Evaluation of Pulsed Radiofrequency Ablation of the Superior Hypogastric Plexus for Treatment of Bladder Pain Syndrome: A Randomized, Placebo-Controlled Pilot Study

Principal Investigator: Eli Medvescek, MD

NCT Number: Not yet assigned

Document date: 16 NOV 2023

EIRB Protocol Template (Version 1.3)

1.0 General Information

***Please enter the full title of your study:**

Evaluation of Pulsed Radiofrequency Ablation of the Superior Hypogastric Plexus for Treatment of Bladder Pain Syndrome: A Randomized, Placebo-Controlled Pilot Study

***Please enter the Protocol Number you would like to use to reference the protocol:**

WRNMMC.1111
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

No

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study:

Primary Dept?	Department Name
◆	**P and R** - Walter Reed National Military Medical Center (WRNMMC)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

Medvescek, Eli David

Select if applicable

☐ Student ☐ Site Chair
☑ Resident ☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Dengler, Katherine Laura, MD LTC
Associate Investigator
Griswold, Lauren Hoepfner, MD Capt

Associate Investigator
Wilson, Sara Merkl
Associate Investigator

B) Research Support Staff

Park, Edward Jongseok, MD CPT
Monitor

3.3 *Please add a Protocol Contact:

Dengler, Katherine Laura, MD LTC
Griswold, Lauren Hoepfner, MD Capt
Medvescek, Eli David
Wilson, Sara Merkl

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

BERRY, KYLE Russel
Department Chair

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 * What department(s) will be associated with this protocol?

	Anesthesiology
	Obstetrics And Gynecology

4.2 * Is the IRB of record for this study an IRB/HRPP that does NOT use EIRB? If Yes, complete the application according to the IRB/HRPP Determination.

If your Projects or Protocols are under the oversight of another IRB that does use EIRB, stop this submission and contact the core site and request an invitation as a performing site.

If your Project or Protocol is now being submitted for the first time to an IRB that does use EIRB, continue with this application and answer the questions to be reviewed by the IRB.

Answering yes means the board of record is an IRB that does NOT use EIRB.

○ Yes ◉ No

4.3 * Is this protocol research, expanded access, or humanitarian use device?

◉ Yes ○ No

4.4 * What type of protocol is this?

- ☐ Behavioral Research
- ☑ Biomedical Research
- ☐ Clinical trial (FDA regulated)
- ☐ Educational Research
- ☐ Expanded Access
- ☐ Humanitarian Use Device (HUD)
- ☐ Psychosocial Research
- ☐ Oral History
- ☐ Other

4.5 Are you conducting this project in pursuit of a personal degree?

○ Yes ◉ No

4.7 * Is this human subjects research? (As defined by 32 CFR 219) Human subject means a living individual about whom an investigator (whether professional or student) conducting research:
(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
(ii) Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens.

◉ Yes ○ No

4.8 * Do you believe this human subjects research is exempt from IRB review?

○ Yes ◉ No

5.0 Personnel Details

5.1 Does the Principal Investigator have a Permanent Change of Station (PCS) Date or Estimated Institutional Departure Date (EIDD)?

◉ Yes ○ No

Principal Investigator

Eli David Medvescek

06/30/2026

5.2 List any Research Team members without EIRB access that are not previously entered in the protocol:

No records have been added

5.3 Are any Contractors or Subcontractors involved in this study? If yes, please list them and describe their role.

○ Yes ◉ No

No records have been added

5.4 Will you have a Research Monitor for this study?

- (•) Yes
- ( ) No
- ( ) N/A

Research Monitor Qualifications
Ensure the individual has expertise consistent with the nature of risk(s) identified within your study and is independent of the team conducting the research.

Research Monitor Role:

1. Promptly reporting any observations and findings to the Institutional Review Board (IRB), the Human Protections Administrator (HPA), or the Institutional Official;
2. Stop the research study in the presence of safety concerns for the human subjects involved in the protocol. The RM may remove human subjects from the study and take any others actions necessary to protect the subjects of the study. The RM may discuss the protocol with the investigators, interview human subjects, and consult with others outside the protocol about the research;
3. Review the study monitoring plans, review Adverse Events and determine their relatedness to the protocol, review Unanticipated Problems Involving Risks to Subjects of Others, make recommendations on changes to the informed consent process based on the review of study events, and review and sign the continuing review report and other substantial submissions to the IRB.
4. Observe recruitment, enrollment, consent procedures and oversee study interventions.

If applicable, you may nominate an individual to serve as the Research Monitor:

Selected Users
Edward Jongseok Park, MD CPT

6.0 Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

- ( ) Yes
- (•) No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
No records have been added		

Total amount of funding:

0

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

All personnel engaged in research must complete and attach a Conflict of Interest (COI) form.

8.0 Study Locations

8.1 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

○ Yes ◉ No

8.2 Study Facilities and Locations:

Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site
DHA	WRNMMC	Lead site				: WRNMMC IRB

Other:

Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site
No records have been added					

8.3 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

○ Yes ◉ No

8.4 Is this an OCONUS (Outside Continental United States) study?

○ Yes ◉ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

○ Yes ○ No

9.0 Study Details

9.1 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

chronic pelvic pain, bladder pain syndrome, interstitial cystitis, superior hypogastric plexus, pulsed radiofrequency ablation

9.2 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

Interstitial cystitis / bladder pain syndrome (IC/BPS) is a complex chronic pain syndrome characterized by bladder pain, pressure, and discomfort with urinary urgency and frequency, without signs of infectious or alternative cause [1]. It disproportionately affects women, with an estimated 3-7% prevalence among women in the United States [2, 3], and with a prevalence of 61% among women with chronic pelvic pain [4]. Pathophysiology is currently poorly understood and the cause is unknown [2, 5]. It is widely accepted that IC/BPS may be broken into Hunner-type and non-Hunner type variants; however, beyond this histopathologic distinction, there remains a wide variety of proposed inflammatory, structural, autoimmune, infectious, functional, and neurogenic contributors to the overall picture of disease [2, 5].

Current treatment of IC/BPS in the United States is guided by recommendations from the American Urological Association (AUA) and the American Urogynecologic Society (AUGS). In 2022, the AUA released updated guidance for treatment of IC/BPS. They outline a graded approach to uncomplicated IC/BPS, including non-pharmacologic and behavioral treatments (diet, education, stress management, physical therapy), oral medications, intravesical instillations, or procedures such as cystoscopy with hydrodistension, onabotulinumtoxinA injections, or neuromodulation [1]. Rather than presenting these therapies in a "step-up" fashion, the AUA notes that initial treatment type should depend on symptom severity and patient preference, and multiple simultaneous therapies may be considered. Surgery with cystectomy or bladder augmentation are considered last-resort therapies. Of note, many of these established treatment options may come with undesirable side effects, intolerable complications, risks associated with general anesthesia, or shorter-than-optimal duration of action.

Some authors note that there is no one consistently effective treatment for IC/BPS [3, 6], and one estimate states that 10% of patients with IC/BPS are refractory to conservative, non-surgical treatments [3]. There is also a substantial psychosocial burden of IC/BPS; most patients with the disease have seen numerous providers before being appropriately diagnosed, and have tried multiple therapies unsuccessfully [6]. These patients frequently experience concomitant voiding and bowel dysfunction, sexual dysfunction, mood disorders, social isolation, and greater unemployment [6].

