Study Tittle: Does Stellate Ganglion Blockade (SGB) in Men Treated for Prostate Cancer Improve Hot Flashes? A Pilot Prospective Cohort Study

Study Protocol Version 3.1 11/25 2019

NCT003796195

STU#:00208657
Version 3.1
11/25/2019

PROTOCOL TITLE: Does Stellate Ganglion Blockade (SGB) in Men Treated for Prostate Cancer Improve Hot Flashes? A Pilot Prospective Cohort Study

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VERSION NUMBER:
3.1

VERSION DATE:
11/25/2019

STUDY SUMMARY:

Special Population(s)	NA
Sample Size	N = 14 is the required number of enrollees who are needed to be evaluable both at baseline and 6 months for the primary outcome. Allowing for dropouts, up to 18 pts might be enrolled
Funding Source	Internal funding
type of consent to be obtained	Written
Site	Single Site
Research Related Radiation Exposure	Yes

1.0 OBJECTIVES:

Scope: Men with prostate cancer with or without metastatic disease treated with androgen deprivation therapy for at least 2 months, with bothersome refractory hot flashes, will be enrolled as participants in this open label clinical trial.

Aim 1: To determine the effect of stellate ganglion blockade (SGB) for reducing hot flash frequency and severity in men with prostate cancer in the 6 months following the intervention.

Aim 2: To evaluate the effect of SGB on daily hot flash (HF) interference and sleep quality.

Hypotheses: Hot flash frequency, interference and sleep quality will be improved in men following stellate ganglion blockade with local anesthetic.

2.0 BACKGROUND:

Androgen Deprivation Therapy (ADT) is a critical component of advanced prostate cancer treatment but causes numerous adverse effects including decreased bone mass, decreased muscle mass, gynecomastia, erectile dysfunction, loss of sexual desire, depression, disordered sleep, urinary symptoms, and hot flashes (HF)(1). HF are unpleasant paroxysmal episodes of flushing, sweating with vasodilation of the face, neck, and chest. These episodes can last for seconds to minutes and are often associated with night sweats, anxiety, and insomnia and have negative effects on quality of life (9).

Although the exact mechanism of HF is unclear, HF in men on ADT appear related to decreased androgen exposure (1-5). Studies confirm that 50-93% of men who receive ADT report HF (1, 3, 6). These symptoms are typically long lasting. They start within two months of ADT initiation and persist 6 months to several years after ADT discontinuation (7). One recent study showed that 27% of men on ADT reported HF as their most distressing side effect of prostate cancer treatment (8). There is considerable psychological distress associated with poorly controlled HF in men (9, 10) that has a negative impact on mental health, including feelings of decreased masculinity and the sense that one's traditional gender role is diminished. Together, these factors compound the psychological, psychosocial and psychosexual stresses of prostate cancer survivorship.

Younger and leaner men typically have more frequent and severe HF from ADT when compared to other groups, and several genetic polymorphisms are associated with a high rate of hot flashes in men on ADT, specifically, those that effect immune function, neurotransmission, vasoconstriction, and circadian rhythms (11). Because of the numerous negative effects of HF on QOL, sleep, and sexuality, HF can make patients less likely to begin hormonal therapy and can lead to the early discontinuation of ADT (7, 12) or poor treatment adherence (13).

Few trials have been done assessing treatment of HF in men with prostate cancer, and those that have been published typically show lackluster or inconsistent outcomes or an unacceptable side effect profile (6, 13-16). Testosterone supplementation is obviously contraindicated.

In women, pharmacological treatments (anti-depressants, anti-epileptics, anti-hypertensives), physical/behavioral treatments (e.g., acupuncture, yoga/exercise, relaxation techniques, cognitive behavioral therapy), and natural health products (e.g., black cohosh, flax, vitamin E, ginseng) have been studied for control of HF, but most have not been critically evaluated by clinical trials in men (17-19). Most medications shown to mitigate HF have their own unique side effects, or require daily compliance to maintain consistent efficacy.

