Project Title: A Multidisciplinary, Multimodal Bundled Care Approach to Chronic Pelvic Pain
NCT Number: NCT05658874
Document Date Approved: 6/13/2024

Summary:

Chronic Pelvic Pain is a debilitating, multimodal disease with several contributing organ systems. As a result, adequate treatment of this disease requires multimodal pain therapy from a team of experts. Other multimodal pain bundles (such as ERAS in the perioperative setting) have been shown to be superior to any bundle component being used as a monotherapy. This study will assess patient response to a bundled-care approach to CPP both pre-and post intervention as well as compared to a site randomized "usual care" cohort.

Background/Rationale:

Chronic pelvic pain (CPP) is a common, debilitating condition experienced by up to 26% of adult women[12], costing billions in direct healthcare costs and indirect productivity costs annually[3]. CPP deeply affects women's quality of life, including everyday functioning and intimacy. Though there is no consensus definition, it is generally defined as generally defined as non-cyclic pain perceived to be in the pelvic area that has persisted for three to six months or longer and is unrelated to pregnancy[4].

CPP is challenging to treat, as it typically is insidious and the pathophysiology involves overlap of several related neuroimmune disorders affecting a litany of pelvic end-organs, including the muscles of the pelvic floor/vagina, bladder, colon and rectum, as well as the bony pelvis and hip girdle[5]. It is closely tied to conditions such as endometriosis, interstitial cystitis, and irritable bowel syndrome. It is also exacerbated by emotional, physical, and sexual trauma, and worsened by central sensitization by depression, anxiety, and substance abuse[6]. Systemic pain conditions such as fibromyalgia and autoimmune diseases are commonly found in women with CPP[7]. On average, women who experience CPP may have a 4-11 year delay in diagnosis[8] and seek the consultation of multiple providers before they find a pelvic pain specialist with an understanding of the complex mechanisms that perpetuate pain.

Most women who present to CPP specialists have tried several monotherapies, including combined oral contraceptive pills, repeated doses of antibiotics, over the counter pain medications, and other psychoactive medications, many of which are part of chronic pain treatment algorithms. In women with interstitial cystitis, the 2015 and 2022 AUA IC/PBS guidelines[91011] for treatment remain algorithmic and stepwise, despite literature that suggests that sequential monotherapy is a poor strategy [12]. Only recently have studies emerged showing that multidisciplinary clinics for female CPP are both clinically effective and cost effective [13] [14] and may improve uptake/compliance with physical therapy[15] and mental health recommendations, which are poor in this cohort[16] [17]While many studies have been done over decades of research on the various mechanistic cascades that perpetuate chronic pain, there has been little to no research done on a "bundled" approach to chronic pain. Care bundles are a set of three to five evidence-informed practices performed collectively and reliably to improve the quality of care[1819].

This approach takes advantage of treating pain as a polymodal affliction[20], requiring treatment for central-neural sensitization pathways[2122], emotional trauma, infectious/microbiome modulation[232425], immune factors, surgical interventions[2627], and physical therapy for end-organ rehabilitation[28]. Similar studies on "bundled care" have been done for infection control and show that no single intervention reduces infection in a significant way, but collectively each component of the care bundle provides dramatic improvements[29]. From an acute and postoperative pain standpoint, Enhanced Recovery After Surgery (ERAS) bundles have shown remarkable effectiveness for improving postoperative recovery[30] despite studies that fail to show effectiveness for components of the bundle as monotherapies[3132]. However a similar bundled, multimodal approach has not been formally presented or studied for CPP.

Objectives:

The goals of this research program are to evaluate the patient-reported outcomes of a multimodal care bundle for patients presenting to a multidisciplinary CPP clinic compared to "usual care" in an FPMRS or Urology clinic.

Primary Aim:

To compare pre and post intervention self-evaluation of pain and function scores in women with chronic pain syndromes with a primary finding of urinary/bladder pain symptoms **and/OR** levator spasm who undergo multi-disciplinary, bundled care compared with usual care in a FPMRS or Urology clinic setting.

Secondary Aims:

a) To identify and phenotype "non-responders" to a bundled approach to IC/PBS/CPP.

Hypothesis: We hypothesize that a bundled, multidisciplinary care approach will significantly improve patient scores on validated outcomes questionnaires compared to usual care.

Methods:

All treatment plans, medications, and procedures recommended for patients involved in this study are within the current standards of care for IC/PBS/CPP, regardless of treatment arm and are known to be safe interventions.

Study Design: Single center, randomized pre-post intervention/prospective cohort study[33] of usual FPMRS care vs. multimodal, multidisciplinary care bundle (MMCB).