One important contributor to the constellation of findings in IC/BPS is a shift towards sympathetically-mediated pain sensation in the setting of chronic pain [5]. Central sensitization is hypothesized to occur in IC/BPS as well as other chronic pelvic pain syndromes [2, 4, 5]. Williams et al found that subjects with IC/BPS had diminished vagal activity and a shift towards sympathetic nervous system dominance as reflected by decreased high-frequency heart rate variability on tilt table testing [7]. Charrua et al had similar findings, showing significantly lower mean variation of the standard deviation of the P wave interval (a marker of sympathetic overactivity) on tilt table testing as well as significantly higher twenty-four hour urinary noradrenaline in patients with IC/BPS [8]. These studies implicate autonomic nervous system aberrancy as a key factor in IC/BPS. Neuromodulation is the intervention of choice for managing hyperalgesic autonomic nervous system dysfunction [4]. While neuromodulation using implantable stimulators has been extensively studied in IC/BPS [3], little research has been done on chemical neurolysis, radiofrequency ablation, or other nerve interruption strategies for pain management in IC/BPS.

Superior hypogastric plexus block (SHPB) is an interventional strategy used in chronic pain management initially investigated for the management of chronic cancer-related pelvic pain [9]. The procedure targets the superior hypogastric nerve plexus, which is a bilateral retroperitoneal structure at the approximate level of L5/S1. The structure provides innervation to pelvic viscera including the bladder, urethra, vagina, vulva, ovaries, uterus, and pelvic floor. A study conducted by Plancarte et al investigated the first use of SHPB for chronic pelvic pain related to cancer in 28

patients. By injecting aqueous phenol in the retroperitoneal space overlying the superior hypogastric plexus, their team demonstrated a mean pain reduction of 70% in those treated with the block, with 3 patients experiencing durable pain relief for over two years [9].

Since it was first described, the method has been studied extensively in the management of chronic pelvic pain, having been demonstrated to be safe and effective in several prospective, retrospective, and randomized-controlled trials [10]. Rocha et al analyzed 180 patients across 10 years treated with the block in a retrospective cohort study; their findings supported those of Plancarte et al, with 50% pain reduction observed in 48.8% of patients at 6 month follow-ups with no major complications or procedure-related morbidity [11]. Literature on the block is steadily growing, with numerous articles showing effective and safe use of the block in the conditions such as endometriosis [12, 13], adenomyosis [13], post-cesarean section pain [14], and even in a case of pain associated with Mayer-Rokitansky-Kuster-Hauser syndrome [15]. SHPB has also been explored for treatment of IC/BPS, though overall studies are lacking. A prospective unblinded randomized trial performed in Egypt [16] found that superior hypogastric plexus chemical neurolysis was inferior to bladder hydrodistention in some markers of IC/BPS relief; however, of note, this study was not placebo-controlled and lacked statistical power.

Since its inception, the SHPB has gone through several iterations. One exciting forefront is the use of pulsed radiofrequency ablation (pRFA) in targeting the nerves of the superior hypogastric plexus. pRFA was first introduced in the mid-1990s, and since then has been used extensively in the treatment of pain conditions such as cervical radicular pain, trigeminal neuralgia, groin and perineal pain, myofascial pain, and complex regional pain syndrome [17, 18]. pRFA works by sending millisecond-duration bursts of current through an electrode tip inserted adjacent to a structure of interest [18]. Its exact mechanism is unknown [18], but is hypothesized to involve local thermal effects, high-intensity electric fields at the electrode tip, lower electric field phenomena that potentiate long-term depression of neuronal transmission, modifications to morphology of mitochondria in target tissues, and disruption of microfilaments and microtubules [17]. The evidence behind pRFA is promising, and its safety is extremely well established [17, 18, 19] however, there is a striking paucity of prospective randomized controlled trials assessing its efficacy [18, 20]. Our literature review uncovered only one article investigating the use of pRFA of the superior hypogastric plexus for treatment of IC/BPS - a case report in which the patient experienced durable symptom relief for over two years. In their conclusion, the authors of this case report note that prospective randomized controlled study is warranted to confirm the clinical efficacy and safety of this procedure for the treatment of interstitial cystitis [21].

Given the factors outlined above - namely, (1) the predominance of central sensitization and sympathetic overactivation in IC/BPS, (2) the efficacy and anatomic relevance of SHPB in multiple pelvic pain syndromes, and (3) the established neuromodulatory utility of pRFA - it is reasonable to consider that pRFA of the superior hypogastric plexus may be an efficacious therapy for treatment of IC/BPS. Therefore, the primary aim of this study is to assess the efficacy of pRFA of the superior hypogastric plexus, as compared to treatment with sham, in patients with IC/BPS. The primary outcome will be post-intervention VAS pain scores at 1, 3, and 6 month follow-ups. Secondary outcomes will include ratings of urinary manifestations, measures of mood symptoms, measures of sexual function, and overall patient satisfaction in both treatment and sham groups.

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Citations:

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[10] Urits I, Schwartz R, Herman J, Berger AA, Lee D, Lee C, Zamarripa AM, Slovek A, Habib K, Manchikanti L, Kaye AD, Viswanath O. A Comprehensive Update of the Superior Hypogastric Block for the Management of Chronic Pelvic Pain. Curr Pain Headache Rep. 2021 Feb 25;25(3): 13. doi: 10.1007/s11916-020-00933-0. PMID: 33630172.

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9.3 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions /hypotheses

Primary aim: Assess the efficacy of pRFA to the superior hypogastric plexus in the treatment of IC/BPS symptoms as compared to treatment with sham, as measured by pre- and post-intervention visual analogue scale (VAS) pain scores at 1, 3, and 6 month follow-ups.

Secondary aims: Assess the efficacy of pRFA to the superior hypogastric plexus in the treatment of IC/BPS symptoms as compared to treatment with sham, as measured by:

1. Pre- and post-intervention urinary symptoms:
    1. O'Leary/Sant (OLS) Voiding and Pain Indices
    2. Number of daytime voids
    3. Number of daytime leaks
    4. Nocturia
2. Pre- and post-intervention mood symptoms as measured by the PHQ-9 at 1, 3, and 6-month follow-ups.
3. Pre- and post-intervention sexual function symptoms as measured by the Female Sexual Function Index (FSFI) at 1, 3, and 6-month follow-ups.
4. Pre- and post-intervention patient satisfaction scores at 1, 3, and 6-month follow-ups as measured by the Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Improvement (PGI-I) at 1, 3, and 6-month follow-ups.

Null Hypotheses:
(1) No difference in VAS pain scores between treatment group and placebo group.

Alternative Hypotheses:
(1) Pain scores will be significantly improved in the treatment group compared to placebo group at all interval follow-ups.

9.4 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

Single-blinded, placebo-controlled, single center prospective randomized clinical pilot trial.

9.5 Target Population:

Describe the population to whom the study findings will be generalized

Women aged ≥ 18 with a diagnosis of IC/BPS who score ≥ 6 on the OLS symptom questionnaire.

9.6 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

Research concerning effective treatment for IC/BPS has important implications for Active Duty servicemembers, their dependents, and retirees. A 2006 paper published in Military Medicine analyzed encounters of 1,737 deployed active duty females during Operation Iraqi Freedom, and found that 150 of these patients had a pelvic pain disorder, accounting for 14% of all patients seen for gynecologic services [22]. Many of these patients received a diagnosis of IC/BPS - this represents a barrier to valuable warfighting power and readiness in an operational environment. Investigating strategies to control symptoms associated with IC/BPS will help re-engage servicewomen in the fight earlier and with fewer symptoms. Retirees in the Veterans Administration (VA) also face a notable disease burden; one estimate lists the prevalence of IC /BPS in VA patient population at 1.4% [23]. Importantly, as is given in the Background above, patients with chronic pain and mental health burdens are at an increased risk for complex and intractable symptoms related to IC/BPS [6]; there is known substantial overlap between these patients and the warfighter, who is at risk for mental health disorders such as PTSD and depression by virtue of Active Duty service [24]. When coupling the troubling disease burden above with the high cost of IC/BPS care (as is evidenced by multiple provider visits until diagnosis, and potentially multiple failed treatments before relief), pursuing novel treatment strategies at the intersection of urology, gynecology and chronic pain anesthesia may help decrease overall cost to the Department of Defense.

