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Optimizing Psychosocial Treatment for Interstitial Cystitis/Bladder Pain Syndrome
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1. ABSTRACT

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating, incurable, and costly pain condition affecting approximately 3-8 million individuals in the United States and is extremely challenging to treat. Evidence suggests psychosocial factors accompany and intensify the illness.
Unaddressed psychosocial co-morbidities are associated with reduced functionality and poorer outcomes, which suggests that psychosocial symptoms and bladder-specific symptoms reinforce each other. While psychosocial self-management interventions have demonstrated efficacy for other pain conditions, the IC/BPS field lacks the gold standard – randomized controlled trials – studying these interventions. At the same time, the chronic pain field is adopting a new approach driven by mechanisms of illness and treatment. Growing evidence suggests that subgroups (called "phenotypes") of patients with IC/BPS respond differently to medical intervention. Presence of central sensitization (CS) largely defines patient subgroups and may be a biological factor affecting response to medical treatment. The **overall goal** of this project is to fully develop, optimize, and evaluate a patient-centered CBT self-management intervention specific to IC/BPS. To achieve this goal, we will develop (Aim 1) and test (Aim 2) an empirically-based psychosocial treatment for IC/BPS compared to attention control, while examining pain mechanisms and subgroup characteristics that may alter treatment response (Aim 3). We **hypothesize** that a) inclusion of a self-management intervention will be more effective than a control treatment for IC/BPS, and that b) treatment effects will be moderated by degree of psychological co-morbidity, presence of chronic overlapping pain conditions, and elevated central sensitization. Successful completion of these aims will determine whether the addition of a tailored self-management intervention for IC/BPS will improve outcomes compared to control, whether particular subgroups are more responsive to this intervention, and whether a biological mechanism (CS) influences treatment responsiveness.

2. BACKGROUND

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating, incurable, and costly pain condition affecting approximately 3-8 million individuals in the United States.[1] Pain is the hallmark symptom of IC/BPS – which occurs in the pelvis, urogenital floor, or external genitalia.[2] Patients also experience urinary urgency, pressure/discomfort, and/or urinary frequency.[3] The economic burden of the condition is substantial, costing the healthcare system upwards of $750 million a year.[2] Understanding of IC/BPS pathophysiology is limited, and most treatments target symptom control. Between 1992-2001, rates of physician office visits for IC/BPS tripled and hospital outpatient visits doubled[2]. Current biomedically-based treatments lack effectiveness.[4]
A high-need, high-cost population,[5] IC/BPS patients have medically complex presentations and often do not respond to surgical intervention. Psychosocial co-morbidities such as anxiety, depression, quality of life, and trauma-related symptoms accompany and intensify the illness.[6,7,8] Table 1 represents a sample of

chronic pain patients with and without IC/BPS (as defined by epidemiological criteria) collected in a recent study at VUMC ([redacted]). Per Table 1, compared to chronic pain conditions without IC/BPS, those with IC/BPS symptoms have significantly worsened psychological functioning, impaired coping, multi-symptomatic complaints, and increased perceived pain.

Table 1: Comparison of psychosocial and pain experiencing in chronic pain (N=137) vs. IC/BPS (N=63) patients using a Wilcoxon Test reported as median (SD)

Assessment Domain	**Chronic Pain (N=137)**	**IC/BPS (N=63)**	***p***
Pain Experiencing (MPQ-II)	3.0 (1.6)	3.6 (2.0)	0.041*
Central Sensitization (CSI-A)	42.0 (16)	57.0 (17)	<0.001***
Catastrophizing (PCS)	16.1 (10.6)	22.8 (13.0)	0.007**
Anxiety Sensitivity (ASI)	15.0 (12)	23.0 (17.0)	0.003**
Anxiety (HADS-A)	8.5 (4.4)	11.0 (5.0)	0.001***
Depression (HADS-D)	6.4 (4.2)	8.2 (4.8)	0.012*
Childhood Trauma Exposure	40.0 (29)	46.0 (28)	0.062
Adulthood Trauma Exposure	5.8 (4.0)	5.5 (3.8)	0.63
PTSD Assessment (PCL-5)	20.1 (15.4)	28.9 (20.9)	0.009**

Psychosocial factors precipitate and perpetuate IC/BPS symptoms, and there is a documented genetic linkage of IC/BPS with panic disorder.[9] Animal studies show that exposure to psychological stress augments bladder nociception,[10] and a large epidemiological study reported that those with IC/BPS and uncontrolled depression or anxiety work less and experience significantly greater impairment and urinary symptoms.[11] In chronic pain, unaddressed psychosocial factors can shape patient perceptions and behavior and lead to poorer, functioning, prognosis, and response to treatment.[12-15] This suggests both a strong association between and reinforcement of psychosocial symptoms and bladder-specific symptoms. **Overall, IC/BPS is a biopsychosocial condition prompting both medical and psychosocial interventions to achieve optimal outcomes.**

A Mechanistic Approach to Treatment

IC/BPS falls into a class of conditions recently termed by the U.S. Congress and National Institute of Health as Chronic Overlapping Pain Conditions (COPC).[16] These conditions often co-occur, affect women predominantly, and are bound by a unifying pathophysiological mechanism of pain or sensory amplification (central sensitivity[17]). In addition to IC/BPS, other COPC examples include fibromyalgia and irritable bowel syndrome. **Researchers are moving away from a disease-specific to a mechanistic classification of chronic pain.** Current research designed to show treatment efficacy in mechanism-based subtypes will inform and help tailor future treatment regimens based upon a patient's mechanistic presentation.[18]
Within each COPC diagnostic category, subgroups of patients, or "phenotypes", emerge that are largely defined by symptom severity, sensory sensitivity, and psychosocial factors that identify those more susceptible to chronic pain and its effects.[18] Leading researchers[19] have defined three IC/BPS phenotypes based on chronic pain distribution: 1) localized pelvic pain 2) pain in 1-2 regions outside the pelvis and 3) widespread pain.[20] In total, 75% of women with IC/BPS report pain outside of the pelvis. Those with widespread pain (38%) have worsened pain severity, psychological distress, and sleep disturbance.[20] It is theorized that individuals with widespread pain, or higher degrees of central sensitivity, respond less to biomedical treatments and may benefit more from an integrative treatment plan including cognitive-behavioral or self-management interventions to comprehensively address pain interference, sleep disturbance, and mood.

National guidelines recommend psychosocial interventions as a first-line treatment for IC/BPS.[21] But these interventions are underutilized secondary to limitations in provider availability and time constraints. We do not know if the recommended "stress management" therapies suggested in these guidelines sufficiently meet patient needs or if patients require a broader pain self-management approach like those used in other forms of chronic pain.[22] Recommended psychological interventions include cognitive-behavioral self-management programs, which help patients build confidence and skills in preventing, coping and reducing pain.[23] There is a paucity of randomized controlled trials evaluating how and in whom these interventions work. Little is known about the impact of treating psychosocial factors on illness presentation, or how patients of different disease phenotypes respond to this type of treatment. Such knowledge may permit targeting of scarce psychosocial treatment resources towards those most likely to benefit from them.

Psychosocial self-management interventions could benefit patients by: 1) bolstering self-efficacy and increasing social support – known to buffer the impact of symptoms,[24,25] 2) improving medical treatment adherence, [26] and 3) reducing the impact of psychological distress that may intensify symptoms. Self-management may be preferable as patients are often not responsive to psychotropic medications.[27] In our IC/BPS urology clinic at VUMC, of *8 patients treated with self-management (N = 8), 6 of 8 (75%) patients reported significantly and meaningfully improved urinary symptoms (X = 4.85) post-treatment*, as measured by the American Urological Association Symptom Index (AUASI[28]) – where a 3 point change in symptoms is considered clinically meaningful.[29] Further, the two patients with unchanged urinary symptoms reported clinically meaningful reductions in pain intensity on the Numeric Rating Scale-11.[30] **While pain and urologic outcomes need to be analyzed separately,[31] they should be considered in unison.**

Psychological distress occurs regardless of severity of pain and urinary symptoms.[32,33] Many patients with only moderate symptoms have significant psychological burden.[32,34] Thus, patients at all stages of this illness may benefit from self-management. A recent survey by the Interstitial Cystitis Association (N

= 1,982[35]) revealed significant interest in employing self-management strategies such as stress reduction, behavioral sleep strategies, relaxation, and active coping strategies to alleviate symptoms. These findings and our preliminary data show that patients are open to and interested in this line of intervention.

Despite demonstrated efficacy in other pain conditions,[36,22] and patient openness to intervention, there has yet to be a high-quality randomized control trial evaluating the impact of psychosocial interventions for IC/BPS and no study of how patient subgroups impact treatment response. Evidence from the Multidisciplinary Approach to Pelvic Pain (MAPP) multisite study indicates that subgroups ("phenotypes") of patients with IC/BPS respond differently to medical intervention.[37] Presence of central sensitization, a centrally-mediated facilitation of pain responsiveness, largely defines this patient phenotype[31,20] and may be a biological factor mediating treatment response.

The 2016 NIDDK Strategic Plan strongly supports research to increase treatment options for IC/BPS. The 2015 National Pain Strategy calls for a stronger focus on patient-centered outcome research for chronic pain conditions, generally including cognitive-behavioral (CBT) self-management strategies. Our preliminary study (n=8) of a tailored self-management intervention for IC/BPS showed that 6 of 8 (75%) patients reported significant and clinically meaningful reduction in urinary symptoms. The **overall goal** of this project is to fully develop, optimize, and evaluate a patient-centered CBT self-management intervention specific to IC/BPS. We **hypothesize** that 1) inclusion of a self-management intervention will be more effective than *[attention control]* for IC/BPS, and that 2) treatment effects will be moderated by degree of psychological co-morbidity, presence of chronic overlapping pain conditions, and elevated central sensitization. Specific aims include:

3. SPECIFIC AIMS

Aim 1: To construct a patient-centered CBT self-management (SM) intervention specific to IC/BPS. We will construct a self-management intervention for IC/BPS with information compiled from patient focus groups (preliminary data), clinical expertise, and effective components of self-management interventions in associated conditions. We will work in collaboration with IC/BPS experts and utilize research collected from an ongoing project (MAPP) to inform intervention design. We will then invite focus group participants to return and review the intervention package for acceptability.

Aim 2: To obtain pilot data comparing the effectiveness of integrating SM interventions into standard care (N = 50) to attention control (AC, N =25) in improving targeted genitourinary symptoms (GUPI,[4] primary outcome) and secondary outcomes of pain, distress, and quality of life**.** We hypothesize that individuals receiving the SM intervention will show improved outcomes relative to control [AC].

Aim 3: To determine whether patient phenotype moderates treatment response to a SM intervention. We will define patient phenotype by: assessment of temporal summation (as a marker of central sensitization), degree of psychological co-morbidities, and presence of chronic overlapping pain conditions. We hypothesize that (1) higher levels of pre-treatment psychological co-morbidities (e.g. depression levels) will be associated with greater SM treatment efficacy, (2) we hypothesize that greater baseline temporal summation will be associated with greater SM treatment efficacy, and (3) we hypothesize that participants with more chronic overlapping pain conditions will exhibit greater SM treatment efficacy.
Successful completion of these aims will determine whether the addition of a tailored self-management intervention for IC/BPS will improve patient symptoms and function, whether particular patient

subgroups are more responsive to this intervention, and whether a potential biological mechanism (central sensitization) influences treatment responsiveness. We summarize these aims in the table below.