STROBE[34] guidelines were utilized.

Setting: Patients will be recruited from an outpatient Female Pelvic Medicine and Reconstructive Surgery (FPMRS) clinic. They will subsequently be randomized to a

Multidisciplinary CPP clinic at an alternate site vs. continuing usual outpatient care in FPMRS as above.

Study Population/Participants: Eligible participants include self-referred women 18 years and older with a clinical diagnosis of IC/PBS (based on history and symptoms) who scored 6 points or greater on the problem OR symptom index of the O'Leary Sant Questionnaire. Every attempt will be made to fulfill a representation quotient[35].

Inclusion Criteria: Female patient 18 years of age or older, clinical diagnosis of CPP and IC/PBS, scoring 6 points or higher on O'Leary Sant Questionnaire **(IC/PBS arm) OR levator spasm diagnosed by an FPMRS specialist.**

Exclusion Criteria: active pelvic or bladder infection within past 2 weeks, contraindications to medications or intervention therapeutics, inability to speak or read English; pelvic floor interventional procedure including bladder instillations 4 weeks prior to study recruitment, meets criteria for diagnostic laparoscopy **(dysmenorrhea, uterine pain, cyclic pelvic pain, dyspareunia, GI symptoms)**

Note: patients are not excluded for currently taking any medication on the treatment list. Patients can be treated for UTI during the study period.

Randomization: If patients meet inclusion criteria and agree to participate, they will be randomized by RedCap[3637] either to remain in "usual" care in the FPMRS or Urology clinic or transition their care to the multidisciplinary CPP clinic at the UPMC Lemieux Center.

Definition of outcome measure and method of ascertainment:

Data collected at baseline, 6 weeks, 12 weeks, 6 months, 1 year

<u>Demographic Data</u>

Age
Self-Identified Race
Height/Weight/BMI
Menopausal Status
Currently using hormones
- -Oral contraceptives (list)
- -Intrauterine device (list)
- -Hormone replacement
- -Hormone-containing topical cream or ointment
- -Other (list)

Other pain conditions
- Fibromyalgia
- Migraine
- Endometriosis

Prior treatments for chronic pelvic or bladder pain (list)
Number of vaginal deliveries
Number of cesarean deliveries
Prior treatments for pelvic bladder pain

Medications
Pelvic floor physical therapy
Cystoscopy with hydrodistention
Other cystoscopy
Pelvic floor injections
History of culture-proven recurrent UTIs (yes/no)
-Give details
History of psychiatric diagnoses
Depression
Anxiety
Bipolar disorder
PTSD
Psychosis/Hallucinations
Other (list)
History of physical or sexual abuse (yes/no)

Primary Outcome
--O'Leary Sant Questionnaire (OLS)[38], comprised of Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI), at 12 weeks from baseline
MCID: 4 points for ICSI

Secondary Outcomes

-NRS Scale
-McGill Pain Questionnaire, Short Form [39]
-Pain Disability Index [40]
-Pelvic Pain and Urgency/Frequency Questionnaire (PUF)[41]
-Pelvic Floor Distress Inventory (PFDI)-20[42]
MCID: 45 points (15%)
-Female Sexual Function Index (FSFI)[43]
MCID: 2.1 points
-Pain Catastrophizing Scale (PCS)[44]
-Patient Global Impression of Improvement (PGI-I)[45]

1) Healthcare utilization defined as number of additional encounters for chronic pelvic and bladder pain diagnosis outside of the defined study period
    a. Phone calls
    b. Office visits
    c. ER visits
    d. Procedures

Intervention:

Components of MMCB (all)

1) MD Evaluation (FPMRS or Urology)
2) Pelvic floor physical therapy (PFPT)

3) Behavioral health consult if patient does not have established behavioral/psychiatric care [46]→with appropriate psychiatric referrals/treatments

4) Central sensitization/neurogenic pain:

Amitriptyline 10-50mg [21]
Or Gabapentin (doses range from 100mg po tid to 600mg po tid)

5) Pudendal/Levator and/or Obturator internus nerve block (120mg Kenalog and 0.25% Marcaine, total 23-33cc) in office or under anesthesia

6) Urinary symptoms IC/PBS ONLY

Spasm: OAB medication chosen based on patient characteristics/insurance, dose may be increased as tolerated (anticholinergic vs. b-agonist)
7) **Pyridium 100-300mg/day**

8) Microbiome: Methenamine[47]
9) Vaginal estrogen[23]

At least once within 12 weeks of initial visit:

10) