, et al. Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006; 295(23): 2742-51.
4.Hunter MS, Grunfeld EA, Mittal S, Sikka P, Ramirez AJ, Fentiman I, et al. Menopausal symptoms in women with breast cancer: prevalence and treatment preferences. Psychooncology. 2004; 13;769-78.

5.Baber R, Hickey M, Kwik M. Therapy for menopausal symptoms during and after treatment for breast cancer : safety considerations. Drug Saf. 2005; 28(12): 1085-100.
6.Hickey M, Saunders CM, Stuckey BG. Management of menopausal symptoms in patients with breast cancer: an evidence-based approach. Lancet Oncol. 2005; 6(9): 687-95.
7. Cella D, Fallowfield LJ. Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy. Breast Cancer Res Treat. 2008; 107(2): 167-80.
8.Pachman DR, Barton D, Carns PE, Novotny PJ, Wolf S, Linquist B, et al. Pilot evaluation of a stellate ganglion block for the treatment of hot flashes. Supportive Care in Cancer. 2011; 19(7): 941-7.
9.Lipov EG, Joshi JR, Sanders S, Wilcox K, Lipov S, Xie H, et al. Effects of stellate-ganglion block on hot flushes and night awakenings in survivors of breast cancer: a pilot study. Lancet Oncol. 2008; 9: 523-32.
10.Haest K, Kumar A, Van Calster B, Leunen K, Smeets A, Amant F, et al. Stellate ganglion block for the management of hot flashes and sleep disturbances in breast cancer survivors: an uncontrolled experimental study with 24 weeks of follow-up. Annals of Oncology. 2012; 23(6): 1449-54.
11. Walega DR, Maki PM, Rubin LH, Banuvar S, Shulman LP. Effects of Stellate Ganglion Blockade on Vasomotor Symptoms: Findings from a Randomized Clinical Trial of Postmenopausal Women. Menopause Aug 2014 PMID 24496086
12. Maki PM, Rubin LH, Savarese A, Walega DR, Banuvar S, Shulman LP. Reductions in Vasomotor Symptom Following Stellate Ganglion Blockade are Related To Improvements in Memory. Maturitas 2014 (accepted for publication)
13. Wulf H, Maier C. Complications and side effects of stellate ganglion blockade. Results of a questionnaire survey. Anaesthesist. 1992; 41(3): 146-51.
14. Otthman AH, Zaky AH. Management of Hot Flushes in Breast Cancer Survivors: Comparison between Stellate ganglion Block and Pregabalin.
15. Guttuso T. Stellate ganglion block for treating hot flashes: a viable option or sham procedure? Maturitas 2013; 76:221-224.
16. Walega DR, Maki PM. Letter to the Editor: Effects of Stellate Ganglion Blockade on Vasomotor Symptoms: Findings from a Randomized Clinical Trial of Postmenopausal Women. Menopause 2014. PMID 24937028