Stellate ganglion blockade (SGB) with local anesthetic may be an effective treatment of HF in men on ADT, but has not been studied in any published clinical trials. 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 as well as some types of cardiac dysrhythmias. 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 HF in women who underwent a single SGB with bupivacaine, a local anesthetic, as compared to a13% decrease in women in the sham control group who underwent an injection of saline. (20).

Another controlled study of SGB in women with breast cancer on endocrine therapy confirmed considerable reductions in frequency and intensity of HF in patients who had SGB (21). Uncontrolled studies of women with breast cancer and heterogeneous populations including postmenopausal women have demonstrated improvements in the frequency and intensity of HF following SGB, with 45-90% reduction in HF frequency or intensity, for durations ranging from 4 weeks to several months (22-24). Together, this literature provides further support of the hypothesis that SGB could be beneficial to men on ADT.

The mechanism of SGB mitigation of HF in men is unclear. The effects of testosterone on prevertebral ganglia are widely variable (25). Anatomic connections between the stellate ganglion and thermoregulatory regions in the brain via third order neurons have been described (26). SGB interrupts the sympathetic nervous system and may modulate norepinephrine levels in these thermoregulatory regions. Androgen deprivation as in ADT appears to change NE levels and activate the sympathetic nervous system in rat models (27), but the detailed interaction between testosterone and NE levels in humans is unclear (25, 28, 29). Some authors have alternatively hypothesized that Nerve Growth Factor (NGF) levels are modulated following SGB (30, 31), and there is evidence that NGF levels may decrease with testosterone withdrawal, affecting neural growth and neural plasticity (32, 33) that could ultimately effect thermoregulation.

We are currently studying SGB effects in postmenopausal women in a sham-controlled clinical trial funded by the National Institute on Aging (NIA R01AG049924-01; PI Walega).

Given the frequency and severity and interference of HF in men on ADT for prostate cancer, in addition to the negative effects HF impose on this patient population and a paucity of effective treatments, finding alternative treatments for HF in this population is needed.

3.0 STUDY ENDPOINTS:

Primary Outcome
Change in frequency of weekly hot flashes by self-report hot flash diary between baseline and 3 months following the intervention.

Secondary Outcomes

1. Change in frequency of weekly hot flashes by self-report hot flash diary between baseline and 1 month following the intervention.
2. Change in frequency of weekly hot flashes by self-report hot flash diary between baseline and 6 months following the intervention.
3. the change in hot flash severity (hot flash frequency * hot flash intensity) between baseline and 1, 3, 6 months following the intervention
4. the change in Hot Flash Related Daily Interference Scale (HFRDIS) between baseline and 1, 3, 6 months following the intervention
5. PROMIS SF4a (sleep)
6. Patient Global Impression of Change Score (PGIC)
7. Number and type of adverse events related to SGB according to NCI-CTCAE v5.0.

Mean frequency= ((Fmo+Fse))/7
where Fmi, Fmo and Fse are the weekly total number of mild, moderate or severe/very severe HF events

Mean severity = (Fmi+2×Fmo+3×Fse)/7
where Fmi, Fmo and Fse are the weekly total number of mild, moderate or severe/very severe HF events In the case of mean severity, frequency of mild vasomotor symptoms (VMS) is not counted at baseline

4.0 STUDY INTERVENTION:

Image Guided Right Sided Stellate Ganglion Block with 0.5% Bupivacaine

5.0 PROCEDURES INVOLVED:

5.1 Study design:

We aim to conduct a single-site, open label trial of SGB in men with prostate cancer on ADT.

5.2 Methods & Study Procedures:

Refer to the Section 5.3, Schedule of Events, for additional information.

Visit 1
Consent
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. Participants will consult with Dr. Walega who will explain the injection procedure and perform a brief physical examination (focus on cervical range of motion and anterior cervical anatomy) to confirm patient eligibility for the

study. The SGB will be scheduled within 2 weeks of this visit, based on convenience and availability of the participant. Participants will be asked to complete a Hot Flash Related Daily Interference Scale and secondary outcome measures at this visit. They will complete a hot flash diary for at least 1 week. To qualify for study inclusion, participants must have ≥ 28 hot flashes per week or will be considered a screen failure and will be excluded.