	Summary	Hypothesis
Aim 1	To construct **a patient-centered CBT self-management (SM) intervention** specific to IC/BPS.	N/A
Aim 2	To obtain pilot data comparing the effectiveness of integrating **SM interventions** into standard care to attention control in improving targeted **genitourinary symptoms** and **secondary outcomes** of pain, distress, and quality of life.	We hypothesize that individuals receiving the SM intervention will show improved outcomes relative to control.
Aim 3	To determine whether **patient phenotype** moderates treatment response to a SM intervention.	Higher levels of pre-treatment psychological co-morbidities (e.g. depression levels) will be associated with greater SM treatment efficacy. Greater baseline temporal summation will be associated with greater SM treatment efficacy. Participants with more chronic overlapping pain conditions will exhibit greater SM treatment efficacy.

4. PARTICIPANT SELECTION

4.1 Recruitment

We will recruit **over a period of three years**. The target population includes the following counties in middle Tennessee that surround the Nashville area: Davidson, Montgomery, Rutherford, and Williamson. According to 2017 U.S. census data, these four counties are home to 1.43 million individuals and are racially, ethically, socioeconomically, and geographically diverse.

We will recruit internally via VUMC and externally in the surrounding community to meet recruitment goals. We will recruit individuals with IC/BPS from VUMC clinics. Externally, we will recruit individuals through ResearchMatch,[5] the VUMC Research Listserv, MyResearch (MRAV) database, online, and in area hospitals and clinics – which the PI has successfully used in previous studies. In addition to VUMC, our prospective recruitment sources include patient organizations, community clinics, support group pages, media advertisements, social media, and local university clinics. Further, we will contact eligible individuals from former investigations conducted by the PI (e.[redacted]) and co-mentors Reynolds, Bruehl, and Crofford who previously consented for further follow-up and expressed interest in participating in further study.

MyResearch (MRAV) is a participant repository recruitment tool available to Vanderbilt researchers that reaches over 18,000 My Health at Vanderbilt users that have previously confirmed they would like to be contacted directly for research. This repository provides investigators a forum for advertising for volunteers for a specific study. Email notifications are limited to IRB approved language (see attached script for approval), describe study specifics and provide contact information. To utilize this initiative, we will complete a MyResearch Access Request with the approved language that is reviewed to ensure the recruitment tool and requested number of contacts are appropriate.

Reporting Workbench (RWB) Reports is a new recruitment tool available to VUMC researchers available/viewable in eStar. These reports are developed using real-time data and can be customized to meet study-specific inclusion/exclusion criteria. Research team members with eStar access and collaboration with the RWB team, and access to the Report Groups, can view/run the reports as frequently as needed. While a RWB report only displays certain variables, it provides easy access to a patient's record for additional screening and confirmation of eligibility.

The RWB Report requested for this study will be created by filtering on the following variables – inclusion criteria: 18+, living in KY/TN, ICD N30.10/N30.11, patients seen in the following clinics - Vanderbilt One Hundred Oaks Primary Care, Vanderbilt Primary Care Franklin, Vanderbilt Center for Women's Health, Vanderbilt Center for Women's Health Cool Springs, Vanderbilt Urology Cool Springs, Vanderbilt Urology TVC3; exclusion criteria: any exclusion criteria in the protocol that may be computable in the EHR. Variables to be displayed in the report will include MRN and demographics, as well as patient research contact preference. Additional chart screening can be performed to confirm eligibility.

This report provides a list of potential study-eligible individuals. A subset of these potentially eligible individuals may have also indicated their preference to be contacted **directly** for research as indicated by OK to Contact or Do Not Contact. If the patient did not explicitly give their permission for OK to Contact, their preference will be listed as Do Not Contact. Patient Research Contact preference will be listed in a column in the RWB report.

We are proposing to use RWB to contact study-eligible individuals in two different ways: one by contact through study eligible individuals' medical providers similar to the process used when using the Subject Locator tool, and second to directly contact those who have previously indicated they would like to be contacted for potential research participation.

1. For those patients with Do Not Contact for their research contact preference, we propose to contact their providers to request that they connect with the patient about this study opportunity, should they deem it appropriate. We will provide them with a recruitment message, once again including access to our REDCap Interest Form, to distribute to patients accordingly. Dr. McKernan has extensive connections to providers through the IC Clinic and throughout VUMC, many of whom have expressed enthusiastic interest about aiding in recruitment efforts.

2. For those patients with Ok to Contact for their research contact preference, we propose direct-messaging, in eStar or via email, these patients with a recruitment message that includes a link to our IRB-approved Interest Form. In eStar, these patients will be sent our direct recruitment message up to two times. From there they can either reply to our message, contact our study team,

or fill out our REDCap form. Per our recruitment procedures, we will give them a final phone screening if they indicate interest.

This condition is greatly understudied and needs more research, as patients subjectively report that even diagnosis alone can take years of ruling out alternative conditions. We also have excellent rates of study enrollment and retention in our first year. Thus, providers and participants alike have largely been overwhelmingly positive about this study. We believe that our goal of n = 75 is in reach and could be helped greatly by incorporation of these EHR-based recruitment options.

One online recruitment tool we will include is researchmatch.org**. ResearchMatch**[5] is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository (see [redacted]). Regarding ResearchMatch, we are requesting IRB approval to send the appended study recruitment message to potential study volunteers through ResearchMatch.org. ResearchMatch confirms IRB-approved recruitment language and that direct study contact information has been removed (email/phone) before sending the study announcement through ResearchMatch to volunteers that appear to be a good match for the study. Potential volunteers will be contacted using the IRB-approved content (attached for approval). Volunteers will then have the option of replying yes or no through a set of quick links available in the notification. If a volunteer chose to respond in the affirmative they will authorize ResearchMatch to release their contact information to me and I will be responsible for managing that information according to institutional guidelines.

Accompanying ResearchMatch, we will also access the **Research Notifications Distribution List**, where VUMC researchers can use a listserv to access over 18,000 faculty, staff, and community members who may be interested in research. This tool uses IRB-approved recruitment scripts (see attached script for approval) and distributes advertisements to the Vanderbilt community and members of the general public locally who have 'opted in' to receive these emails. We successfully used these tools to recruit for a recent study on IC/BPS conducting focus groups to collect preliminary data for this proposal ([redacted]). We will also be registered on clinicaltrials.gov as a clinical trial and anticipate participant interest from this registration.

We will facilitate recruitment from **existing VUMC clinical services** targeting current patients and new referrals at VUMC entities including urology, the Osher Center for Integrative Medicine, primary care, and rheumatology clinics as examples. This includes patients from the existing IC/BPS clinic in outpatient urology and additional clinics conducted by study co- mentors ([redacted] In the outpatient IC/BPS clinic at Vanderbilt, we see 2-3 new patients per week, or an average of 10 per month. We will also recruit with assistance from outpatient provides at the Osher Center for Integrative Medicine (OCIM) who evaluate and treat adults with chronic overlapping pain conditions, whom the PI has worked with for 5 years, and include [redacted]

To specifically target individuals diagnosed with IC/BPS, we will also use VUMC's **Subject Locator** to identify potential research subjects based on data available in VUMC clinical systems (e.g. STAR Panel, EPIC, WizOrder, Clinic Scheduling). The subject locator program is part of a toolset available through

the Vanderbilt Center for Translational Research that enables teams to specify inclusion/exclusion criteria for a specific study. Study criteria are codified for computable use and combined with data coming through VU Clinical Systems to proactively identify individuals who might qualify for a study. Once a 'match' is made, research study personnel are alerted using confidential messaging or a secure web portal and they may then use the information to further review the patient's information using the Vanderbilt Electronic Medical Record. If the patient is further deemed a candidate for the study, the study personnel will notify the patient's care provider who will then ask the patient if they would be interested in communicating with study personnel about research participation, at which point the potential subject will be screened for inclusion and exclusion criteria.

In instances where participants have not previously consented to being contacted for follow-up, or responded to a study announcement expressing interest, individuals initially approaching potential participants about the study will be those with an existing clinical relationship (e.g. providers at OCIM) prior to study screening.

We will monitor enrollment **diversity** on a regular basis throughout the study. Our inclusion of local hospitals and clinics in the community such as Nashville General Hospital at Meharry (a historically African-American academic health science center) and will enhance our ability to achieve our goals for minority representation and gender distribution, as both of these clinical services treat a large number of minority patients and men. The PI's primary mentor ([redacted]) is an attending at Nashville General Hospital and has successfully recruited for clinical trials at this site, and will assist the candidate with facilitating recruitment as needed to meet recruitment goals.

Recruitment tracking will occur through our study databases. We will have a REDcap study database for screening, as well as a spreadsheet for tracking recruitment, enrollment, and scheduling, to assure we appropriately capture all subjects screened. This will also allow us to maintain records of criteria leading to study exclusion, and once subjects have enrolled, will capture reasons for study discontinuation or early withdrawal. This will assure we capture all required information for accurate completion of the CONSORT checklist and flow diagram.

4.2 Screening

Outpatient providers at VUMC will have access to an "IC/BPS Intervention Referral Form" (**Appendix A**) to be completed with interested patients. This form will either be completed on paper, online, or via electronic health record once available. Prior to completing study eligibility questions, participants will undergo brief consenting procedures for eligibility screening where they will be informed of the screening purpose, duration, and that their participation is strictly voluntary. This form assesses for the presence of IC/BPS, current symptoms, and appropriateness for treatment. In the event that screening cannot occur in person, prospective participants will complete screening questions via telephone or online in Redcap. We are requesting a waiver of documentation for this stage of the screening process.

Regarding the telephone screening and contact with interested participants, research team members will follow a script (**Appendix B**) informing patients of the study purpose and inclusion/exclusion criteria. Research assistants will also follow an in-person screening script (**Appendix C**) if recruiting in person. Inclusion/exclusion criteria will follow a structured checklist that prospective participants will complete via these methods or online by answering questions in Redcap.

During recruitment and screening, any participants who indicate that they are having thoughts of self-harm or suicide will be provided with resources for follow-up immediately (i.e. the telephone number to the National Crisis Hotline and website www.suicidepreventionlifeline.org to chat with support staff online, and PI office number). Additionally, the research team member will inform the PI, who will also follow-up with the potential participant within 24-48 hours to assess if further assistance or referrals are necessary in order to provide adequate support. The PI will also provide a direct phone number to call during business hours to be available to participants for additional support and to make any necessary referrals. These participants will not be eligible for study participation.

Those who indicate they are interested in participating in research during screening procedures and meet inclusion criteria will be contacted by the PI or a member of the research team (e.g. research coordinator, post-doctoral fellow, or research assistant) to discuss study procedures, answer any questions, and confirm dates/times of appointments. This will occur via telephone, secure zoom video conferencing software, or in-clinic if a member of the research team is available. Participants will then schedule a time to undergo consenting procedures (separate consents for the intervention study and optional psychophysical testing) and a pre-treatment assessment. At the initial visit, the pre-treatment assessment will involve a series of (1) self-report instruments to assess physical and emotional functioning, and (2) in-person psychophysical measures including pain sensory testing and blood draws (optional). Those who use opioids regularly will be instructed to not use opioids prior to their psychophysical testing, as this could impact its outcome. Those who elect to participate in in-person assessment visits will undergo blood draws to assess for potential inflammatory responses to pain. Participants will also provide urine samples for analysis of the presence of infection. Total time in both stages of this assessment will be approximately 90 minutes - approximately 45 minutes to complete patient-reported outcomes and approximately 45 minutes to complete in-person psychophysical assessments.

4.3 Inclusion criteria

Inclusion and exclusion criteria will be assessed with a structured checklist by the individual screening the participant (**Appendix D**).

1. 18 years of age or older;*
2. Diagnosis of IC/BPS as given by providers or indicated by assessments (RICE screening criteria).