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Additional citations:

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10.0 Study Procedures, Data Management, and Privacy

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

All staff providers and fellows on the Walter Reed Urogynecology team and the Walter Reed Chronic Pain team will be briefed on the study goals, objectives, and inclusion criteria. Potential participants will be identified by healthcare providers on the above teams as part of regular clinical care. In order to adhere to WRNMMC's recruitment policy, research activities will take place after clinic visit has ended.

WRNMMC healthcare providers will screen potentially eligible patients age 18 or older (inclusive) presenting to Urogynecology or Chronic Pain Clinic for IC/BPS treatment. These healthcare providers will briefly introduce the study and refer patients that express interest to the research team for formal consent. Designated providers in these clinics will provide an informational sheet, explain the study, express the voluntary nature of participation, assess interest in participating, and screen the potential participant for eligibility.

If the potential participant meets eligibility criteria as determined by the inclusion/exclusion criteria and expresses interest in participating in the study, an authorized study team member will initiate the formal consent discussion and obtain informed consent. If the potential participant is uncertain about their interest at the time of screening, they may contact the study team at a later date via email/phone provided on the study information sheet (which will be provided during the screening process) if they desire participation.

Consent will be obtained during the first study intake appointment in Chronic Pain by a member of the research team. During the consenting process, potential study subjects will be informed

that the purpose of the study is to assess the efficacy of pulsed radiofrequency ablation of the superior hypogastric plexus for treatment of pain, urinary symptoms, sexual function, and mood symptoms associated with IC/BPS. They will be informed that the study is a randomized controlled trial and they will not be told whether they are receiving ablation or sham intervention. The procedure will be described to the patient. Potential complications and alternatives will be reviewed. The patient will be informed that they may withdraw their consent at any time, should they provide it, and that all participants will be offered the treatment at the conclusion of the study. If the subject provides consent, they will be randomized equally to a treatment group (pulsed radiofrequency ablation) or a sham group (50-50 split).

The first appointment at Chronic Pain will review intake information and obtain baseline data, including: baseline VAS scores for IC/BPS, baseline OLS Voiding and Pain Indices, number of daytime voids, number of daytime leaks, frequency of nocturia, administration of the PHQ-9, administration of FSFI, current therapies (if any) for IC/BPS, and score rating current level of satisfaction with IC/BPS treatment as measured by PGI-S and PGI-I. These forms will be compiled in the patient's study packet, which will include denotation of their treatment/placebo status and a coded identifier associated with the patient. This packet will be stored in a locked cabinet in the Chronic Pain Clinic. Data gathered at intake will also be transferred to a secure spreadsheet to which only study personnel have access, located on the internal Walter Reed network. After the intake interview, the patient will be consented for pulsed radiofrequency ablation utilizing a standardized pre-approved DD Form 522. The procedure will then be performed by a board-certified pain medicine physician who is a credentialed in performing the procedure.

Prior to the procedure, cefazolin 2 mg IV will be administered for antibiotic prophylaxis. If the patient has an anaphylactic allergy to cefazolin, clindamycin 900 mg IV will be used for antibiotic prophylaxis. American Society of Anesthesiology (ASA) standard monitors will be applied (electrocardiogram, blood pressure cuff, pulse oximetry). Patients will be laid in the prone position with a pillow under their iliac crest. The L5-S1 interspace will be identified using fluoroscopy. The skin overlying this space will be prepared and draped in the usual sterile fashion utilizing chlorhexidine. Local anesthesia at the level of the skin and subcutaneous tissue, approximately 5-7cm bilateral to the midline at the level of the L4-L5 interspace, will be achieved using 1% lidocaine with bicarbonate. Thereafter, a hollow needle will be inserted at the site of local anesthesia directed towards the midline, angled approximately 30 degrees from the transverse plane and 45 degrees from the coronal plane. The needle will be advanced, also under fluoroscopic guidance, until the tip is observed at the anterolateral aspect of L5. The needle tip will then be advanced approximately 1 cm past the vertebral body, through the ipsilateral psoas muscle, into the retroperitoneal space. When both needles are inserted in identical fashion, soluble contrast will be injected to confirm correct placement in the retroperitoneum.

- For treatment arm: A microelectrode will be inserted through the hollow needle. A test pulse will be delivered so the provider can assess for tingling/discomfort in the appropriate anatomic distribution. When proper positioning has been confirmed, 4mL of 1% lidocaine without epinephrine will be administered to reduce discomfort associated with radiofrequency ablation. Pulsed radiofrequency ablation will then be performed at a pulse frequency of 2Hz, pulse width of 20ms, temperature of 42 degrees Celsius, total duration 120 seconds. The microelectrode and hollow-tip needle will then be withdrawn.
- For sham arm: A microelectrode will be inserted through the hollow needle. A test pulse will be delivered so the provider can assess for tingling/discomfort in the appropriate anatomic distribution (although this is the sham group, this is consistent with previous sham operation of pulsed radiofrequency ablation; see [25, 26]). Sham pulsed radiofrequency ablation will then be performed with the radiofrequency generator disconnected from the microelectrode. The duration of the sham procedure will be 120 seconds. The microelectrode and hollow-tip needle will then be withdrawn.

The study participants will be monitored in the Chronic Pain clinic for 30 minutes post-procedure to assess for complications. The intake appointment will last approximately 1 - 1.5 hours. Prior to leaving the clinic, they will be scheduled for 1-month follow-up visit.

At subsequent follow-ups, patients will complete surveys identical to those performed at intake - VAS score, OLS Voiding and Pain Indices, number of daytime voids, number of daytime leaks, frequency of nocturia, PHQ-9, number and type of treatments used in interim, and current level of satisfaction with IC/BPS treatment. Patients will not be restricted from using alternative IC /BPS standard of care therapies (as outlined by the American Urological Association [AUA IC/BPS

Treatment Algorithm 2022]) in the period between study treatments. These forms will be stored in the patient's original packet. Follow-ups will occur at approximately 1-month, 3-month, and 6-month intervals. Follow-up appointments will last approximately 30 minutes.

If a participant fails to follow-up in the clinic, the participant will be contacted via telephone to reschedule as soon as possible.

If complications related to the block occur, these patients will be referred to the Emergency Department for evaluation and managed on a case-by-case basis.

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Additional citations:

[25] Van Zundert J, Patijn J, Kessels A, Lamé I, van Suijlekom H, van Kleef M. Pulsed radiofrequency adjacent to the cervical dorsal root ganglion in chronic cervical radicular pain: a double blind sham controlled randomized clinical trial. Pain. 2007 Jan;127(1-2):173-82. doi: 10.1016/j.pain.2006.09.002. Epub 2006 Oct 18. PMID: 17055165.

[26] Maatman RC, van Kuijk SMJ, Steegers MAH, Boelens OBA, Lim TC, Scheltinga MRM, Roumen RMH. A Randomized Controlled Trial to Evaluate the Effect of Pulsed Radiofrequency as a Treatment for Anterior Cutaneous Nerve Entrapment Syndrome in Comparison to Anterior Neurectomy. Pain Pract. 2019 Sep;19(7):751-761. doi: 10.1111/papr.12806. Epub 2019 Jul 19. PMID: 31188514.

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, and how the data will be operationally measured.