Visit 2

Intervention

Participants will be NPO for 6 hours prior to the intervention and will arrange transportation home. At the time of the injection procedure, an angiocatheter will be placed in the hand/arm for peripheral intravenous access as a safety precaution. Participants will be positioned supine in cervical extension on a procedure table in the fluoroscopy suite of the NMH Pain Clinic (Lavin 1400). The anterior neck will be prepped with chlorhexidine and draped in the standard sterile manner.

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 (5 mL) will be injected and the needle will be removed.

Monitoring after SGB

Participants will be transferred to a recovery area and monitored in a reclining position for approximately 20-30 minutes after the SGB to assess potential adverse effects of the injection. Vital signs will be measured approximately every 5 minutes during the recovery phase. Presence of a Horner's sign (miosis, ptosis, anhydrosis) will be recorded and will validate successful SGB. Expected adverse events and serious adverse events may include any of the following:

Adverse Events (Immediate Post-Procedure):
Local anesthetic toxicity (seizure, loss of consciousness)
Inability to swallow (superior laryngeal nerve spread of local anesthetic)
Difficulty with phonation (recurrent laryngeal nerve spread of local anesthetic)
Weakness of arm (brachial plexus spread of local anesthetic)
Weakness of arms and legs (epidural spread of local anesthetic)
Shortness of breath (phrenic nerve spread of local anesthetic)
These effects would be clinically apparent in the Post-Anesthesia Care Unit (PACU) during the 30 minute post injection observation period; patients are not discharged until vital signs, motor and sensory function of the upper and lower extremities are assessed as normal, and patient is able to phonate and swallow liquids.

Follow-Up

- 24h follow-up (+3 days to allow for scheduling constraints with weekends)

Participants will be contacted one day following the intervention to assess for any adverse events or side effects. Expected adverse events may include any of the following:
Pain at injection site
Swelling at injection site
Severe bruising at injection site

- Long-term follow-up at 1, 3, and 6 months

Participants will complete daily hot flash diaries and weekly HFRDIS scales via REDcap email for the duration of the 6 month follow up. Secondary measures will be collected at 1, 3 and 6 months after the intervention. Participants will have the opportunity to share any new concerns or problems with research personnel during these interactions, and will be instructed to contact Dr. Walega (PI) if any more urgent concerns arise. Contact information is provided in the ICF.

Patients will be contacted via telephone or via REDcap generated email on a weekly basis, if needed, to encourage continued participation in follow up measures, and data will be collected via REDcap. Reminder phone calls will be made if the participant forgets to send their information.

Schedule of Events

	Screening and Baseline Assessments[7]	Registration[7]	Day of Intervention[8]	1 day follow-up (+ 3 day window)	1 month follow-up (± 7 day window)	3 month follow-up (± 7 day window)	6 month follow-up (± 7 day window)
Informed consent	X						
Demographic information and medical history[1]	X						
Physical exam, height, and weight[2]	X						
AE assessment[3]	X		X	X	X		
HF severity assessment[5]	X (collect HF data for ≥ 1 week prior to the day of intervention)				X	X	X
HFRDIS[6]	X			Weekly during follow-up per Section 5.2			
PROMIS SF4a[6]	X				X	X	X
PGIC score[6]					X	X	X
Registration[7]		X					
SGB Intervention[8]			X				
Horner's sign assessment post-SGC intervention[8]			X				
Timed vitals during recovery[9]			X				
Follow-up contact[10]				X	X	X	X
Weekly reminders[11]	X						
Hot flash diary[12, 5]	X						