4.4 Exclusion criteria

1. Comorbid neurological conditions including spinal cord injury or systematic neurologic illnesses, or central nervous system diseases such as brain tumor or stroke.
2. Current or history of diagnosis of primary psychotic or major thought disorder within the past five years;
3. Hospitalization for psychiatric reasons other than suicidal ideation, homicidal ideation, and/or PTSD (within the past 5 years);
4. Psychiatric or behavioral conditions in which symptoms are unstable or severe (e.g. current delirium, mania, psychosis, active suicidal ideation, homicidal ideation, substance abuse dependency) reported within the past six months;
5. Non-English speaking
6. Presenting symptoms at time of screening that would interfere with participation, specifically active suicidal ideation with intent to harm oneself or active delusional or psychotic thinking;

7. Difficulties or limitations communicating over the telephone.
8. Any planned life events that would interfere with participating in the key elements of the study.
9. Any major active medical issues that could preclude participation.
10. Currently being treated for cancer.
11. Cancer-related pain.
12. Currently engaged in individual counseling/psychotherapy or unwilling to pause this treatment for the trial duration.

*There will not be an upper age cutoff for study participation because individuals of all ages can be successfully treated, including those over 80 years old.

5. STUDY PROCEDURES

5.1 Overview

Participants will complete a total of three assessments before, immediately after, and 3 months following an 8-week period where they will either receive an 8-week series of psychosocial intervention or attention control visits. This equals a total of 11 visits with VUMC. Based on attrition rates from investigations in similar chronic pain conditions,[38] we will assume a conservative study dropout rate of 30%, and will recruit up to 96 participants in order to attain complete data on 75 subjects. In order to recruit 96 participants including follow-up we anticipate this study will occur over the course of three to four years. Below we detail a summary of the visit structure along with a figure indicating study flow.

The assessments corresponding to the study will occur in two stages at each of the three timepoints: (1) completion of patient-reported outcomes online, and optional (2) completion of psychophysical testing and the collection of biological samples in person at the CRC. Participants will have the option of enrolling in the first or both stages of these assessment visits, each of which will have separate consent forms.

Once patients pass the phone screen, they will be scheduled for a Study Enrollment visit, to take place remotely over the phone or online. They will present for a remote assessment visit to complete consenting procedures and will be sent patient-reported outcome measures online via REDCap. Those who elected to participate in in-person psychophysical testing procedures will then be scheduled for the CRC. Patients in the Study Enrollment Visit will complete separate consent forms corresponding to the online and in-person study procedures. The eligibility checklist will be reviewed again to ensure participants meet criteria and assessment battery will be given. Participants who enroll in the study will be randomized after the assessment (see section 5.3 for full description of randomization procedures).

<u>Pretreatment visit (1, T0)</u>:
Once patients are screened and determined to be eligible to participate in the study, they will complete informed consent and an assessment battery remotely. If they agree to undergo psychophysical testing, they will be scheduled to do so at the **Clinical Research Center** (CRC) for their first pre-treatment assessment visit (procedures detailed below).

<u>Visits (2-9, T1)</u>:

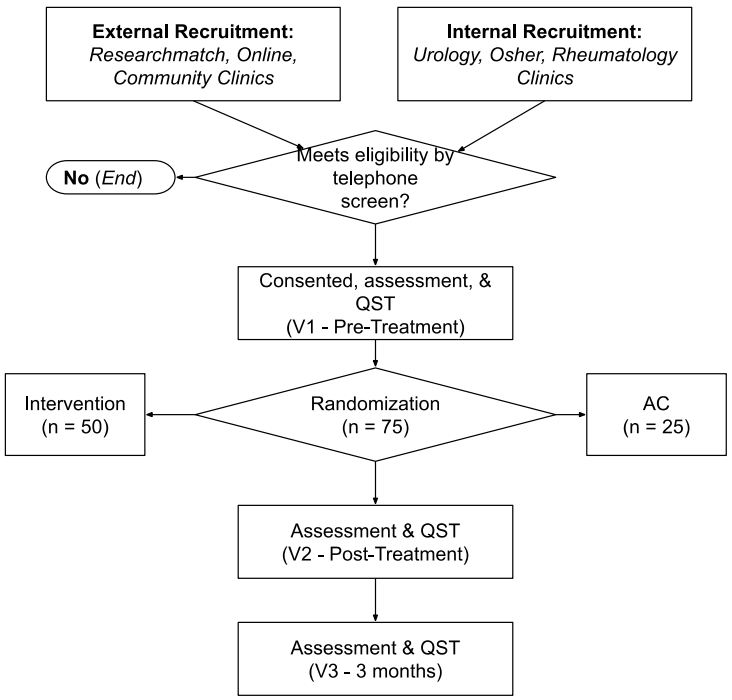
Participants will either receive a series of 8-week psychosocial intervention or attention control visits for an 8-week period at the Osher Center for Integrative Medicine, online, or via telephone. Each of the 8 treatment condition appointments will span 50 minutes.

Post-treatment Visit (10, T2):
Participants will complete a repeat corresponding battery of psychological (stage 1), psychophysical, and biological testing (stage 2) immediately after 8 weeks of visits.

3-month Follow-up Visit (11, T3):
Participants will complete a repeat battery of testing to investigate effects at follow-up.

5.1.1 Visit schedule adjustments due to infection precautions:
If circumstances arise where individuals cannot attend assessment visits in-person (e.g. due to system-wide precautions related to infection control), participants will engage in screening and assessment procedures remotely as applicable. Participants electing to participate in Stage 2 of the assessment process will then be invited at a later date to return on site to complete in-person assessment visits as timing and infection control procedures permit.

Figure 1: Study Flow



5.2 Screening phase

We will screen individuals either at the point of care or by telephone. Screening may also occur online via Redcap with a follow-up telephone call from study personnel. Following screening, we will schedule

eligible participants for a study enrollment visit to undergo consenting procedures and a one or two-stage clinical assessment (1) psychological measures online, and 2) in person psychophysical measures, and biological samples). Participants will then be randomized to an 8-week intervention or control condition. See Screening (section 4.2) for more information.

5.3 Randomization procedures

Patients will be randomized to the psychosocial self-management group (SM) or attentional control (AC) group after their first assessment visit. Randomization will occur at a 2:1 rate favoring our treatment condition, which will increase power in planned subgroup analyses. Randomization will be unblinded and occur through stratified permuted block methods using randomly-assigned variable blocks (2, 4, and 6). Participants will be stratified by opioid use levels, with those who take opioids more than 3 days per week defined as "regularly using opioids." Randomization will occur following participants' study enrollment visit and online assessment completion (Stage 1 assessment) to avoid any selection bias and to ensure adequate balance between treatment groups throughout the study accrual period. These procedures will be conducted by a study biostatistician so that the blocking factor is not known to the study PI or enrollment team to guard against any further selection bias.

5.4 Enrollment

We propose to enroll 96 participants in order to ensure complete data from 75 participants, assuming a very conservative 30% drop-out rate. We will monitor the dropout rate on an ongoing basis, and modify the number of participants recruited as needed to ensure a final sample of N = 75 study completers.

The study will enroll up to a total of 96 consecutive adults (aged >= 18 years) with IC/BPS to participate in baseline and follow-up clinical assessment and quantitative sensory testing. Eligible participants will be randomized to an intervention (cognitive-behavioral self-management) or active control condition at a 2:1 rate. Following randomization, ⅔ of participants will be provided with a cognitive-behavioral self-management intervention, and the other ⅓ will engage in an active attention control condition. Those enrolled in the study will also be followed after the intervention time period of 8 weeks and again at 3 months.

The registration process will occur through VUMC either at the Osher Center for Integrative Medicine at Vanderbilt, located at [redacted], Nashville, TN 37203, online, or at the VUMC Clinical Research Center at [redacted], Nashville, TN 37232. All participants will have a VUMC medical record identification number prior to beginning the study. Consenting will occur in-person or remotely where questions can be answered by a member of the research team, and assessment measures will be completed electronically on-site at VUMC or remotely online through a secure RedCap link. Consenting procedures will occur electronically in eConsent format online or on site using an electronic device where participants can fill out study measures online through RedCap. Psychophysical and Quantitative Sensory Testing will occur at the same site. After participants enroll in the study and complete their pre-treatment assessment, they will be randomized to the treatment or control condition.

For aims 2 and 3, we anticipate enrolling our first patient in the second half of the study's first year. Given our recruitment strategies, we anticipate consistent enrollment of subjects in years 1 (N=10), 2 (N=43), 3 (N=43) of the project, peaking in years 2 and 3. We aim to reserve the majority of year 4 to conclude data collection and focus on data analysis, manuscript preparation, and additional grant

applications. Data cleaning and quality monitoring will occur following enrollment of our first subject throughout the end of year 4 of the award. The final year will focus primarily on data analysis, dissemination, and manuscript preparation.

5.5 Retention

Our **retention strategy** will be informed by the PI's experience-to-date and mentor experience. We will track planned contacts and regular communication to improve data collection and promote study engagement. After initial screening, we will schedule regular follow-up contacts per study protocol including appointment reminders for follow-up. Planned contacts will occur through participants' preferred methods of either text, calling, or emailing. Moreover, a study interventionist interacts with every participant at each visit for an extended period of time, depending on the subject's group assignment. Participants are additionally provided with contact information for the PI and her study team to facilitate good communication.

Treatment phase

5.6.1 Psychosocial Self-Management (SM)

The psychosocial SM intervention consists of 8 weekly 50- minute individual visits with an assigned trained therapist. Sessions follow the content from a structured treatment protocol developed by the PI following a series of focus groups with the patient population (i.e. IRB #170653). Treatment modules are optimized from similar approaches toward chronic pain and tailored specifically to the condition based on voiced patient needs. Modules include relaxation training, pain coping strategies, IC/BPS and pain psychoeducation, and assertiveness skills. At the first visit, patient and provider will co-construct treatment goals, which will also affect the ordering of modules provided in the treatment to reflect the patient's primary needs. Therapists will follow a summarized session-by-session 'guide' to ensure they adhere to the major content of each session for fidelity monitoring purposes. Patients will be given a patient manual to coincide with treatment. The current therapist manual, therapist field guide, and patient treatment manual have been provided for IRB approval.

5.6.1.1 Intervention delivery adjustments and online access:

Due to infection precautions, in-visit restrictions may occur which could impact participants' ability to come on site. As such, we will conduct SM intervention visits to HIPAA-compliant videoconferencing platform (Zoom.us) for the duration of the SM intervention to prevent treatment interruption and trial delay.

Participants will be asked about their internet access during screening so that they can be properly scheduled. If a participant does not have a stable internet connection but desires to participate in the study, we will keep their contact information in the event that we elect to conduct in-person visits in the future.

5.6.2 Attentional Control (AC)

The AC will reflect a similar visit pattern as intervention sessions. Sessions will occur under the premise of monitoring symptoms and understanding lifestyle and health. Sessions will occur via scheduled

telephone calls and follow a structured procedure. In each phone call, the therapist will follow a script and orally administer and document responses from structured assessments inquiring about symptom patterns such as the Symptom and Healthcare Utilization Questionnaire[39], Self-Evaluation of Quality of Life,[40] and Ryff Scale of Psychological Wellbeing[41]. Selected content will reflect questions commonly asked at routine medical visits in urology, along with questions about general health and wellness. Participants attempting to discuss issues beyond the script will be told, "I'm sorry but as this is a research study, we need to focus on monitoring your current symptoms." AC will control for patient contact to better isolate intervention effects.