The research team will collect the following information at intake (prior to pulsed radiofrequency ablation) and at follow-up appointments:

- Demographic data (only measured at intake, not at follow-up): Age, race, ethnicity, height, weight, Active Duty military status)
- VAS pain score at time of encounter: The visual analog scale (VAS) is a validated, subjective measure for pain. Scores are recorded by making a mark at any number of defined intervals on a 10-cm line that represents a continuum between "no pain" (0) and "worst pain" (10).
- O' Leary-Sant Voiding and Pain Indices: Standardized, validated survey querying numerical ratings of urinary urgency, urinary frequency, nocturia, and bladder pain /burning.
- Average number of daytime voids over the prior week
- Average number of daytime episodes of urinary incontinence over the prior week
- PHQ-9: The PHQ-9 is a validated, 9-question tool to assess for the degree of depression present in an individual
- Number of treatments tried in the past for BPS (**only measured at intake, not at follow-up**).
- Number of treatments currently taking for BPS
- Current level of satisfaction with BPS treatment: measured by PGI-S and PGI-I.

The source of the data is the patient interview during intake and follow-up appointments. All data is measured as discrete quantitative variables, with patient satisfaction converted to a numerical rating (scale 1-5).

10.3 At any point in the study, will you request, use, or access health information in any form, including verbal, hard copy and electronic?

(•) Yes ( ) No

10.4 Review the definitions below and respond to the following two questions. If you are not sure of the answers, email DHA.PrivacyBoard@mail.mil for assistance. The *Military Health System (MHS)* is defined as all DoD health plans and DoD health care providers that are organized under the management authority of, or in the case of covered individual providers, assigned to or employed by, the Defense Health Agency (DHA), the Army, the Navy, or the Air Force *MHS workforce members* are employees, volunteers, trainees, and other persons whose conduct, in the performance of work for the MHS, is under the direct control of the MHS, whether or not they are paid by the MHS. *MHS business associates* are persons or entities that provide a service to the MHS and require protected health information (PHI) to provide the service.

Are you an MHS workforce member?

(•) Yes, I am an MHS workforce member
( ) No, I am not an MHS workforce member

10.5 Have you consulted with an MHS data expert to determine the data elements required for your study?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (**DHA.PrivacyBoard@mail.mil**)

( ) Yes, then complete the questions below according to the data consult
(•) No, then complete the questions below according to the best of your knowledge

10.6 Indicate how you will request data from the MHS. Select all that apply.

☐ Talking with MHS health care providers or MHS health plans about specific research participants
☐ Obtaining MHS hard copy records specific to research participants
☑ Obtaining data from an MHS information system(s)

10.7 If you are obtaining data from an MHS information system(s), indicate whether you plan to receive a data extract or whether you plan to access an MHS information system directly to create a data set.

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

☐ Data Extract
☑ Access

10.8 Do you intend to request de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:
1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information
2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

( ) Yes (•) No

10.9 Indicate the MHS information system(s) from which you will seek to obtain data

If you do not know which system(s) contains the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or request guidance from an MHS data expert at: **DHA.PrivacyBoard@mail.mil**.

Below is a list of commonly used MHS systems. If the system from which you seek to obtain data is not listed below, list the name of the system in the "Other MHS Systems" category below
PHI Systems:

MHS Information System	Requesting Data
: MHS Genesis	: Yes

PII-Only Systems:

MHS Information System	Requesting Data
No records have been added	

De-Identified Data & Other Systems:

Information System	Requesting Data
No records have been added	

10.10 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

- ○ Yes, will merge data
- ◉ No, will not merge data

10.11 Indicate the data elements about research participants or relatives, employers, or household members of the research participants that you will request from MHS hard copies or from MHS information systems.
If you will merge data, also indicate non-MHS data elements about research participants or relatives, employers, or household members of the research participants that you will have access to in any form or medium.

Direct and Indirect Identifiable Data Elements	DHA Hard Copies	DHA Data Elements to be Accessed	DHA Data Elements Verbal	Extracted DHA Digital Data	Downloaded DHA Digital Data	Non-DHA Hard Copies or Digital
1. Names	☐	☐	☐	☐	☐	☐
2. Postal address with only town, city, state, and zip code	☐	☐	☐	☐	☐	☐
3. Postal address with all geographic subdivisions smaller than state, including street						

address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code from all such geographic units containing 20,000 or fewer people is changed to 000	☐	☐	☐	☐	☐	☐
4. Dates including all elements (except year) directly related to an individual, including birthdate, admission date, discharge date, and date of death	☐	☐	☐	☐	☐	☐
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of	☐	☐	☐	☐	☐	☐

"age 90 or older"						
6. Telephone Numbers	☐	☑	☐	☐	☐	☐
7. Fax Numbers	☐	☐	☐	☐	☐	☐
8. Email Addresses	☐	☑	☐	☐	☐	☐
9. Social Security Numbers	☐	☐	☐	☐	☐	☐
10. Medical Record Numbers (MRN) (including record ID)	☐	☐	☐	☐	☐	☐
11. Health Plan Beneficiary Numbers (including DEERS ID, Electronic Data Interchange Personal Identifier (EDIPI) or Number (EDIPN))	☐	☐	☐	☐	☐	☐
12. Account Numbers	☐	☐	☐	☐	☐	☐
13. Certificate /License Numbers	☐	☐	☐	☐	☐	☐
14. Vehicle identifiers and serial numbers, including license plate numbers	☐	☐	☐	☐	☐	☐
15. Device identifiers and serial numbers	☐	☐	☐	☐	☐	☐

16. Web Universal Resource Locators (URLs)	☐	☐	☐	☐	☐	☐
17. Internet Protocol (IP) address numbers	☐	☐	☐	☐	☐	☐
18. Biometric identifiers, including finger and voice prints	☐	☐	☐	☐	☐	☐
19. Full-face photographic images and any comparable images	☐	☐	☐	☐	☐	☐
20. Any other unique identifying number, characteristic, or code (including non-military provider IDs)	☐	☐	☐	☐	☐	☐
21. Free Text Fields	☐	☐	☐	☐	☐	☐

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used.

Due to guidelines stated within DoDI 1000.30, Reduction of SSN Use within DoD, the reduction or elimination of SSN usage must occur wherever possible. If SSNs are required to complete the project, the PI must provide a justification and explanation as to why a substitution cannot be used.
For example:

- If alternatives to SSN (e.g., EDIPNs or pseudo person IDs) are sufficient in other instances, will those alternatives to SSN usage be sufficient to respond to Congressional inquiries and /or Senior DoD stakeholders inquiries?
- Are alternatives to SSN used first?
- Are those alternatives to SSN insufficient to combine data from multiple data sources? Is the issue that some individuals do not possess alternatives ID numbers and SSN is the only way to identify them?

N/A - Not accessing SSNs.

a. Will you receive or obtain health information?

Note: *If you indicate you are not receiving health information, the answer must be consistent with the DHA data source. For a non-health information data request, if you are a non-MHS employee or non-MHS business associate, you may not access an information system that has PHI or LDS. For both MHS and Non-MHS employees and MHS business associates, you may* ***NOT*** *include data elements in the above table on: 1) lines 10 or 11, 2) line 21 if the free text field comes from a PHI or LDS system, and 3) lines 12, 13, or 18 if the account numbers, certificate and license numbers, biometric data, or any other data elements are health information created or received by an MHS health care provider, health plan, or business associate in relation to the physical or mental health or condition of an individual or payment for health care.*

- (•) Yes, I will receive or obtain health information
- ( ) No, I will not receive or obtain health information

b. If no data elements were checked in the above table, is it possible that the requested DHA data is or will be identifiable because of any unique data elements, triangulation, or small cell size*?*

- [x] Data elements were checked in the above table, STOP HERE.