1. Demographic information and medical history to include: age, body mass index, race, years of education, marital status, Gleason score, duration of hot flashes (months), type of ADT (specify) per Section 5.4. Height and weight to be collected for BMI calculation. Pathology report to be collected to determine Gleason Score.
2. Brief physician-directed physical exam to focus on cervical range of motion and anterior cervical anatomy per Section 5.2.
3. Refer to Section 5.6 for details on the collection of AEs and SAEs. In brief, AEs that are related to the intervention (irrespective of expectedness) will be collected from the time of consent (baseline) through the 30 days after the intervention (the 1 month follow-up visit). All SAEs (irrespective of attribution/relatedness or expectedness) will be collected from the time of consent (baseline) through 30 days after the intervention (the 1 month follow-up visit).
4. Screening labs not required for this study; not a standard of care
5. Patient-reported hot flash (HF) frequency and HF intensity to be collected, based on the participant's hot flash diary. These values will be used to calculate a HF severity score, per Section 3.0. Participants must complete the diary for at least 1 week prior to receipt of the intervention to be able to determine the baseline HF severity score.
6. HFRDIS, PROMIS SF4a, and PGIC score questionnaires to be administered via REDCap. Other methods may also be used (i.e. in person, over the phone, through mail or email, etc.) if required.
7. All screening assessments to be conducted 0-14 days prior to registration, unless otherwise indicated. Participants must register to the trial prior to receipt of the study intervention. Refer to Section 12.0 for registration instructions.
8. The SGB intervention should take place AFTER registration and within 1-2 weeks after the baseline/screening assessments per Section 5.2. Participants are to complete the diary daily starting at least 1 week prior to receipt of the SGB intervention. Details of the SGB intervention and Horner's sign assessment are described in Section 5.2
9. Vitals are to be assessed approximately every 5 minutes for approximately 20-30 minutes while participants are in recovery, after receipt of SGB.
10. Participants will be contacted for follow-up via their preferred method of contact (phone call, in-person visit, email, etc.) 1 day and 1 month after the intervention to collect AE/SAE data. They will also be contacted (via REDcap or other means) at 1 month, 3 months, and 6 months to collect information for secondary outcomes.
11. Qualified research staff may contact participants via their preferred method of contact (phone call, in-person visit, email, REDcap generated email, etc.) approximately once a week (or less frequently as needed) throughout the course of the study to remind participants to comply with study procedures, including but not limited to: scheduling appointments; completing the HF diary; completing the HFRDIS, PROMIS SF4a, and PGIC score questionnaires; assessing AEs/SAEs.
12. Participants will be instructed to begin completing the hot flash diary at the time of screening/baseline assessments. Participants are to complete the diary daily starting at least 1 week prior to receipt of the SGB intervention and through the 6-month follow-up time point. Weekly phone calls (or other preferred method of contact) may be used to remind participants to comply.

5.4 Outcome Measures

Hot Flash Diary
Daily Hot Flash Diaries (daily throughout entire study): daily diaries include measures of: (a) hot flashes frequency while awake; (b) the number of night sweats; (c) intensity of hot flashes while awake, with
0 = none
1 = mild (1 or 2 episodes of heat)
2 = moderate (3 to 4 episodes of heat with discrete sweating)
3 = severe (5 or more sudden episodes of heat accompanied by sweating, sleep disturbance, feelings of irritation or anxiety).

Hot Flash Related Daily Interference Scale (HFRDIS)(34)
This validated measure assesses the impact of hot flashes on overall quality of life as well as on work, social activities, leisure activities, sleep, mood, concentration, relations with others, sexuality, and enjoyment of life. A total of 10 areas are assessed with a 0-10 scale. The maximum score, demonstrating the most severe interference of HF is 100.

PROMIS SF4a (sleep)
One of the PROMIS measures, this is a 4-item questionnaire that queries sleep duration, quality, and interruption.

Patient Global Impression of Change
This outcome has the participant assess how much improvement they believe they have experienced from an intervention. This will be collected at 1, 3, and 6 month time points.