5.6.3 Fidelity monitoring

The PI will oversee intervention training and delivery by adhering to NIH Behavioral Change Consortium guidelines[42] recently reviewed as applied to clinical pain trials in Edmond (2018).[43] This will include structured training in intervention delivery, recording of sessions, and the PI engaging in weekly supervision with trial therapists to review content summary guide checklists and session material.

Clinical assessments

The battery of assessments below will be given at pretreatment, posttreatment, and at the three-month follow-up mark. Assessments will be completed in two stages at each timepoint: 1) online patient reported outcome measures and 2) in person psychophysiological testing and the collection of biological samples.

5.7.1 Patient-Reported Outcome measures

We selected measures that provide continuity between recently- reviewed pre-existing literature on IC/BPS, expert recommendations,[44] and results of ongoing trials.[45] Please see Protocol Table (**Appendix L**) for the timing of each measure as well as planned contacts.

<u>Consent/eConsent</u>
Patients will read and sign online consent form(s) written in accessible language outlining the potential treatment courses, risks and benefits, privacy, and the assessments and testing that will be performed. Consent forms will correspond to each of the two assessment stages: with one consent form to separately reflect in-person psychophysical assessment procedures. eConsent can be completed on REDcap.

<u>Demographics</u>
DEMO: Patients will complete a brief demographic questionnaire indicating items such as age, sex, gender, ethnicity, religious orientation, and household income. Patients will also indicate their diagnoses and information regarding diagnosis/treatment and medication use. The questionnaire will take approximately 3 minutes to complete.

<u>Urologic Symptoms</u>
GUPI[4]: The Genitourinary Pain Index (**GUPI-primary outcome**) is a 15-item symptom scale examining gender-specific pain, urinary symptoms, and quality of life impact. It is a validated and responsive instrument to assess symptom severity in both men and women with genitourinary pain complaints.[46] The

GUPI measures pain and urinary symptoms separately and cumulatively, reflecting IC/BPS assessment recommendations for clinical trials and takes <2 minutes to complete.[47]

RICE[48]: The RAND Interstitial Cystitis Epidemiology (RICE) scale is an 11-item self-report measure designed to identify women with IC/BPS symptoms and describe their symptoms, taking approximately 2 minutes to complete. This measure was developed using a rigorous, consensus-based protocol and validated against the current gold standard of clinical diagnoses by medical experts. It has demonstrated high specificity and sensitivity, and is recommended for prevalence-based studies[48]. It takes <1 minute to complete.

Pain Experiencing

MBM-II[49]: The Michigan Body Map-II (MBM-II) is a self-report measure used to assess the location(s) of chronic pain complaints and widespread body pain. It is a two-sided body image with check-box responses for 35 potential body areas where chronic pain (defined as pain > 3 months) might exist, and a box for "no chronic pain." It takes 2-3 minutes to complete. In this study, the measure is being used as an indication of centralized pain and pain sensitivity. We will use an open source version of the body map created in Redcap for the Collaborative Health Outcomes Information Registry initiative.

Comorbidity

FS[50]: the Fibromyalgia Symptom Scale is a 7-item questionnaire assessing modified 2010 American College of Rheumatology diagnostic criteria for fibromyalgia and includes a) an index of widespread pain and b) an index of symptom severity via patient self-report. This survey was designed by experts for epidemiologic study. It is administered with a pain body map. A total score on this scale ranges from 0-31, with scores ≥ 13 indicating a high likelihood of fibromyalgia. This scale takes approximately 3 minutes to complete.

MISCI[51]: The Multidimensional Inventory of Subjective Cognitive Impairment (MISCI) is a 10-item self-report measure assessing cognitive difficulties in fibromyalgia patients. Items address the past seven days and exist on a Likert scale of 1 to 5, with 5 indicating higher levels of cognitive impairment. The internal reliability and convergent validity of the item are dependable. The MISCI takes <1 minute to complete.

Quality of Life

FSFI[52]: The Female Sexual Function Index (FSFI) is a 19-item questionnaire with six domains of female sexual functioning. It takes <2 minutes to complete.

IIEF[53, 54]: The International Index of Erectile Dysfunction (IIEF) consists of 15 items and five domains pertinent to male sexual functioning. It has been studied in varied cultural contexts and translated into 10 languages. The item is reliable and valid, detecting clinical changes well. It takes <2 minutes to complete.

PISES[55]: The Painful Intercourse Self Efficacy Scale (PISES) is a version of the Arthritis Self Efficacy Scale adapted to assess dimensions of sexual experience. It is an 8-item measure that contains items rating self-efficacy related to pain from sexual intercourse on a 10-point likert scale. Using this scale, [redacted] adapted wording to IC/BPS-relevant symptoms based on information gathered in patient interviews in a former investigation (#170653). This measure has been adapted for similar populations used in previous

investigations as a domain of sexual functioning not captured in traditional sexual dysfunction measures.[55]

Affective Vulnerability

PROMIS-29 Scale [56,57]: The Patient-Reported Outcomes Measurement Information System® (PROMIS®) was designed to develop, validate, and standardize item banks to measure key domains of physical, mental, and social health in chronic conditions. The PROMIS-29 scale consists of 29 items asking about specific symptoms related to pain, fatigue, function, and physical and emotional health. These scales have been developed by experts for use in clinical trials and validated across populations. [redacted] use an abbreviated form of this scale, excluding redundant questions covered by the PHQ-8 and GAD-7 described below. This scale takes approximately 4 minutes to complete.

PHQ-8[58]: The eight-item Patient Health Questionnaire depression scale (PHQ-8) is established as a valid diagnostic and severity measure for depressive disorders in large clinical studies. It consists of 8 questions where participants indicate on a Likert scale the extent to which [redacted] have experienced symptoms of depression within the past two weeks, with 0 being "not at all" and 3 being "nearly every day." It takes <1 minute to complete.

GAD-7[59]: The Generalized Anxiety Disorder (GAD) questionnaire is a self-administered 7 item instrument that uses some of the DSM-V criteria for GAD to identify probable cases of GAD along with measuring anxiety symptom severity. It can also be used as a screening measure of panic, social anxiety, and PTSD. It was modeled after the PHQ-9 to be used quickly and effectively within a primary care setting.

PCL-5[60]: The PTSD Checklist for the DSM-5[60] is a 20-item measure with a five-point Likert scale that assesses the presence of post-traumatic stress. It utilizes the symptom checklist for PTSD in the DSM-5 and inquires about trauma-induced thoughts and behaviors in the past month. The item takes about 5 minutes to complete.

Environmental/Social

THQ[61]: The Trauma History Questionnaire[61] (THQ) is a 24-item self-report measure that examines experiences with potentially traumatic events such as crime, general disaster, and sexual and physical assault using a yes/no format. For each event endorsed, respondents are asked to provide the frequency of the event as well as their age at the time of the event. The THQ takes approximately 5-10 minutes to complete and has been determined to be reliable and valid in clinical and non-clinical samples[62]. This measure will be given in conjunction with the PCL-5 to provide an index trauma by which potential PTSD symptoms are related to. This measure will be given at baseline only.

Beliefs and Attitudes

CSQ-CAT[63] : The Coping Strategies Questionnaire- Catastrophizing scale (CSQ-CAT)[63] contains six questions and a seven-point Likert scale (from "never do that" to "always do that") regarding the negative, escalating cognitions that patients can experience as a result of pain. It takes <1 minute to complete.

Treatment Response

PGI-C[64]: Patient Global Impression of Improvement (PGI) [64] is a global index used to rate the response of a condition to an intervention. Patients rate their impression of change on a 7-point likert scale ranging

from “very much improved” to “very much worse.” This question is routinely used in clinical care and has been validated as a tool to assess perceived impact of disease management[65]. This questionnaire will be given post-treatment and at follow-up only and takes <1 minute to complete.

Treatment Utilization
The Health Utilization Form, created by our lab, is a self-report questionnaire containing sixteen questions that pertain to care utilized during the five-month period of the study. This measure will be given at post-treatment and follow-up to gather further information about treatment utilization during the study period.

5.7.2 Psychophysical (QST) measures (applies to the second assessment stage only)

Psychophysical testing applies different types of stimuli, such as pressure or heat, to measure central sensitization and pain responsiveness in the body.[65] In this investigation, psychophysical testing methods will replicate protocols currently used by mentors ([redacted])[66-69] and include the following elements: 1) an evaluation of temporal summation (as a biomarker for central sensitization[70], 2) thermal pain threshold and tolerance, and 3) pressure pain threshold. These methods are validated, replicable, and widely used in the pain field to index central sensitization, including in ongoing studies examining pelvic pain, and pain phenotypes.[39,71-73,] In replication, we will use a Medoc TSAII NeuroSensory Analyzer with a 9-cm^2 peltier thermode delivering a controlled heat stimulus able to rapidly return to baseline temperature by active cooling (at 10°C/second). We will assess temporal summation using software provided with the unit that administers a standardized oscillating thermal stimulation protocol designed specifically to elicit C-fiber mediated temporal summation.[66-68] We will evaluate temporal summation on the forearm at two target temperatures (47°C and 49°C), by applying a sequence of 10 heat pulses in a fixed position at each target temperature. These pulses (each 0.5 seconds) begin at 40°C and increase to the target temperature with rapid return to baseline at 0.4 Hz, a frequency known to elicit C-fiber mediated wind-up in the dorsal horn.[74] In each sequence, immediately after each heat pulse, subjects provide a verbal numeric pain intensity rating on a 0–100 scale (0 = “No Pain or Warmth” and 100 = “Worst Possible Pain”). The standardized slope of the line fitted to the series of 10 pulses at each temperature indexes temporal summation and serves as a quantitative marker of central sensitization.[66] Additional techniques will assess thermal pain threshold and tolerance, and pressure pain threshold as previously described. [66-68] Thermal measures involve four pain threshold trials, followed by four pain tolerance trials, with the probe applied to slightly different target sites for each trial to avoid local sensitization. Means for the four threshold and tolerance trials are separately derived. Pressure pain threshold testing[39] uses an algometer to assess pain threshold at four sites: the upper fibers of the trapezius, the tibialis anterior, forearm, and pelvic region. This total process takes approximately 30 minutes to complete.

5.7.3 Biological samples to be taken (applies to the second assessment stage only)

Urinalysis (UA): All participants will provide urine samples and undergo a urinalysis (UA) following their assessment visit to assess for the presence of infection. Participants will undergo repeat UA at follow-up visits to assess the potential impact of infection symptoms on pain responding and patient phenotype. Urine samples given will be transferred to a lab in Medical Center North ([redacted]), frozen, and undergo urinary microbiome and biomarker analyses at a later date to facilitate patient phenotyping.

Blood samples: Participants will undergo blood draws to obtain serum and plasma for research purposes. These will be obtained at a single timepoint during the assessment visit, prior to sensory testing. As such a trained Registered Nurse of the VUMC Clinical Research Center (CRC) will follow clinic procedures to secure these samples, which will be stored on-site at the CRC. We will use a warm compress beforehand as needed to help facilitate the procedure. We will collect 12cc of blood, using two lavender K2-ETDA 4ml vials for plasma analysis, one 3.5ml yellow top vial aliquot for serum blood collection, and a 2ml vial coated in lipopolysaccharide (LPS) to examine LPS-stimulated cytokines. Study research nurses will spin down serum and plasma samples and place into a cryotube for each patient during the in-person assessment visit. A subset (2ml) of the samples placed in LPS-coated vials will be stimulated in an agitator at 37 degrees for 24 hours, after which the supernatant is isolated with a valve separator accompanying the vial. The isolated supernatant will be placed in cryotubes by CRC nursing staff at 24 hours and frozen at -80 degrees Celsius the following day. Samples will be labeled and stored in the CRC laboratory during data collection. Samples that have yet to be analyzed at the conclusion of data collection will be transferred to a secure, temperature-controlled location under the purview of the PI and study primary mentor [redacted] in her laboratory space ([redacted] Samples will be taken to assess for inflammatory biomarkers, including LPS-stimulated cytokines to facilitate patient phenotyping.