NOTE: *A unique data element includes any unique features that alone are not identifiable but that could be used to identify an individual within the context of other information, such as any type of code (such as diagnosis or procedural), rank of general or admiral, gender, or race. Triangulation means using different data elements that when combined can be used to identify an individual, such as including the above lists of unique data elements in a data set. Determining whether an individual is identifiable through triangulation requires consideration of all data elements in combination. Within the military, the use of rank and/or diagnosis code, procedural codes, or any other code that changes on a predictable basis, increases the possibility of identification. Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Department of Defense Manual 6025.13, Medical Quality Assurance and Clinical Quality Management in the Military Health System MHS, provides that the threshold for de-identifying data within the MHS requires a cell size of three, but also states that the de-identification standards must meet the DoD implementation of the HIPAA Privacy Rule. Centers for Medicare and Medicaid also gives guidance on small cell size stating that no data cell less than 11 may be published or displayed. However, the Office for Civil Rights' OCR, which is the official regulatory office for the HIPAA Privacy Rule, provides that OCR does not designate a universal value for small cell size in accordance with the de-identification standard; instead, the cell size should be set at a level that is appropriate to mitigate risk of identification by the anticipated recipient of the data set. This means that a cell size of 3 or 11 may not meet the HIPAA Privacy Rule requirements if the cell size level does not appropriately mitigate risk of identification by the anticipated recipient of the data set.*

Note: If dates are altered as a means of de-identifying the data, diagnosis and procedural codes need to be rolled-up or collapsed. If dates are provided "as time between events," the roll-up is not necessary.

- [ ] Yes, the DHA data will become identifiable
- [ ] No, the DHA data will not become identifiable

10.12 Do you believe it is possible for the MHS data to become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would use rank and race together to determine the identity of an individual with a particular health condition.

Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30, so the rank category may need to be expanded to include lower ranks.

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 20 of the table above (in Section 10.10), but that could be used to identify an individual. Unique data elements include characteristics that are not themselves identifying, such as the rank of general or admiral, or a race or gender, but within the context of other information could be identifiable.

- ○ Yes, I believe there is a reasonable possibility the MHS data will become identifiable
- ◉ No, I believe there is no reasonable possibility the MHS data will become identifiable

10.13 Have you completed and uploaded an appropriate HIPAA document (i.e. HIPAA Authorization will be obtained or Waiver/alteration of HIPAA Authorization is being requested)?

- ◉ Yes
- ○ No
- ○ N/A

If yes, please check which one.

- ☑ HIPAA Authorization
- ☐ HIPAA Waiver (Full or Partial)
- ☐ Other (please provide copies when uploading Other Study Documents)

10.14 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

Initial data will be collected at the Chronic Pain intake and study consenting appointment. Information to include PHI (name, telephone number) will be annotated on a physical Intake Data Collection Sheet (see protocol attachment). Data collection sheets will be coded to associate each subject with a number. Subjects will be asked about past medical and surgical history as well as allergies and current medications. Data variables as outlined in section 10.2 above will also be gathered and stored on the physical Intake Data Collection Sheet.

All data sheets will be collected at the completion of each day and placed in a locked cabinet in a locked office in the Chronic Pain clinic. These data sheets will be transcribed within one week to a master data collection sheet (data repository), which will include coded subject identifiers as well as data variables as outlined above. This master data collection sheet will be an Excel document kept exclusively on Walter Reed servers, requiring CAC as well as invitation-only folder access. These documents (hard copy and electric) can only be accessed by the Research Team (PI, AIs, study coordinators). The Primary Investigator will be available for debriefing of any subject after the study is completed if the subject desires. The PI will also be available for any questions during the course of the study. Data in the Excel spreadsheet will be analyzed with the assistance of a biostatistician. At the conclusion of the study, any associations between coded data and identity of participants will be destroyed, thereby de-identifying any data retained for future research (see 10.15 below).

The Principal Investigator agrees to maintain a Study File that must be kept for three years from the date the study is closed (32 CFR 219.115(b)) and that HIPAA authorizations will be retained for 6 years after the study is closed and provided to WRNMMC upon request. PI acknowledges that research data are the property of the Command and will not be removed without prior approval. When PI is scheduled for permanent change of station (PCS) or end of time in service (ETS), study records will be given to a new PI.

Is this a data repository?

◉ Yes ○ No

If Yes, provide name of the Repository.

PRFA_SHPB_REPO

Who will have access to the Repository?

Principal investigator and associate investigators.

What data type will be stored in the Repository?

- [ ] Protected Health Information
- [ ] Limited Data Set
- [x] De-identified Data

10.15 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens/data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed.

This study will involve the retention of de-identified data for potential future research. Consent for retention of data will be obtained at the initial intake appointment via the Informed Consent process. Subjects have the option to decline retaining their de-identified data for future research. Subjects have the option to withdraw their data from the study at any time during or after their study participation. However, subjects will not be re-contacted or re-consented for use of their data after the initial Informed Consent process.

De-identified data will be stored electronically in a CAC-protected, invitation-only folder local to Walter Reed servers. The original hard-copy data, containing subject PHI, will be maintained for three years as given in 10.14 above, then destroyed. Any associations, master list, or other markers that allow connection between data and subjects will be destroyed at the conclusion of the study. When the PI is scheduled for permanent change of station (PCS) or end of time in service (ETS), de-identified electronic study records for use in future research will be given to the Department Head if the study as outlined in this IRB proposal has concluded.

Is this a data repository?

(•) Yes ( ) No

If Yes, provide the name of the Repository

PRFA_SHPB_REPO

Who will have access to the Repository?

Principal investigator and associate investigators.

What data type will be stored in the Repository?

- [ ] Protected Health Information
- [ ] Limited Data Set
- [x] De-identified Data

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

See sections 11.2-11.6.

11.2 Sample Size:

N=38.

11.3 Total number of subjects requested (including records and specimens):

38

11.4 If you are recruiting by study arm, please identify the arms of the study and how many subjects will be enrolled in each arm

(1) Pulsed radiofrequency ablation of superior hypogastric plexus: 15 evaluable patients (19 due to anticipated dropout ~20%)
(2) Sham intervention of superior hypogastric plexus: 15 evaluable patients (19 due to anticipated dropout ~20%)

11.5 Please provide a justification for your sample size

This is a pilot study. Thus, sample size will be informed by the size of previous studies within similar disciplines.

Numerous previous prospective studies investigating superior hypogastric plexus block with chemical neurolysis show the following sample sizes:

- Plancarte 1990, prospective patient series, n=28 [9]
- Yang 2018; prospective patient series, n=25 [13]
- El-Hefnawy 2015, RCT, n=24 [16]
- Gamal 2006, RCT, n=30 [27]
- Bhatnagar 2012, prospective patient series, n=18 [28]
- Mishra 2013, RCT, n=50 [29]
- Ghoneim 2014, RCT, n=30 [30]
- Erdine 2003, prospective patient series, n=20 [31]

Likewise, previous randomized controlled trials investigating radiofrequency ablation in the treatment of other chronic pain syndromes show the following sample sizes:

- Manjunath 2008, complex regional pain syndrome, n=20 [32]
- Bang 2019, abdominal pain, n=26 [33]
- Shaaban 2018, various chronic pain syndromes, n=40 [34]

Based on the above, we argue that n=30 is an appropriate, scientifically-supported sample size. When factoring in for anticipated dropout (~20%), this yields a total sample size of 38.