General Demographic and Health Status Information
We will obtain sociodemographic and clinical variables based on participant report, including

- age
- body mass index
- race
- years of education
- marital status
- Gleason score
- duration of hot flashes (months)
- type of ADT (specify)

5.5 SGB Risks & Safety:

Stellate ganglion injections are commonly performed in the U.S., have been in clinical use for more than 50 years, and are considered safe and effective in treating a variety of neuropathic syndromes and ischemic pain states and cardiac dysrhythmias (Complex Regional Pain Syndrome Type I and II, herpes zoster, frostbite, Raynaud's syndrome, vascular headaches, refractory ventricular tachycardia, pulmonary artery hypertension, for example). Several more recent studies have demonstrated clinical effectiveness in treating vasomotor symptoms

in women and no adverse events have been reported from these more recent trials.

SGB is considered safe when performed with image guidance and by an experienced injectionist. The published rate of adverse events with SGB, pre-dating image guided procedures, is 0.17%. Severe injury related to SGB is very rare. The incidence of unanticipated bleeding complications following SGB is 1:100,000. It follows that image guided injections, as with fluoroscopy, would have far fewer complications, as critical vascular or neural structures can be visualized in real time and thus can be avoided. Dr. Walega has been performing this injection for 20 years and has 3 other active clinical trials assessing the effects of SGB in women, including a study funded by the National Institute on Aging, of which Dr. Walega is the PI.

In none of these studies has an adverse event occurred. Adverse events will be assessed at the time of the study intervention, at discharge from the post-anesthesia care unit (PACU), at the 24 hour post-injection follow-up, and at the 1 month follow-up. All adverse events that are possibly, probably, or definitely related to the intervention will be collected. All SAEs, regardless of attribution, will be collected. Refer to Section 5.6 for details.

The following potential adverse events are expected:

Risks of Stellate Ganglion Injection
Stellate ganglion injection carries the potential risk of infection, bleeding, transient seizure, or nerve injury which may result in paresthesia or weakness. Risks are mitigated and effectively minimized with the use of fluoroscopic guidance and confirmatory contrast dye study during the SGB.

Risks Related to Needle Placement
Temporary bruising or swelling at the site of the injection on the right anterior neck
Hematoma (pocket of blood caused by bleeding from a broken blood vessel)
Injury to the nerves around the injection site
Puncture of the lung or a blood vessel which may compress the lung and require further medical treatment.
Infection of the tissues of the neck, nerves, bone or disc material in the area of injection

Risks Related to spread of local anesthetic
Allergic reaction to local anesthetics (lidocaine or bupivacaine) or contrast dye
Temporary voice hoarseness
Temporary difficulty swallowing
Temporary weakness of the right diaphragm which may cause shortness of breath or mild difficulty in breathing
Temporary high or low blood pressure
Temporary numbness on the anterior neck region and right shoulder
Temporary numbness or weakness of the arms and legs with short term inability to talk or swallow

*As the half-life of bupivacaine is 6-8 hours, all of the above would resolve within this 6-8 hour time period
*Antidotes to local anesthetic toxicity, including propofol and lipid emulsion, are immediately available in the Omnicell of the Pain Clinic
*A crash cart is immediately available in the recovery room of the Pain Clinic
*The Pain Clinic is staffed by 3 anesthesiologists daily, in addition to 2-3 RNs

Risks Related to Fluoroscopy
The dose of radiation used in the procedure is approximately equal to 25 days of natural environmental radiation the average person receives in the United States.

Radiation Dosimetry Form

5.6 Adverse Events (AE) and Serious Adverse Events (SAE)

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The level of risk attributed to this study requires moderate intensity monitoring, as outlined in the DSMP. All SAEs will be reported in real time to Northwestern University's Quality Assurance (QA) Dept. and the Northwestern IRB. All AEs that are possibly, probably, or definitely related to the intervention will be reported to Northwestern University's QA Dept. on a semi-annual basis. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

5.6.1 Adverse Event Monitoring & Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Sections 5.2 and 5.3 for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

5.6.2 Definitions & Descriptions

5.6.2.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or

frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

For this study, only AEs that are possibly, probably, or definitely related to the intervention will be collected *(Refer to Section 5.6.2.3 for separate criteria for collection of SAEs)**.*** Expected symptoms are listed in Sections 5.2 and 5.5 and/or can be found in the U.S. FDA drug package insert. AEs that are possibly, probably, or definitely related to the intervention will be collected from the time of signing informed consent until 30 days after receipt of the intervention at the 1 month follow-up time point. Refer to Sections 5.2 and 5.3 for additional information on the time points for AE collection.