Post-treatment and follow-up assessments

Post-treatment and follow-up assessments will occur immediately following the conclusion of the 8-week treatment or control period, and then 3 months following. These visits will occur again in two stages both online and at the CRC (as applicable) and reflect the same process as the pre-treatment assessment, including self-report assessments, psychophysical testing and biological samples taken. Each visit will take approximately 60-90 minutes in total.

Visit schedule adjustments in the event of infection precautions:
If circumstances arise where individuals cannot attend assessment visits in-person (e.g. due to system-wide precautions related to infection control), participants will engage in screening and assessment procedures remotely as applicable. Participants electing to participate in in-person assessment procedures will then be invited at a later date to return on site to complete in-person assessment visits as timing permits.

5.8.1 Study Compensation

Participants will be compensated for their participation at a rate of up to $100 per visit ($40 per patient-reported outcome, $60 per in-person assessment visit) for a total of $300 over the course of treatment. Those driving outside of Davidson County will also be offered either transportation assistance or compensation for mileage traveled on an as-needed basis.

5.9 Study withdrawal

Participants may withdraw from any part of the study at any time. If this occurs, only data collected prior to the time of study withdrawal will be kept for analysis purposes, except for the circumstance where the patient discontinues the intervention (such as for reasons outlined below) but wishes to complete follow-up assessments.

5.10 Treatment discontinuation

As per standard clinical procedures, a participant will be withdrawn from the treatment intervention if:

- Noncompliance to protocol, including but not limited to:
    - Participant engages in behavior that is disruptive,
    - Participant engages in behavior that interferes with the appropriate administration of treatment
    - Participant does not attend scheduled sessions
- The study must close for any reason
- Intercurrent illness or condition that would, in the judgment of the PI and mentorship team (including multiple MDs), affect assessment of clinical status to a significant degree or require discontinuation of study treatment
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the PI and mentorship team
- The subject desires to withdraw

Participants who are withdrawn from the study treatment intervention will be invited to complete study assessments during treatment, post-treatment, 3-month and 6-month follow-up in order to allow for complete data for the planned intent-to-treat analyses. Participants will receive payment for the time it takes to provide outcome data at each assessment point.

5.11 Replacement of patients who discontinue early

The study intends that patients will complete the full 8 weeks of treatment. If a patient discontinues study treatment then that patient may be replaced with a new patient.

6. RISK MINIMIZATION

Below we detail risks as they relate to different aspects of our study and efforts to minimize risk. [redacted] categorize potential risks in regards to the screening, assessment and treatment period. Risks related to privacy and confidentiality are also reviewed.

6.1 Screening Procedures

Regarding the telephone screening, research team members will follow an IRB-approved script informing patients of the study purpose and inclusion/exclusion criteria. If participants complete screening procedures online, they will answer the same series of structured questions and be provided with crisis services information embedded in the questions online. Research team members will also follow an IRB-approved in-person screening script if recruiting in person. Participants who indicate that they are having thoughts of self-harm or suicide will be provided with resources for follow-up immediately (i.e. the telephone number to the National Crisis Hotline and website www.suicidepreventionlifeline.org to chat with support staff online, and PI office number). Additionally, if this occurs in person or over the telephone, the RA will inform the PI, who will also follow-up with the potential participant within 24- 48 hours to assess if further assistance or referrals are necessary in order to provide adequate support. These resources will also be available online for those completing screening procedures electronically. The PI will provide a direct phone number to call during business hours for participant use for additional support and to make any necessary referrals. These participants will be ineligible for study participation. We have

successfully implemented these screening procedures in ongoing projects [redacted]).

6.2 Self-report assessments

Regarding the assessment battery, participants may experience temporary physical discomfort from prolonged sitting and/or temporary emotional discomfort answering questions about current emotional states and pain levels. To mitigate this risk participants will be informed that they do not have to answer any questions they feel uncomfortable answering. Further, participants may take as much time as needed to complete the assessments.

There is potential risk for transient emotional discomfort following answering questions about pain, psychological health, and overall wellness. During screening procedures, any individual with acute emotional distress will not be eligible for study participation, which minimizes this risk.

6.3 Psychophysical (QST) assessments

Risks associated with quantitative sensory testing are minimal. Participation in psychophysical testing is optional to participants. The procedure is designed to elicit the perception of pain, discomfort, or unpleasant sensations on various bodily quadrants. Participation may elicit these sensations for a brief period but this does not result in prolonged pain. Subjects will experience brief, moderate intensity acute pain upon application of the ischemic and thermal pain stimuli use both for acute pain evaluation and conditioned pain modulation assessment. However, subjects have total control over the duration of their exposure to this pain because they terminate the task by indicating when they have reached their tolerance limit. There are established protocols with limits of thermal temperature, which maximum temperature elicited is 127 degrees Fahrenheit. QST protocols have been reviewed extensively,[76] deemed a valuable measure of central and peripheral sensitization, and determined to be safe and do not stimulate pain crisis.[77] Additionally, participants are provided with instructions that testing can stop at any point in time. Previous research indicates that these tasks are safe, with safety of the thermal task further insured by a hardware cutoff in the TSA-II equipment that immediately cools the heat stimulus if a temperature greater than 51 deg C is reached (i.e., below the temperature at which tissue damage occurs). Because subjects have total control over the duration of the task, its psychological impact is expected to be minimal. At VUMC, both acute pain tasks have been used previously in numerous studies involving both chronic pain patients and healthy controls without incident, including work by [redacted].

6.4 Collection of biological samples

Collection of blood may be associated with pain or bruising at the venipuncture site. Further, individuals may in rare cases have a vasovagal response to needles or blood collection. All sample collection will be conducted with trained nursing personnel present to provide any additional support should this occur. Further, patients will be positioned in a seated or laying down position when providing blood samples to reduce risk. Participating in the collection of biological sampels is optional to participants.

6.5 Treatment phase

The control condition will involve participants being asked about their health, symptoms and current functioning and oral administration of validated self-report assessments via telephone. This also may

produce temporary emotional discomfort in answering questions about pain and emotion, or temporary physical discomfort from prolonged sitting. In the same vein, participants will be informed they do not have to answer any questions that make them uncomfortable, and will be free to move around as needed to alleviate or prevent physical discomfort when speaking with study personnel.

Participating in self-management interventions with a psychologist can at times produce emotional discomfort as therapists can assist patients through encountering and approaching avoided tasks and emotions. Psychologists adhere to clinical judgment and ethical principles of nonmaleficence and beneficence and have patients' best interests and collaboratively established treatment goals in mind when engaging in treatment with participants. Participants choose how, when, and which goals to work toward with the assistance of the therapist. Participants are also free to withdraw from the intervention or control condition at any time.

In the event than an individual does not express any distress during screening but does so during visits with an interventionist, interventionists will operate by ethical guidelines established by the psychology profession and State of Tennessee Board of Examiners in Psychology to ensure and prioritize patient safety. Risk will be minimized of this event with the screening procedures in place to assess for acute emotional distress prior to enrollment.

6.6 Privacy and Confidentiality Issues

Only persons directly involved in the study will have access to written or electronic study data identifying individual patients. All research assistants will complete training in the responsible conduct of research prior to engaging in the study.

Informed consent will be obtained electronically for each participant in the study prior to their participation. Assessment data will be entered and stored using RedCap/SPSS in encrypted files on an encrypted laptop computer belonging to the PI. Participant tracking information will be stored on a separate password-protected excel file only accessible to the PI and a research team member. Participant tracking information, along with all study-related documents and files can also be stored in VUMC Box. They will be given a unique number, with tracking information of this number only accessible to the PI and members of the research team. A limited data set, containing no identifying information, may be shared with collaborating individuals at regional institutions. Such individuals will have signed Data Use Agreements with VUMC and will abide by these contracts prior to having access to any such information.

When they occur, remote visits (enrollment procedures, study visits) will occur through the use of Zoom teleconferencing software. This is a HIPAA-compliant, password-protected teleconferencing software that is highly secure. This is the same system used for remote clinical VUMC visits and all trained interventionists and study team personnel have high familiarity with the technology.

Assessment and consenting data will be collected and stored primarily online in a secure server in a secure RedCap database. In the event that assessments are completed on paper (e.g. if a participant is not comfortable using a computer), paper assessment data will be coded and de-identified, and stored separately in a locked drawer at OCIM. To maintain confidentiality in this circumstance, the PI will store all financial reporting and consent forms in a separate locked drawer in her office. Assessment data will be entered and stored using RedCap in encrypted files on an encrypted laptop computer belonging to the

PI. Participant tracking information will be stored on a separate password-protected form only accessible to the PI and authorized members of the research team. Session recordings will be reviewed by the PI for the purpose of fidelity monitoring and then erased. Access to these data and other patient recruitment materials will be restricted to study personnel only.

7. ADVERSE EVENT REPORTING

In accordance with VUMC policy, adverse events and unanticipated problems involving risk to participants or others that fall under VUMC IRB jurisdiction will be reported to the VUMC IRB within 10 working days after learning of the event or problem.

8. DATA AND SAFETY MONITORING

The PI (Dr. McKernan) will form a data and safety monitoring board (DSMB) to overview the study, including safe keeping of stored data and monitoring/supervising research staff in the responsible conduct of research. The DSMB will have content experts and an independent biostatistician to review study progress and any adverse events. Experts include VUMC faculty with expertise in biostatistics, the provision of clinical trials with psychosocial interventions, integrative medicine, and pain psychology. Safety after sensory testing will be the responsibility of the research team member present with the participant and CRC nurse. This testing procedure will be conducted in a clinical setting with physicians and staff on site. Should safety concerns arise during the study, Dr. McKernan will be responsible for immediately notifying the treating physician. Dr. McKernan will also be responsible for monitoring safety of participants involved in the self-management intervention or attention control conditions. Should concerns arise with the emotional stability of a participant or a potential participant (during recruitment), Dr. McKernan will follow the above procedures and also notify treating physicians as needed. The DSMB for the study will be updated monthly regarding any adverse events and convene annually to review study progress. As required by the institution and IRB, any adverse events will be reported to the IRB within 10 days.

9. STATISTICAL CONSIDERATIONS

9.1 Analytic Plan by Aim

Aim 1: To construct a patient-centered CBT self-management (SM) intervention specific to IC/BPS. Pre-work for this aim will include a theme analysis of coded transcripts from focus groups using NVivo 9 to code, analyze, and interpret transcripts using elements of grounded theory.[78] For the project period, this aim will primarily involve consolidating qualitative work and will use descriptive statistics where appropriate.

Aim 2: To obtain preliminary data comparing the effectiveness of integrating SM interventions into usual treatment (N = 50) to control (AC, N = 25) in improving targeted primary (symptom improvement [≥7 point reduction in GUPI]) and secondary (pain, distress, quality of life) outcomes.

Power and sample size considerations: [redacted] are comparing GUPI-Total Score, a continuous variable, between the SM group and a matched AC group with a 2:1 randomization scheme. The GUPI-Total Score tends to be normally distributed with a standard deviation of 8.61.[47, 79] A 7-point decrease in total GUPI score is considered clinically meaningful[79] and a robust assessment of response to treatment.[4]

Assuming a Type I error of 0.05 and power of .90, we will need 50 experimental subjects and 25 control subjects to reject the null hypothesis that the sample means of both treatment groups are equal post-treatment. [redacted] intend to have 50 experimental and 25 control subjects to obtain even groups for analytical purposes, as recommended by [redacted] DSMB. Given our use of statistical models, [redacted] power is increased when [redacted] appropriately adjust for covariates.