Using GPower 3.1, power can be calculated for a range of effect sizes with alpha = 0.05, one-tailed t-test, and total sample size n = 30:

Effect size Power
0.1 ---------- 8.4%
0.3 ---------- 20.0%
0.5 ---------- 37.9%
0.7 ---------- 59.0%
0.9 ---------- 77.6%

Given that this is a pilot study, as well as the numbers above, we do not expect to achieve power = 80%.

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Additional citations:

[27] Gamal G, Helaly M, Labib YM. Superior hypogastric block: transdiscal versus classic posterior approach in pelvic cancer pain. Clin J Pain. 2006 Jul-Aug;22(6):544-7. doi: 10.1097/01.ajp.0000202978.06045.24. PMID: 16788341.

[28] Bhatnagar S, Khanna S, Roshni S, Goyal GN, Mishra S, Rana SP, Thulkar S. Early ultrasound-guided neurolysis for pain management in gastrointestinal and pelvic malignancies: an observational study in a tertiary care center of urban India. Pain Pract. 2012 Jan;12(1):23-32. doi: 10.1111/j.1533-2500.2011.00467.x. Epub 2011 May 26. PMID: 21615855.

[29] Mishra S, Bhatnagar S, Rana SP, Khurana D, Thulkar S. Efficacy of the anterior ultrasound-guided superior hypogastric plexus neurolysis in pelvic cancer pain in advanced gynecological cancer patients. Pain Med. 2013 Jun;14(6):837-42. doi: 10.1111/pme.12106. Epub 2013 Apr 11. PMID: 23577819.

[30] Ghoneim AA, Mansour SM. Comparative study between computed tomography guided superior hypogastric plexus block and the classic posterior approach: A prospective randomized study. Saudi J Anaesth. 2014 Jul;8(3):378-83. doi: 10.4103/1658-354X.136625. PMID: 25191191; PMCID: PMC4141389.

[31] Erdine S, Yucel A, Celik M, Talu GK. Transdiscal approach for hypogastric plexus block. Reg Anesth Pain Med. 2003 Jul-Aug;28(4):304-8. doi: 10.1016/s1098-7339(03)00191-3. PMID: 12945023.

[32] Manjunath PS, Jayalakshmi TS, Dureja GP, Prevost AT. Management of lower limb complex regional pain syndrome type 1: an evaluation of percutaneous radiofrequency thermal lumbar sympathectomy versus phenol lumbar sympathetic neurolysis--a pilot study. Anesth Analg. 2008 Feb;106(2):647-9, table of contents. doi: 10.1213/01.ane.0000298285.39480.28. PMID: 18227328.

[33] Bang JY, Sutton B, Hawes RH, Varadarajulu S. EUS-guided celiac ganglion radiofrequency ablation versus celiac plexus neurolysis for palliation of pain in pancreatic cancer: a randomized controlled trial (with videos). Gastrointest Endosc. 2019 Jan;89(1):58-66.e3. doi: 10.1016/j.gie.2018.08.005. Epub 2018 Aug 16. PMID: 30120957.

[34] Shaaban MH, Reyad RM, Ghobrial HZ, Hashem RH. Ultrasound guided versus fluroscopic guided pulsed radiofrequency therapy of the stellate ganglion in neuropathic pain: a prospective controlled comparative study. Egypt J Radiol Nucl Med. 2018;49(1):71–75. doi: 10.1016/j.ejrnm.2017.06.008

11.6 Data Analysis Plan: Complete description: Background, Objectives, Design, Step by Step how the project is going to be done, Data analysis plan:

- As per the CONSORT guidelines for randomized controlled trials, a patient flow diagram will be presented to describe recruitment, exclusions, randomization, dropouts, loss to follow-up and subjects included in the analysis.
- Baseline demographic data, as well as number of treatments tried in the past for IC/BPS, for both intervention (pulsed radiofrequency ablation of the superior hypogastric plexus) and sham groups will be collected at intake and presented using means and standard deviations. These groups will be compared to assess for statistically significant findings between treatment and sham group.

- The primary outcome of interest is the subject's bladder pain score on a VAS numerical rating scale from 0-10, completed prior to the procedure as well as at 1-, 3-, and 6-month follow-ups in both the intervention and sham groups. Subjects will be scheduled as closely as possible to these follow-up timelines, although small variations (+/- 10 days) will be tolerated due to clinic availability, subject availability, holiday closures, and other unanticipated barriers to follow-up. The primary outcome will be reported as a mean and standard deviation for both intervention and sham groups. Assuming normality, means between treatment and sham groups will be compared with repeated measures analysis of variance.
- Secondary outcomes of interest will also be completed prior to the procedure as well as at 1-, 3-, and 6-month follow-ups and include the following. These outcomes will be reported using mean and standard deviation and compared between the intervention group and the sham group using repeated measures analysis of variance.
    - O' Leary-Sant Voiding and Pain Indices
    - Average number of daytime voids over the prior week
    - Average number of daytime episodes of urinary incontinence over the prior week
    - PHQ-9 scores
    - FSFI scores
    - Number of treatments currently taking for BPS
    - Current level of satisfaction with BPS treatment as measured by PGI-S and PGI-I scores.
- The pattern of any adverse events will be described. Although the rates of these outcomes are likely to be low in this small sample size, if sufficient numbers of adverse events occur, we will compare the rate of adverse events using either binomial or Poisson regression models.

12.0 Participant Information

12.1 Subject Population:

DEERS-eligible women aged ≥ 18 with a diagnosis of IC/BPS who score ≥ 6 on the OLS symptom questionnaire, seen in Walter Reed Urogynecology or Chronic Pain clinics for treatment of IC /BPS.

12.2 Age Range:

Check all the boxes that apply. if the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.

- ☐ 0-17
- ☑ 18-24
- ☑ 25-34
- ☑ 35-44
- ☑ 45-54
- ☑ 55-64
- ☑ 65-74
- ☑ 75+

12.3 Gender:

- ☐ Male

- [x] Female
- [ ] Other

12.4 Special categories, check all that apply

- [ ] Minors /Children
- [x] Students
- [x] Employees - Civilian
- [ ] Employees - Contractor
- [x] Resident/trainee
- [x] Cadets /Midshipmen
- [x] Active Duty Military Personnel
- [x] Wounded Warriors
- [ ] Economically Disadvantaged Persons
- [ ] Educationally Disadvantaged Persons
- [ ] Physically Challenged (Physical challenges include visual and/or auditory impairment)
- [ ] Persons with Impaired Decisional Capacity
- [ ] Prisoners
- [ ] Pregnant Women, Fetuses, and Neonates
- [ ] Non-English Speakers
- [ ] International Research involving Foreign Nationals - Headquarters Review is necessary

You must also consider the requirements of DoDI 3216.02, paragraph 7.e.

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraphs 7.e. and 12.

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

Depending on your intended subjects' status, you may also need to consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

12.5 Inclusion Criteria:

Order Number	Criteria
1	Female sex
2	Age ≥ 18
3	Diagnosis of bladder pain syndrome
4	Score of ≥ 6 on O'Leary-Sant Voiding and Pain Indices
5	DEERS-eligible health care beneficiaries.

12.6 Exclusion Criteria:

Order Number	Criteria
1	Patients with current enabled implantable neurostimulation (i.e. TENS, Interstim)
3	Current active pelvic or gynecologic malignancy

4	Coagulation disorder
5	Local infection at injection site
6	Sepsis
7	Decompensated cardiac or hemodynamic disorders
8	Neurogenic bladder and patients with spinal cord injury
8	Current pregnancy
9	Structural abnormalities of the spine that prevent performance of the procedure
10	Intravesical onabotulinumtoxin A injection within the last 3 months.