5.6.2.2 Severity of Adverse Events

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5.0 is available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

5.6.2.3 Serious Adverse Events

All serious adverse events (SAEs), regardless of expectedness and attribution, occurring from the time of signed informed consent, through 30 days after the last administration of study drug (i.e. at the 1 month follow-up time point), must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**
- **Is *life-threatening*.**
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.**
- Results in *persistent or significant disability or incapacity*.
- Is a *congenital anomaly/birth defect.*
- Is an *important medical event.*
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event". For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

5.6.2.4 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO)

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

5.6.2.5 Expedited Reporting to Northwestern University's QAM/DMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number

- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to and reviewed by the DMC at their next meeting.

5.6.2.6 Expedited Reporting to Northwestern University's IRB

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

5.6.2.7 Routine Reporting to Northwestern University's QAM/DMC

All routine AEs (those that are possibly, probably, or definitely related to the intervention) must be reported to the assigned QAM on a semi-annual basis.

6.0 DATA AND SPECIMEN BANKING

NA

7.0 SHARING RESULTS WITH PARTICIPANTS

Specific or detailed study results will not be shared with the study participants

8.0 STUDY TIMELINES

IRB submission and approval process 1 month
Recruitment 6 months
Participant follow-up 6 months
Statistical analysis and Manuscript development 2 months
Duration of participation for each subject is approximately 6.5 months

9.0 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria:

1. Men with prostate cancer (with or without metastatic disease) on ADT for at least 2 months
2. Must have greater than 28 hot flashes per week
3. Age ≥18 years and less than ≤ 70 years
4. Body Mass Index (BMI) less than 32
5. Willingness to undergo image guided intervention
6. Must have the ability to understand and the willingness to sign a written informed consent prior to registration on study

Exclusion criteria:

1. Conditions that preclude SGB or sham intervention (e.g., anatomic abnormalities of the anterior neck or cervical spine; metastatic disease in or near the cervical spine; goiter; cardiac/pulmonary compromise; sleep apnea; acute illness/infection; coagulopathy or history of bleeding disorder; allergic reactions/contraindications to a local anesthetic or contrast dye)
2. Current treatment of prostate cancer with radium or chemotherapy at the time of registration, or within ≤ 14 days prior to the date of SGB intervention.
3. Use of treatments in the past two months that can affect HF (e.g., testosterone or androgen supplementation)
   Note: SSRIs, serotonin norepinephrine uptake inhibitors, and membrane stabilizers will be allowed but must be on stable unchanged dose for at least 8 weeks prior to registration.
4. Inability to write, speak, or read in English
5. Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints

10.0 VULNERABLE POPULATIONS

NA

11.0 PARTICIPANT POPULATION

Accrual Number:	Category/Group: Adults	Consented: Maximum Number to be Consented or Reviewed/Collected/Screened	Enrolled: Number to Complete the Study or Needed to Address the Research Question
Total:	18	18	14

12.0 RECRUITMENT METHODS & REGISTRATION

12.1 Recruitment Methods

Participants will be recruited from Dr. Morgans' practice in addition to other prostate cancer oncologists and caregivers in the NM Division of Hematology & Oncology. Participants will call the study team to go through the 10 minute screening survey. This includes a baseline HFRDIS questionnaire to ensure the patient would qualify. The participant needs to have a score of >40 to be eligible for the study. Once it is determined they meet the criteria for the HFRDIS subjects will be asked to come to the research office for consenting if they are interested in the study.

Flyers will be posted around the NMH medical center to advertise the study.

The trial will be posted on clinical trials.gov

12.2 Registration Procedures

For potential patients for this study, study teams are asked to inform the Quality Assurance Monitor (QAM) of the date and time that the patient will need to be registered (croqualityassurance@northwestern.edu).