[redacted] will test the hypothesis that those receiving the SM intervention will show improved outcomes relative to AC. [redacted] will use generalized linear mixed models to compare responses on the Genitourinary Pain Index (GUPI[80]-Primary Outcome) between treatment groups, adjusting for baseline GUPI and covariates. As recent evidence recommends the examination of pain and urinary symptoms separately,[25] [redacted] will examine the GUPI pain subscale and GUPI urinary subscale separately in secondary analyses. [redacted] will perform one interim analysis at approximately 50% completion of data collection using the O'Brien-Fleming method to preserve alpha accounting for repeat testing.

[redacted] will examine changes in secondary outcomes of interest, including pre- to post-treatment changes in emotional distress (e.g. PHQ-8, GAD-7, PCL-5, CSQ), quality of life and wellness (e.g. PROMIS-29), widespread pain (MBM/Choir bodymap), and perceived treatment benefit (PGI) using similar approaches: linear models for continuous outcomes, proportional odds models for ordinal outcomes, and logistic models for binary outcomes. As [redacted] training in data analysis progresses, [redacted] will apply more sophisticated approaches, such as hierarchical modeling. As [redacted] anticipate potential confounding from factors such as age and time since diagnosis, we will account for these as covariates in the analyses. Further, as opiate use is associated with increased pain sensitivity and decreased pain thresholds on psychophysical testing,[73] [redacted] will stratify groups by opiate use during randomization. [redacted] will additionally consider opiate use as a covariate in the analyses. To address sex as biologic variable, we will examine sex as a moderator of treatment effects, since men and women perceive pain differently in self-report[74] and sensory testing.[81]

Aim 3: To determine whether patient phenotype moderates treatment response to a SM intervention. As an exploratory aim, [redacted] will assess the hypotheses that a) higher pre-treatment psychological distress, b) higher baseline temporal summation, and c) number of chronic overlapping pain conditions will be associated with greater SM treatment efficacy. To avoid loss of power from testing a phenotype x treatment x time interaction, [redacted] will model the change in GUPI and treatment response (PGI) using a proportional odds model adjusted for baseline GUPI, and test for a treatment x phenotype interaction. A positive finding would suggest treatment effects depend on these moderating factors. [redacted] increased our sample size for this analysis by applying a 2:1 randomization scheme; however, given that our treatment group still constitutes a small sample size (n=50), [redacted] will set a threshold of $p<.2$ for the interaction before proceeding with a responder or mediation analysis. [redacted] will use these analyses to identify factors needing consideration in future studies expanding the generalizability of SM.

10. FOLLOW UP-AND RECORD RETENTION

The study duration is estimated at four years. Data will be stored for five years after publication in de-identified form and informed consent forms will be kept for 3 years as per federal law. All data will be stored electronically where available. Information collected in databases may be archived indefinitely to support future research efforts.

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IC/BPS REFERRAL FORM

IC/BPS Investigation Referral Form, Provider Pre-Screening

Referred by:_____ Date:_____

Patient Name: _____
Patient MRN: _____

Please **circle** which ICD-10 Diagnosis for Interstitial Cystitis/Bladder Pain Syndrome this patient meets criteria for:

- N30.10 (without hematuria) or
- N30.11 (with hematuria)

Was this IC/BPS diagnosis made following a cystoscopy?

- ❑ YES
- ❑ NO

Is this individual age 18+ and able to read, write, and understand English? (if YES, proceed)

Please indicate if this patient has any of the following (if YES to any of the items below, patient is not appropriate for this study):

- ❑ Comorbid neurological conditions including spinal cord injury or systematic neurologic illnesses, or central nervous system diseases such as brain tumor or stroke.
- ❑ Current or history of diagnosis of primary psychotic or major thought disorder within the past five years;
- ❑ Hospitalization for psychiatric reasons other than suicidal ideation, homicidal ideation, and/or PTSD (within the past 5 years);
- ❑ Psychiatric or behavioral conditions in which symptoms are unstable or severe (e.g. current delirium, mania, psychosis, suicidal ideation, homicidal ideation, substance abuse dependency) reported within the past six months;
- ❑ Current symptoms that would interfere with study participation, specifically active suicidal ideation with intent to harm oneself or active delusional or psychotic thinking;
- ❑ Difficulties or limitations communicating over the telephone;
- ❑ Any planned life events that would interfere with participating in the key elements of the study;
- ❑ Any active major medical issue that would preclude participation;
- ❑ Currently being treated for cancer;
- ❑ Cancer-related pain.
- ❑ Currently engaged in individual counseling/psychotherapy or unwilling to pause this treatment for the trial duration.

Does patient have access to a reliable internet connection?
(circle) YES NO

Is the patient interested in participating in this trial?

- ❑ YES
- ❑ NO

If yes, best # to

contact: Email:

Would you prefer a

call/text?

- ❑ CALL
- ❑ TEXT

13. APPENDIX B: TELEPHONE SCRIPT

TELEPHONE SCRIPT

Note to screening provider: prior to contacting a participant, please have a 'screening form' ready to fill out in corroboration with the individual's responses to screening questions.

Mr/Ms._____, my name is_____and I work for Vanderbilt University Medical Center. You recently responded to an advertisement for a clinical study or we referred to us as an individual who has Interstitial Cystitis that may be interested in being a part of our project. The purpose of this phone call is to first tell you more about the study to see if you are interested in participating. If you are interested, I can then ask some questions to see if you are eligible to participate in the study. If you would like to proceed with the screening call, it will take approximately ten minutes. This call is strictly voluntary. Would you like to continue?

Yes, continue

No. May I call you back at a more convenient time?

- Yes. Schedule a time to call back.
- No. Thank you for your time. End phone call

This study is a clinical trial specifically for Interstitial Cystitis (IC). The purpose of this research study is to examine treatments for interstitial cystitis and to learn about different presentations of the condition. Participation involves three assessment visits, and either 8 additional weekly visits that will occur in person, online, or over the phone.

The assessment visits would occur in two parts, with the second being optional. Part 1 of the assessment would involve completing a series of questionnaires online. Part 2 would occur in-person and involve providing blood and urine samples, and undergoing testing that evaluates how your body assesses and responds to pain.

The weekly visits will either consist of speaking with a provider via telephone to monitor and discuss your symptom patterns week-by-week or to meet in person or online with a provider to enhance self-management of IC. We will provide compensation for the assessment visits and for travel expenses in some cases.

Do you think you may be interested in taking part in this research study?

- No. Thank them for their time and end phone call.
- Yes, continue.

Great. I would like to ask you some questions to see if you will be eligible for the study.

Can you please tell me your current age (if over 18, continue)?

Have you been diagnosed with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS)?

If not, then it does not appear that you qualify for the study. (Thank them for their time and end call) Note: if participant states they suspect they have interstitial cystitis but have not been formally diagnosed, continue and ask RICE screening questions.

Are you currently taking prescription medicines that are opiates?

- **If YES**, can you please tell me the name of the medicine and the dosage? How often do you take the medicine, on average?

What state do you currently reside in? (Record answer)

Please answer yes or no to the following questions:

- Do you have a neurological condition or illness such as: spinal cord injury, general neurologic illness, brain tumor, or stroke?
- Have you ever experienced seeing things that other people cannot see or hearing things that other people cannot hear (within the past five years)?
- Have you had any psychiatric hospitalizations in the past 5 years? (Still eligible if PTSD or SI/HI.)
- Have you had any severe psychiatric or behavioral conditions in the past six months (e.g. current delirium, mania, psychosis, suicidal ideation, homicidal ideation, substance abuse dependency)?
- Do you speak English fluently?
- Do you have difficulties or limitations communicating over the telephone?
- Do you have any planned life events that would interfere with participating in the key elements of the study (e.g. participant would not be available for weekly appointments)?
- Are you experiencing any major medical issues at the moment?
- Are you currently undergoing cancer treatment?
- Are you experiencing any cancer-related pain?
- Are you currently engaged in individual counseling/psychotherapy? If so, are you willing to pause this treatment for the duration of the trial? (proceed if NO to individual psychotherapy or YES to willing to pause treatment)
- Are you experiencing any active thoughts of harming yourself or seeing/hearing things that are not there?

If YES: for support, please call the national suicide crisis hotline at 1-800-273- 8255 or visit www.suicidepreventionlifeline.org to chat online with support staff. Note: Also contact the PI for follow-up with the individual and provide the individual with the PI's office number (615) 875-9990.

If yes to any of the above (other than pausing psychotherapy for duration of trial and speaking English): it does not appear that you qualify for the study. Thank them for their time and end call (note: if patient endorses

suicidal ideation contact PI).

- Do you have a stable internet connection/access at home? (circle YES or NO, proceed regardless of answer)

If unsure about any of the above…I may need to ask some additional questions based on your responses today to see if you qualify for the study. Would it be possible for me to call you back with more information (note: contact PI to clarify as needed)?

If no to all of the above, proceed with questions regarding current symptoms: I'd like to ask you a few questions about your current symptoms:

[RESEARCH PERSONNEL MOVE TO RICE CRITERIA AND ASK QUESTIONS]

If qualified via RICE Questionnaire…… then it appears that you qualify to be in the study. Are you interested in taking part in this study?

- No. Thank you for your time.
- Yes. Great. Ask internet question:

Do you have a stable internet connection/access at home? (circle YES or NO, proceed regardless of answer; enrollment might be delayed if NO due to COVID-19, but they will be provided with more information in the future)

If patient does not have a stable internet connection: please inform the participant that due to COVID visitation restrictions we are conducting visits online and that potential study participation will need to be delayed. If this changes in the future we will contact the participant at that time.

Finally, provide available times for intake appointment and schedule with participant.

Note for individuals who are currently taking opiates: Please note that as [redacted] study evaluates how [redacted] body responds to pain, it is important to not take any medicines the day of the assessment that could change how [redacted] may or may not feel pain. If [redacted] are taking opiates, [redacted] ask that you do not take them before the assessment appointment. [redacted] will remind you about this closer to the date as well.

[redacted] are very much looking forward to meeting you and having you be a part of this project. Can you please provide me with the best number to reach you and an email address? To make things easier, we would like to remind you of your appointment in a way that best suits you. Can [redacted] please let us know if you would prefer a call or a text message?

14. APPENDIX C: IN-PERSON SCRIPT

IN-PERSON SCRIPT

Note to screening provider: prior to contacting a participant, please have a 'screening form' ready to fill out in corroboration with the individual's responses to screening questions.

Hello Mr. Mrs.

My name is _____and I work at Vanderbilt University Medical Center. We are conducting a new trial for Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) and would like to see if you are interested in participating.

The purpose of this discussion is to first tell you more about the study to see if you are interested in participating. I will ask you a brief set of questions about your current symptoms and medical experiences. If you are interested, I can then ask some questions to see if you are eligible to participate in the study. If you would like to proceed with our conversation, it will take approximately ten minutes. This discussion is strictly voluntary. Would you like to continue?

- If YES, proceed
- If NO, thank them for their time and end the conversation

This study is a clinical trial specifically for Interstitial Cystitis (IC). The purpose of this research study is to examine treatments for interstitial cystitis and to learn about different presentations of the condition. Participation involves three assessment visits, and either 8 additional weekly visits that will occur in person, online or over the phone.