13.0 Recruitment and Consent

13.1 Please describe the recruitment process, including how subjects will be identified and selected for the study.

The Urogynecology clinic schedule will be reviewed for appointments for IC/BPS on a daily basis by WRNMMC Urogynecology staff physicians and fellows. Likewise, the Chronic Pain Service will be reviewed for appointments for IC/BPS on a daily basis by WRNMMC Chronic Pain staff physicians and fellows. Screening will occur at this time. All female subjects 18 years of age or older with a diagnosis of IC/BPS from Urology or Urogynecology, currently eligible to receive care at WRNMMC, with OLS score ≥ 6, and without evidence of exclusion criteria, will be considered candidates for recruitment in this study. These subjects will be recruited at the time of their appointment by a staff physician or fellow not associated with the study, who will provide study verbal information and an informational handout. In order to adhere to WRNMMC's recruitment policy, research activities will take place after clinic visit has ended. No patients will be pressured or coerced into participating in the study.

If a potential subject is screened for study participation, they will be added by clinic staff to a protected Shared Drive patient list accessible only by study personnel. If they express interest in study participation, this will be denoted on the patient list and a Referral Request 2.0 will be placed by the referring Urogynecology provider (or a follow-up appointment booked by the referring Chronic Pain provider) for the Chronic Pain clinic for intake appointment. Specific mention of study participation will be made in the Referral Request 2.0. Consent for study participation will occur at the first Chronic Pain intake appointment by an authorized member of the research team.

13.2 Compensation for Participation:

There is no monetary compensation for joining the study.

13.3 Please describe the pre-screening process. If no pre-screening, enter Not Applicable in the text editor

See section 13.1.

13.4 Consent Process: Revised Common Rule, Section 219.116: General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. Broad consent may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and

(c) of this section only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens.

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

Informed Consent Process

Formal consent will occur at the subject's first Chronic Pain intake appointment; prior to this, the subject will have received information about the study via in-person discussion and handout as outlined above in section 13.1. An overview of the study will be recapitulated when administering consent. Study participants will then review the study consent form in detail with a member of the Chronic Pain Anesthesia team present. Adequate time will be allowed for answering questions or concerns. After signing, the subject will be given a copy of the signed consent, and a copy will remain on file in a locked cabinet in the Chronic Pain Clinic. If the subject elects to not participate or not provide consent, they will nevertheless be offered the opportunity to complete their appointment with a Chronic Pain clinician, should they desire discussion about other pain management options within the standard of care. Subjects may choose to leave the study at any point without consequence.

13.5 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

◉ N/A
○ Propose ombudsman

13.6 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

Subjects can decide to withdraw from study participation at any time by informing the PI or research staff via phone, in-person, in-writing, or electronic mail. Withdrawal will not affect future care at WRNMMC. Those that withdraw will be offered the opportunity to withdraw their data from the study as well.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

Breakage of the skin for the purposes of intervention poses principal risks of bleeding, infection, and damage to surrounding structures. Given the anatomic location of intervention, vascular structures with potential for accidental injury include the distal abdominal aorta as well as left /right common iliac arteries, left/right common iliac veins, and inferior vena cava. The ureters are similarly exposed to potential injury in this procedure. Inadvertent puncture of an

intervertebral disc when passing the needle lateral to the vertebral body holds the theoretical risk of discitis. Although the superior hypogastric plexus is located retroperitoneally, accidental passage into the peritoneum could lead to bowel or bladder injury. These risks will be minimized by (1) using fluoroscopic and tactile guidance in multiple planes of view to ensure appropriate anatomic positioning of the needle; (2) pre-procedure administration of cefazolin 2g for antibiotic prophylaxis against infection; (3) use of sterile technique; and (4) use of expert operators training in anesthesia and chronic pain.

There is a very low risk of transient hypotension associated with the procedure. Patients will be connected to standard ASA monitors including blood pressure, pulse oximetry, and electrocardiogram in order to quickly detect hemodynamic abnormalities. Vasoactive medications as well as blood products will be available in the event of severe intractable hypotension and/or intra-abdominal bleeding. Patients will be monitored in the post-procedure period for 30 minutes for detection of hemodynamic abnormalities.

Patients are exposed to risk secondary to small doses of radiation applied for imaging guidance. This risk will be minimized by using the smallest dose of radiation necessary for facilitation of needle placement. Fluoroscopy will only be used over the anatomic area of interest, with protection of adjacent areas with lead aprons.

Given the abundance of structures located in the target area of therapy, participants are at risk for nonspecific discomfort, such as backache, transient hematuria, or numbness and tingling of the lower extremities, both during and after the procedure. The full range of these nonspecific discomforts cannot be predicted. Conservative, supportive care will be available as needed to help minimize discomfort.

There is a risk that the intervention does not lead to resolution of pain, voiding, and/or mood symptoms for patients with IC/BPS.

Breach of confidentiality is always a risk when working with confidential information. However all data collected will be accessible only to research team members and stored in a locked, secure location either in the Chronic Pain clinic or on a Walter Reed network drive.

A comprehensive update of the superior hypogastric plexus block for the management of chronic pelvic pain by Urits et al (2021) analyzes chemical neurolysis of the superior hypogastric plexus in numerous prospective, retrospective, and randomized controlled studies as well as case reports and case series; 300+ patients were collectively analyzed with no complications greater than Clavien Dindo Grade I reported. This demonstrates a large body of evidence suggesting safety of the procedure across multiple prior studies.

14.2 Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

Measures to minimize/eliminate risk provided in-line in section 14.1.

14.3 Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e. g., child or spouse abuse

Once a patient is enrolled in the study, the treating provider on the Chronic Pain team will assign a subject identifier (01, 02, 03, etc) and record this identifier on the subject's physical intake forms. Immediately after the subject's intake appointment, the physical intake forms (including data and consents) will be placed in a folder and stored in a single locked cabinet in an office in the Chronic Pain clinic. Data from physical intake forms will be transferred to electronic data in a coded manner using the subject identifiers given above (i.e. only storage of coded data) on a government-issued computer Excel document that is password and CAC protected and only exists on local WRNMMC servers.

Subjects will be asked in their initial consent for permission to maintain their de-identified data after the completion of the study for use in future research. Data will be modified from coded to de-identified at the conclusion of the study by the removal of all numbering, connections, and/or master lists that allow association between subject code and data. All subjects will have their physical data shredded and disposed of in a HIPAA-compliant bin at the conclusion of the study, with the exception of those documents required to be retained by the Principal Investigator by 32 CFR 219.115(b). In addition, those patients that decline maintenance of their data will have their electronic data deleted at the conclusion of the study. The informed consent document with HIPAA Authorization will be held for a minimum of 6 years and then shredded and disposed in a HIPAA compliant receptacle per WRNMMC protocol. The Principal Investigator or a designee on the research team will be responsible for destroying this information.

14.4 Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

Subjects may benefit by having a decrease in the bladder or pelvic pain, decrease in pain medication use, decrease risk of medication side effects, decreased adverse urinary symptoms, improved mood, and improved quality of life.

14.5 Privacy for Subjects:

Describe the measures to protect subject’s privacy during recruitment, the consent process, and all research activities, etc.

The subject’s privacy will be protected by performing all study procedures in a private room; this includes obtaining consent and medical history, performing exams, and administration of the intervention. The only personnel that will be present will be the study investigators, research coordinator, and staff, such as nurses, who will assist with procedures under the direction of the study investigator. The subject and her family member(s) or spouse will be made to feel at ease by limiting the number of personnel present, and encouraging the subjects to ask questions and notify the staff if she is uncomfortable in any way.