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive a subject identification number:
• Eligibility eCRF (complete in NOTIS at https://notis.fsm.northwestern.edu)
• Eligibility checklist (signed and dated by the treating physician – upload in NOTIS)
• Signed and dated informed consent document (upload in NOTIS)

The QAM will review the above registration materials, register the patient, assign an identification number, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

13.0 COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participants will receive $100 by check mailed to their address at the completion of the study to compensate for their time and effort in this study. They will receive parking passes for the on-site study visits.

14.0 WITHDRAWAL OF PARTICIPANTS

Patients can be taken off the study treatment and/or the study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate CRF. An example of when participants may be withdrawn from the research without their consent is if they are non-compliant with providing outcome measures and/or if they begin using a medication known to have an effect on HF. In such cases, or if the participant communicates in writing that he wishes to withdraw, this will be communicated to the study team and the participant and status will be changed from "active" to "inactive".

15.0 RISKS TO PARTICIPANTS

See "Risks & Safety" in PROCEDURES above

16.0 POTENTIAL BENEFITS TO PARTICIPANTS

Individual participants may experience an improvement in hot flashes as a result of this research, with secondary improvements in quality of life, mood and sleep.

17.0 STATISTICS, DATA MANAGEMENT AND CONFIDENTIALITY

Power Analysis

We derived our sample size estimates for the analysis of the primary endpoint for this study, i.e., change in weekly frequency of severe hot flashes at 6 months post-intervention vs. baseline (pre-intervention), based on data in the literature from a randomized controlled trial comparing different treatments for HF in men with prostate cancer on ADT. The pre-treatment baseline weekly frequency of severe hot flashes was assumed to be 46.0 ± 43 (mean ± SD)[35].

Because there are no published data on the variability of within-person differences between the 6-month and baseline measures for severe hot flashes, we estimated the variance for this 6-month change variable using the equation for the variance of the difference between two possibly correlated measurements, as provided in the textbook by Rosner, 7th edition, pg. 305. This equation depends on the baseline standard deviation (SD1), the standard deviation of the 6-month assessment (SD2), and the within-person correlation (ρ) between the baseline and 6 month follow-up variables. We allowed the original baseline and 6-month SDs to differ at the two assessment times but varied the within-person correlation between pre- and 6-month post-treatment measurements (range: ρ =0.5 to ρ=0.8, in increments of 0.1).

The results below assumed a value of 21 for SD2 and assume the properties of the exponential distribution are approximately valid for the severe hot flashes measure (i.e., we assumed that the underlying mean and standard deviation are approximately equal).

Using a paired one-sample t-test comparing changes between 6-month assessment and baseline, a sample size of 14 participants will provide 80% power with a two-sided α = 0.05 to detect a reduction of 52% in mean frequency of severe hot flashes (Δ=23.9) if ρ=0.8 (e.g., from a mean of 46.0 at baseline to 22.1 at 6-months following treatment)[20]. As an exploratory calculation, if our assumptions were revised to ρ=0.7, then the corresponding sample size required would be 17 participants.

If we expect up to about 20% attrition in studies such as this, then we will recruit up to a total of 18 participants in this pilot study.

Statistical Plan

Nominal patient characteristics data will be summarized descriptively as number and percent of participants in each category. Ordinal and continuous patient data that are not approximately normally distributed will be summarized as median and interquartile range (IQR). Normally distributed continuous patient data will be presented as mean ± SD.

Data required for the primary outcome variable, i.e., mean daily frequency of severe hot flashes in the study sample at 6 months after the intervention vs. the baseline daily frequency of hot flashes in the study sample, will be reported as the mean ± SD if appropriate, or as the median (IQR) otherwise. The primary outcome data will be evaluated using a paired t-test if the data are approximately normally distributed, or using with the Wilcoxon matched pairs signed rank test if they are not. The mean difference and 95% CI will be calculated. The criterion for rejection of the null hypothesis (i.e. no change over the baseline to 6-month follow-up assessment of the mean weekly frequency of severe hot flashes) will be a two-tailed $p < 0.05$.