The assessment visits would occur in two parts, with the second being optional. Part 1 of the assessment would involve completing a series of questionnaires online. Part 2 would occur in-person and involve providing blood and urine samples, and undergoing testing that evaluates how your body assesses and responds to pain.

The weekly visits will either consist of speaking with a provider via telephone to monitor and discuss your symptom patterns week-by-week or to meet in person or online with a provider to enhance self-management of IC. We will provide compensation for the assessment visits and for travel expenses in some cases.

Do you think you may be interested in taking part in this research study?

- **No**. Thank them for their time and end phone call.
- **Yes**, continue.

Great. I would like to ask you some questions to see if you will be eligible for the study.

Can you please tell me your current age (if over 18, continue)?

Have you been diagnosed with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS)?

If not, then it does not appear that you qualify for the study. (Thank them for their time and end call) Note: if participant states they suspect they have interstitial cystitis but have not been formally diagnosed, continue and ask RICE screening questions.

Are you currently taking prescription medicines that are opiates?

- ❑ **If YES**, can you please tell me the name of the medicine and the dosage? How often do you take the medicine, on average?

What state do you currently reside in? (record answer)

Please answer yes or no to the following questions:

- ❑ Do you have a neurological condition or illness such as: spinal cord injury, general neurologic illness, brain tumor, or stroke?
- ❑ Have you ever experienced seeing things that other people cannot see or hearing things that other people cannot hear (within the past five years)?
- ❑ Have you had any psychiatric hospitalizations in the past 5 years? (Still eligible if PTSD or SI/HI.)
- ❑ Have you had any severe psychiatric or behavioral conditions in the past six months (e.g. current delirium, mania, psychosis, suicidal ideation, homicidal ideation, substance abuse dependency)?
- ❑ Do you speak English fluently?
- ❑ Do you have difficulties or limitations communicating over the telephone?
- ❑ Do you have any planned life events that would interfere with participating in the key elements of the study (e.g. participant would not be available for weekly appointments)?
- ❑ Are you experiencing any major medical issues at the moment?
- ❑ Are you currently undergoing cancer treatment?
- ❑ Are you experiencing any cancer-related pain?
- ❑ Are you currently engaged in individual counseling/psychotherapy?
- ❑If so, are you willing to pause this treatment for the duration of the trial? (must answer YES)
- ❑ Are you experiencing any active thoughts of harming yourself or seeing/hearing things that are not there?

If YES: for support, please call the national suicide crisis hotline at 1-800-273- 8255 or visit www.suicidepreventionlifeline.org to chat online with support staff.
Note: Also contact the PI for follow-up with the individual and provide the individual with the PI's office number (615) 875-9990.

If yes to any of the above (other than pausing psychotherapy for duration of trial and speaking English): it does not appear that you qualify for the study. Thank them for their time and end call (note: if patient endorses suicidal

ideation contact PI).

If screening provider is unsure about any of the above…I may need to ask some additional questions based on your responses today to see if you qualify for the study. Would it be possible for me to call you back with more information (note: contact PI to clarify as needed)?

If no to all of the above, proceed with questions regarding current symptoms: I'd like to ask you a few questions about your current symptoms:

[RESEARCH PERSONNEL MOVE TO RICE CRITERIA ON SCORING FORM AND ASK QUESTIONS]

If qualified via RICE Questionnaire…… then it appears that you qualify to be in the study. Are you interested in taking part in this study?

- No. Thank you for your time.
- Yes. Great. Ask internet question:

Do you have a stable internet connection/access at home? (circle YES or NO, proceed regardless of answer; enrollment might be delayed if NO due to COVID-19, but they will be provided with more information in the future)

If patient does not have a stable internet connection: please inform the participant that due to COVID visitation restrictions we are conducting visits online and that potential study participation will need to be delayed. If this changes in the future we will contact the participant at that time.

Finally, provide available times for intake appointment and schedule with participant.

Note for individuals who are currently taking opiates: Please note that as our study evaluates how our body responds to pain, it is important to not take any medicines the day of the assessment that could change how we may or may not feel pain. If you are taking opiates, we ask that you do not take them before the assessment appointment. We will remind you about this closer to the date as well.

We are very much looking forward to meeting you and having you be a part of this project. Can you please provide me with the best number to reach you and an email address? To make things easier, we would like to remind you of your appointment in a way that best suits you. Can you please let us know if you would prefer a call or a text message?

15. APPENDIX D: INCLUSION/EXCLUSION CHECKLIST

INCLUSION/EXCLUSION CHECKLIST

Inclusion/Exclusion Criteria Checklist

Inclusion criteria (must answer YES):

- ❑ 18 years of age or older.
- ❑ Diagnosis of IC/BPS as given by providers or indicated by

assessments

Exclusion criteria (must answer NO to all):

- ❑ Comorbid neurological conditions including spinal cord injury or systematic neurologic illnesses, or central nervous system diseases such as brain tumor or stroke.
- ❑ Current or history of diagnosis of primary psychotic or major thought disorder within the past five years;
- ❑ Hospitalization for psychiatric reasons other than suicidal ideation, homicidal ideation, and/or PTSD (within the past 5 years);
- ❑ Psychiatric or behavioral conditions in which symptoms are unstable or severe (e.g. current delirium, mania, psychosis, suicidal ideation, homicidal ideation, substance abuse dependency) reported within the past six months;
- ❑ Non-English speaking
- ❑ Presenting symptoms at time of screening that would interfere with participation, specifically active suicidal ideation with intent to harm oneself or active delusional or psychotic thinking;
- ❑ Difficulties or limitations communicating over the telephone.
- ❑ Any planned life events that would interfere with participating in the key elements of the study.
- ❑ Any active major medical issues that would preclude participation.
- ❑ Currently being treated for cancer.
- ❑ Cancer-related pain.
- ❑ Currently engaged in individual counseling/psychotherapy or unwilling to pause this treatment for the trial duration.

16. APPENDIX E: REMINDER SCRIPT

Optimizing Psychosocial Treatment for IC/BPS- Phone/email reminder script

Hello, (insert name here), this is (name) from Vanderbilt University Medical Center. I am contacting you about the Interstitial Cystitis (IC/BPS) treatment study. I would like to remind you that you have an upcoming visit (place) at (time) on (date). I am calling to confirm your appointment and also see if you have any questions about the visit.

If call/text,

(if applicable-)Would you like directions to your visit at the Clinical Research Center/Osher Center for Integrative Medicine?
If YES, provide directions.
Do you have any questions?
If YES, answer questions.

Can you please confirm that you will be at the appointment?

Wonderful, we will see you for your appointment then. Please feel free to call or text me with any questions you may have. If you need to cancel, please let us know in advance as best you can by calling (provide phone number).
Take care!

End call/text.

If email,
Directions to the Clinical Research Center (plug in your starting point)
Address: [redacted], Nashville, TN 37232
Directions to the Osher Center for Integrative Medicine (plug in your starting point)
Address: [redacted], Nashville, TN 37203

Can you please confirm that you will be at the appointment?

If you need to cancel, please let us know in advance as best you can by calling (provide phone number).

Please feel free to email me with any questions you may have. See you then!

Thank you,
The research team

17. APPENDIX F: RESEARCH MATCH SCRIPT (MEN)

RESEARCH MATCH SCRIPT (MEN)

Are you a male with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) interested in participating in a research study?

We are looking for men with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) to participate in a clinical trial.

Study purpose: The purpose of this research study is to examine treatments for interstitial cystitis and to learn about different presentations of the condition.

Study duration: Participation involves three assessment visits that can be done completely online if desired, ranging from 45 to 90 minutes each. Also, the study will have 8 additional weekly visits that will occur either in person, online, or over the phone that will be up to 50 minutes each. The assessments and visits will occur over the course of 5 months.

Eligible individuals are adults (18+) with IC/BPS who do not have any of the following: diagnosed neurological conditions including spinal cord injury, brain injury, or stroke, certain psychological conditions including psychotic or bipolar disorder, current severe psychiatric distress, current cancer treatment or cancer-related pain. Participants need to speak English fluently, be able to speak over the phone, have a stable internet connection (if applicable), and be available for eight weekly visits during study participation which may occur in person, online, or by telephone.

Participants will be compensated up to $300 for their time.

Note: Eligibility will be further determined upon contact and/or completion of the eligibility survey.

18. APPENDIX G: RESEARCH MATCH SCRIPT (WOMEN)

RESEARCH MATCH SCRIPT
(WOMEN)

Are you a woman with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) interested in participating in a research study?

We are looking for women with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) to participate in a clinical trial.

Study purpose: The purpose of this research study is to examine treatments for interstitial cystitis and to learn about different presentations of the condition.

Study duration: Participation involves three assessment visits that can be done completely online if desired, ranging from 45 to 90 minutes each. Also, the study will have 8 additional weekly visits that will occur either in person, online, or over the phone that will be up to 50 minutes each. The assessments and visits will occur over the course of 5 months.

Eligible individuals are adults (18+) with IC/BPS who do not have any of the following: diagnosed neurological conditions including spinal cord injury, brain injury, or stroke, certain psychological conditions including psychotic or bipolar disorder, current severe psychiatric distress, current cancer treatment or cancer-related pain. Participants need to speak English fluently, be able to speak over the phone, have a stable internet connection (if applicable), and be available for eight weekly visits during study participation which may occur in person, online, or by telephone.

Participants will be compensated up to $300 for their time.

Note: Eligibility will be further determined upon contact and/or completion of the eligibility survey.

19. APPENDIX H: RESEARCH MATCH SCRIPT (GENERAL)

RESEARCH MATCH SCRIPT
(GENERAL)

Do you currently have Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) and are you interested in participating in a research study?

We are looking for individuals with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) to participate in a clinical trial.

Study purpose: The purpose of this research study is to examine treatments for interstitial cystitis and to learn about different presentations of the condition.

Study duration: Participation involves three assessment visits that can be done completely online if desired, ranging from 45 to 90 minutes each. Also, the study will have 8 additional weekly visits that will occur either in person, online, or over the phone that will be up to 50 minutes each. The assessments and visits will occur over the course of 5 months.

Eligible individuals are adults (18+) with IC/BPS who do not have any of the following: diagnosed neurological conditions including spinal cord injury, brain injury, or stroke, certain psychological conditions including psychotic or bipolar disorder, current severe psychiatric distress, current cancer treatment or cancer-related pain. Participants need to speak English fluently, be able to speak over the phone, have a stable internet connection (if applicable), and be available for eight weekly visits during study participation which may occur in person, online, or by telephone.

Participants will be compensated up to $225 for their time.

Note: Eligibility will be further determined upon contact and/or completion of the eligibility survey.

20. APPENDIX I: LISTSERV SCRIPT (MEN)

LISTSERV SCRIPT (MEN)

Are you a male with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) interested in participating in a research study?

We are looking for men with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) to participate in a clinical trial.

Study purpose: The purpose of this research study is to examine treatments for interstitial cystitis and to learn about different presentations of the condition.

Study duration: Participation involves three assessment visits that can be done completely online if desired, ranging from 45 to 90 minutes each. Also, the study will have 8 additional weekly visits that will occur either in person, online, or over the phone that will be up to 50 minutes each. The assessments and visits will occur over the course of 5 months.

Eligible individuals are adults (18+) with IC/BPS who do not have any of the following: diagnosed neurological conditions including spinal cord injury, brain injury, or stroke, certain psychological conditions including psychotic or bipolar disorder, current severe psychiatric distress, current cancer treatment or cancer-related pain. Participants need to speak English fluently, be able to speak over the phone, have a stable internet connection (if applicable), and be available for eight weekly visits during study participation which may occur in person, online, or by telephone.