14.6 Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject’s participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report

results to appropriate military or civilian authorities and explain the potential impact on the subject

Participants will be informed of any incidental findings. Depending on the type of incidental finding, the participant may be contacted by phone. In the case of a potential serious emergency, the PI or designee will be responsible for informing the participant right away. Participants will not have an option to decline receiving information about an incidental finding. A qualified person (usually a member of the research team) will talk with the participant if there is an incidental finding. The participant will be referred to an appropriate doctor for further evaluation.

15.0 Study Monitoring

15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB).

- (•) DSMP
- ( ) DSMB
- ( ) Both
- ( ) Not Applicable

A DSMP should describe the plan to monitor the data to verify that the data are collected and analyzed as specified in the protocol. Include who will conduct the monitoring, what will be monitored, and the frequency of monitoring. It should also include the plan to ensure the safety of subjects

The PI will be responsible for ensuring all data that are collected and analyzed are being performed as specified per protocol. Prior to the start of the study, the PI will meet with all clinicians performing the recruitment (Urogynecology, Chronic Pain) and pulsed radiofrequency ablation (Chronic Pain) to present the study protocol. Any points of clarification or concern will be addressed at that time by the PI, and at any point during the study period if questions or issues arise. Data sheets will be reviewed by the principal or associate investigators on a bi-weekly basis to ensure completion and accuracy. The data being monitored includes all questionnaires (demographic data sheet, OLS questionnaire, VAS pain scores, PHQ-9 questionnaires, overall satisfaction scores, and all other data collected at intake and follow-up appointments contained within participant packets) as well as adverse outcomes. Safety of subjects will be ensured by employing standard technique for approach and access to the superior hypogastric plexus, and using pulsed radiofrequency ablation equipment in an approved manner, all by expert operators with fellowship training in Chronic Pain. All subjects will be monitored for any immediate or delayed adverse effects of the study interventions.

Subjects will be administered the PHQ-9 survey as part of data collection. This survey screens for depressive symptoms including suicidal ideation. If the PHQ-9 reveals concern for depression, the results will be discussed with the patient directly and a referral for mental health will be placed if the patient does not already have an established mental health provider. If indicators of suicidal ideation are identified, this will also be directly discussed with the patient. Dr. Worthington, the mental health provider embedded within the Gynecology clinic, would be contacted to see the patient immediately if available. If she is not available, the patient would be walked down to the emergency department and a warm hand-off given to the emergency provider.

16.0 Reportable Events

16.1 Reportable Events: Consult with the research office at your institution to ensure requirements are met. Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event.

Consult with the research office at your institution to ensure requirements are met

• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short-term management and any long-term implications of each expected event)

• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

Reportable Events include adverse events (AE), serious adverse events (SAE), unanticipated problems involving risks to subjects or others (UPIRTSO), and protocol deviations as defined by the WRNMMC IRB Handbook.

Expected reportable events and events that are not related to study participation are reported on the Continuing Review (CR) Progress Report. CR is generally performed on a 12-month cycle. More frequent Progress Reports may be required at the discretion of the IRB.

Serious Adverse Events: The PI, within 24 hours, must report all related or possibly-related AND serious adverse events (SAE) occurring in subjects enrolled at WRNMMC. This is accomplished by submitting an adverse event report to the IRB via eIRB. For protocols involving investigational drugs or devices, the investigator must also report a serious adverse event to the sponsor of the IND or IDE immediately (within 24 hours). Serious adverse events must be reported even if the PI believes that the adverse events are unrelated to the protocol.

UPIRTSOs, unexpected AEs, and SAEs (in the opinion of the PI) that are possibly related to participation AND places subjects or others at a greater risk of harm that was previously known or recognized in the protocol and must be reported to the IRB and Research Monitor via email or telephone within 24 hours of discovery and a written follow up report within 5 business days. When a protocol deviation occurs, the investigator shall report the occurrence to the IRB. The investigator is required to make the determination whether the deviation meets the criteria for an unanticipated problem involving risks to subjects or others. The IRB Chair or IRB staff member shall also make the determination if the protocol deviation meets the definition of an unanticipated problem involving risks to participants or others. If the IRB Chair or IRB Staff member determines and documents that the deviation is an unanticipated problem involving risks to subjects or others or the deviation resulted from serious or continuing noncompliance, the IRB staff member shall place the deviation on the agenda of the next available IRB meeting for review. If the IRB Chair or IRB Staff member determines and documents that the deviation is not an unanticipated problem involving risks to subjects or others, the IRB Chair or staff member shall acknowledge the submission and complete the review through an administrative review procedure. Deviations that are determined to be minor as defined by the WRNMMC IRB Handbook are reported on the Continuing Review (CR) Progress Report as stated above.

As a reminder, according to DoDI 3216.02 (November 8, 2011), the IRB shall approve an independent research monitor by name for all DoD-conducted research involving human subjects, determined by the IRB to involve more than minimal risk to human subjects. Additionally, the research monitor may be identified by an investigator or appointed by an IRB or Institutional Official (IO) for research involving human subjects determined to involve minimal risk.

The research monitor may perform oversight functions and will report their observations to the IRB or a designated official. The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have the authority to stop a research protocol in progress, remove individual subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

The research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol, and they shall be independent of the team conducting the research involving human subjects.

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs, dietary supplements, biologics, or devices be utilized in this study?

- ☐ Drugs
- ☐ Dietary Supplements
- ☐ Biologics
- ☑ Devices
- ☐ N/A

18.3 Device Details:

- ☑ Are device(s) in this research being used in accordance to the approved labeling?
- ☐ Are device(s) in this research being used in a manner other than its approved labeling?

When adding a device indicate in the details section of the device if the use is either used in accordance to the approved labeling or in a manner other than it's approved labeling

View Details	Device Name
⊟	Radiopaque Radiofrequency Cannula

Manufacturer/Supplier of Device	Avanos
Where will the Devices Be Stored	Chronic Pain Clinic
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Who holds the IDE	N/A
IDE details	

⊟	Radiofrequency Probe, Long

Manufacturer/Supplier of Device	Kimberly-Clark
Where will the Devices Be Stored	Chronic Pain Clinic
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Who holds the IDE	N/A
IDE details	

⊟	Multi-Radiofrequency Module

Manufacturer/Supplier of Device	Kimberly-Clark
Where will the Devices Be Stored	Chronic Pain Clinic
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Who holds the IDE	N/A
IDE details	

⊟	Pain Management Generator, Advanced, v4

Manufacturer/Supplier of Device	Kimberly-Clark
Where will the Devices Be Stored	Chronic Pain Clinic
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Who holds the IDE	N/A
IDE details	

18.4 Reporting Requirements for FDA-regulated research under IND and IDE:

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

N/A

18.5 Sponsor (organization/institution/company):

☑ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

- ○ Registration is not required
- ◉ Registration pending
- ○ Registration complete

19.2 Defense Technical Information Center Registration (Optional):

- ◉ Registration is not required
- ○ Registration pending
- ○ Registration complete

20.0 References and Glossary

20.1 References:

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20.2 Abbreviations and Acronyms:

AUGS: American Urogynecologic Society
AUA: American Urological Association
ASA: American Society of Anesthesiologists
FSFI: Female Sexual Function Index
IC / BPS: Interstitial cystitis / bladder pain syndrome
OLS: O' Leary-Sant Voiding and Pain Indices
PGI-S: Patient Global Impression of Severity
PGI-I: Patient Global Impression of Improvement
PHQ: Patient Health Questionnaire
pRFA: Pulsed radiofrequency ablation
PTSD: Post-traumatic stress disorder
SHPB: Superior hypogastric plexus block
TENS: Transcutaneous electrical nerve stimulation
VAS: Visual analog scale
VA: Veterans Administration
WRNMMC: Walter Reed National Military Medical Center