For AE analysis, safety and tolerability will be summarized descriptively by providing the frequency of adverse events by severity, type, and attribution.

Differences from baseline and associated 95% CIs will be calculated for planned analyses. Variables that are approximately normally distributed (e.g., hot flash frequency) will be summarized as mean ± SD. These data at baseline, 1, 3, and 6 months will be compared using the one-way repeated measures analysis of variance with pairwise multiple comparison with baseline made using the Holm-Sidak method when appropriate.

The criterion for rejection of the null hypothesis for all of the secondary analyses will be a two-tailed $P < 0.05$, as this is an exploratory study.

With severe HF frequency selected as the primary outcome, > 35% reduction from baseline to 6 months will be considered to be clinically significant. However, as this is an exploratory study, a larger reduction was used for the power analysis presented above.

If this study shows meaningful treatment effects in this study population, we plan to further evaluate our hypotheses in a larger, randomized blinded sham controlled study.

We anticipate that results of the current proposed study will provide more accurate estimates of HF frequency and variability than currently available in the literature, and these data can be used to design a rigorous larger RCT.

Given the small sample size, we do not plan on a midterm analysis or futility assessment.

All data will be de-identified and recorded in duplicate on electronic study-specific case report forms (CRFs) REDcap. Participants will be given a study identification number that will be reported on all CRFs and source documents. Only the PI and authorized staff, according to the list of Authorized Study Personnel, are entitled to make entries on the CRF. Personal patient data will be kept confidential. Patient documentation will identify a patient by initials and study number only. The PI will keep in his file a Patient Identification and Enrollment List. To allow compliance with GCP principles, each patient will be asked for consent regarding the access to source documents for monitoring, audits, and inspections. Data both electronic and paper will be destroyed 5 years after manuscript completion using current vendors and department protocol.

18.0 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Data will be de-identified and given a study identification number. The PI will keep in his file a subject identifier log. To allow compliance with GCP principles, each patient will be

asked for consent regarding the access to source documents for monitoring, audits, and inspections. During the consent process they will be reassured that their data will be de-identified and personal patient data will be kept confidential

19.0 COMPENSATION FOR RESEARCH-RELATED INJURY

N/A

20.0 ECONOMIC BURDEN TO PARTICIPANTS

N/A

21.0 CONSENT PROCESS

Participants will be consented in the NMH Pain Clinic (259 East Erie Street, Suite 1400) or other similar location by authorized research staff. Authorized research staff will explain the consent document. Each section of the form will be discussed, taking time to highlight the purpose of the study, procedures, risks, confidentiality measures taken to protect the participant, and how to revoke/withdraw consent, if desired, and to answer any questions the participant may have. They will also be informed that participation in this study is completely optional and regardless of their participation their care will not be negatively impacted. Subjects will be given ample time as they need to make their decision. The participants will receive a signed copy of the consent.

22.0 PROTECTED HEALTH INFORMATION/HIPPA

HIPPA 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 subjects name, address, or phone number. Health information we 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
•Records about study devices

23.0 QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

There are > 1000 patients with prostate cancer treated annually at NMH, ensuring the patient sample projections can be achieved. The principal investigator has over 20+ years of clinical experience performing the SGB intervention, and has ongoing NIH sponsored research studying the effects of SGB in postmenopausal women. He has authored several peer reviewed articles on the topic of SGB for pain indications and for hot flashes. Authorized research personnel have years of clinical research experience. All research team members have completed the necessary regulatory training. We anticipate 1-2 potential cases per week. Authorized research personnel will have dedicated time to recruit patients. All authorized research personnel are informed about the protocol and their duties and functions.

24.0 WAIVER OR ALTERATION OF CONSENT PROCESS

NA

25.0 NON-ENGLISH SPEAKING PARTICIPANTS

NA

26.0 STUDY-WIDE RECRUITMENT METHODS

Local methods previously described.

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