If you are interested in participating and would like to know if you are eligible, please **contact our study team** at 615-875-7214, **email** our office at research.ocim@vumc.org (please include a phone number to reach you in the email), or **fill out** our Interest Form.

Participants will be compensated up to $300 for their time.

Note: Eligibility will be further determined upon contact and/or completion of the eligibility survey.

21. APPENDIX J: LISTSERV SCRIPT (WOMEN)

LISTSERV SCRIPT (WOMEN)

Are you a woman with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) and are you interested in participating in a research study?

We are looking for women with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) to participate in a clinical trial.

Study purpose: The purpose of this research study is to examine treatments for interstitial cystitis and to learn about different presentations of the condition.

Study duration: Participation involves three assessment visits that can be done completely online if desired, ranging from 45 to 90 minutes each. Also, the study will have 8 additional weekly visits that will occur either in person, online, or over the phone that will be up to 50 minutes each. The assessments and visits will occur over the course of 5 months.

Eligible individuals are adults (18+) with IC/BPS who do not have any of the following: diagnosed neurological conditions including spinal cord injury, brain injury, or stroke, certain psychological conditions including psychotic or bipolar disorder, current severe psychiatric distress, current cancer treatment or cancer-related pain. Participants need to speak English fluently, be able to speak over the phone, have a stable internet connection (if applicable), and be available for eight weekly visits during study participation which may occur in person, online, or by telephone.

If you are interested in participating and would like to know if you are eligible, please **contact our study team** at 615-875-7214, **email** our office at research.ocim@vumc.org (please include a phone number to reach you in the email), or **fill out** our Interest Form.

Participants will be compensated up to $300 for their time.

Note: Eligibility will be further determined upon contact and/or completion of the eligibility survey.

22. APPENDIX K: LISTSERV SCRIPT (GENERAL)

LISTSERV SCRIPT (GENERAL)

Do you currently have Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) and are you interested in participating in a research study?

We are looking for individuals with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) to participate in a clinical trial.

Study purpose: The purpose of this research study is to examine treatments for interstitial cystitis and to learn about different presentations of the condition.

Study duration: Participation involves three assessment visits that can be done completely online if desired, ranging from 45 to 90 minutes each. Also, the study will have 8 additional weekly visits that will occur either in person, online, or over the phone that will be up to 50 minutes each. The assessments and visits will occur over the course of 5 months.

Eligible individuals are adults (18+) with IC/BPS who do not have any of the following: diagnosed neurological conditions including spinal cord injury, brain injury, or stroke, certain psychological conditions including psychotic or bipolar disorder, current severe psychiatric distress, current cancer treatment or cancer-related pain. Participants need to speak English fluently, be able to speak over the phone, have a stable internet connection (if applicable), and be available for eight weekly visits during study participation which may occur in person, online, or by telephone.

If you are interested in participating and would like to know if you are eligible, please **contact our study team** at 615-875-7214, **email** our office at research.ocim@vumc.org (please include a phone number to reach you in the email), or **fill out** our Interest Form.

Participants will be compensated up to $300 for their time.

Note: Eligibility will be further determined upon contact and/or completion of the eligibility survey.

23. APPENDIX L: TEXT RECRUITMENT SCRIPT

TEXT RECRUITMENT SCRIPT

TEXT 1:
Do you currently have Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) and are you interested in participating in a research study to examine treatments for Interstitial Cystitis? If so, reply to this text!

[IF PERSON INDICATES INTEREST, PROCEED TO TEXT 2 AND 3]

TEXT 2:
We are seeking to develop treatments for IC / BPS and learn about different presentations of the condition. This study will involve a series of three online symptom assessment visits (with the option for additional in-person assessment) and eight weekly visits that will occur over the phone or online.

TEXT 3:
If Interest Form has not been completed:
To learn more, complete our Interest Form by clicking on this link: LINK HERE and entering this access code: CODE HERE. Alternatively, reach out to us by calling this number: NUMBER HERE. Thank you and take care!

If Interest Form has been completed:
We will need to give you a call for screening purposes. Please text us with a couple of good times and days to reach you. Alternatively, reach out to us by calling this number: NUMBER HERE. Thank you and take care!

24. APPENDIX M: Message for providers

Dear [provider name],

I hope all is well! This is Rachel, a study coordinator for Dr. Lindsey McKernan's lab at VUMC. We received your information via [insert referral source] as a potential referral source for our project. Using our eStar reports, we have access to names of patients who have Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS). We have found that you have one or more patients who might be eligible for our study.

- Specifically [MRN] on [appointment date] may be an eligible study candidate.

We are currently recruiting for a NIH-funded clinical trial for IC/BPS and are seeking referrals from VUMC providers. This study builds upon years of patient interviews of individuals with IC, and is testing the benefits of an IC-focused psychological intervention (versus active symptom monitoring) on symptom reduction. If successful, we intend to deliver this intervention to a wider audience.

Would you consider giving information about our study to your patient? Alternatively, you could simply provide our contact information so that they can reach out to us to learn more. We have also provided text below to use in the event that you'd like to pass along study information electronically.

Lab phone number: 615-875-7214
Lab email address: research.ocim@vumc.org
Interest form link: https://redcap.vanderbilt.edu/surveys/?s=YLCELM9YYN
Text for messaging: (pasted below)

Lastly, if you are open to being contacted about other potential candidates in the future and would prefer we contact you via eStar, or through an alternative contact (e.g. nursing staff), please let us know. Thank you for your consideration!

Best,

The McKernan Lab

Do you currently have Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) and are you interested in participating in a research study?

We are looking for individuals with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) to participate in a clinical trial.

Study purpose: The purpose of this research study is to examine treatments for interstitial cystitis and to learn about different presentations of the condition.

Study duration: Participation involves three assessment visits that can be done completely online if desired, ranging from 45 to 90 minutes each. Also, the study will have 8 additional weekly visits that will occur either in person, online, or over the phone that will be up to 50 minutes each. The assessments and visits will occur over the course of 5 months.

Eligible individuals are adults (18+) with IC/BPS who do not have any of the following: diagnosed neurological conditions including spinal cord injury, brain injury, or stroke, certain psychological conditions including psychotic or bipolar disorder, current severe psychiatric distress, current cancer treatment or cancer-related pain. Participants need to speak English fluently, be able to speak over the phone, have a stable internet connection (if applicable), and be available for eight weekly visits during study participation which may occur in person, online, or by telephone.

*If you are interested in participating and would like to know if you are eligible, please **contact our study team** at 615-875-7214, **email** our office at research.ocim@vumc.org (please include a phone number to reach you in the email), or **fill out** our Interest Form, linked here: https://redcap.vanderbilt.edu/surveys/?s=YLCELM9YYN.*

Participants will be compensated up to $300 for their time.

Note: Eligibility will be further determined upon contact and/or completion of the eligibility survey.

25. APPENDIX N: eStar Recruitment Script

In the past, you've shown interest in learning about research studies at Vanderbilt. We are reaching out about a study you may be interested in. More information about the study is below.

We are looking for individuals with Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) to participate in a clinical trial.

Study purpose: The purpose of this research study is to examine treatments for interstitial cystitis and to learn about different presentations of the condition.

Study duration: Participation involves three assessment visits that can be done completely online if desired, ranging from 45 to 90 minutes each. Also, the study will have 8 additional weekly visits that will occur either in person, online, or over the phone that will be up to 50 minutes each. The assessments and visits will occur over the course of 5 months.

Eligible individuals are adults (18+) with IC/BPS who do not have any of the following: diagnosed neurological conditions including spinal cord injury, brain injury, or stroke, certain psychological conditions including psychotic or bipolar disorder, current severe psychiatric distress, current cancer treatment or cancer-related pain. Participants need to speak English fluently, be able to speak over the phone, have a stable internet connection (if applicable), and be available for eight weekly visits during study participation which may occur in person, online, or by telephone.

*If you are interested in participating and would like to know if you are eligible, please **contact our study team** at 615-875-7214, **email** our office at research.ocim@vumc.org (please include a phone number to reach you in the email), or **fill out** our Interest Form, linked here: https://redcap.vanderbilt.edu/surveys/?s=YLCELM9YYN.*

Participants will be compensated up to $300 for their time.

Note: Eligibility will be further determined upon contact and/or completion of the eligibility survey.

Thank you for your consideration!

Best,

The McKernan Lab

26 . APPENDIX O : PROTOCOL TABLE

Measures	Domain	Purpose	Number of Items	Screening	Before first visit	Pre-Treatment	Before Post-Treatment	Post-Treatment	Before Follow-Up	Follow-Up (3 mo.)
IC/BPS Intervention Referral Form	Screening	Screening for Eligibility/Interest	N/A	x						
DEMO	Demographics	Patient characteristics	15			x				
GUPI[4]	Urologic symptoms	Pain and urinary symptoms. Likert scale. Subscales: pain, urinary, QOL Impact.	9			x		x		x
PHQ-8[58]	Affective vulnerability	More detailed and sensitive assessment of depression. 4-point Likert scale.	8			x		x		x
MBM-II[49] (with CHOIR bodymap)	Pain experiencing	Widespread pain. Indication via check marks of which body regions experience chronic pain.	1			x		x		x
Fibromyalgia Symptom (FS) scale[50] /ACR FM diagnostic criteria	Quality of life	Symptom severity scale. Subscales: Widespread Pain Index (WPI)- check marks for pain areas, Symptom Severity Score (SS)- half is 4-point Likert scale, half is symptom checklist. Used with CHOIR bodymap to determine presence of fibromyalgia.	6			x		x		x
PISES[55]	Quality of life	Sexual pain, fear, and dysfunction. Subscales: self-efficacy for sexual function, self-efficacy for controlling other	25			x		x		x

		symptoms, self-efficacy for controlling pain during intercourse.								
PROMIS-29 Scale[56,57] (without anxiety and depression scales)	Quality of life	Pain, fatigue, function, and physical and emotional health. Likert scale from 1-5 for all but last subscale (0-10). Anxiety and depression subscales omitted. Subscales: physical function, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, pain intensity.	29			x		x		x
PCL-5 with Criterion A[60]	Affective vulnerability	Post-traumatic stress. Parts: traumatic events checklist, questions about worst event, PTSD checklist with a 5-point Likert scale.	25			x		x		x
THQ (baseline only)[61]	Environmental/Social	Trauma exposure and PTSD assessment; used in conjunction w/ PCL to evaluate for trauma. Domains include: crime-related events, general disaster and trauma, physical and sexual experiences.	6, 7			x				
CSQ-CAT[63]	Beliefs and Attitudes	Catastrophizing measure, 7-pt Likert scale.	6			x		x		x
PGI-C[64]	Treatment response	Perceived response to treatment, 7-pt Likert scale.	1					x		x
Patient Reminder Script	Reminder	Give patient info on upcoming visit.	N/A		x		x		x	
MISCI[51]	Cognition	Cognitive dysfunction associated with widespread pain. 5-pt Likert scale. Domains: mental clarity, memory, attention/concentration, executive functioning, language.	10			x		x		x
GAD-7[59]	Affective vulnerability	Assessment of anxiety, 4-pt Likert scale.	7			x		x		x

RICE[48]	Screening	Surrogate for diagnosis in patients outside of system. 11 items.		x						
FSFI[52], IIEF[53,54]	Quality of life	Sexual dysfunction - F/M. FSFI subscales: desire, arousal, lubrication, orgasm, sexual satisfaction, pain. Likert scale. IIEF domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction. Likert scale.	19, 15			x		x		x
HUF	Treatment Utilization	Self-report questionnaire containing questions that pertain to care utilized during the five-month period of the study.	16					x		x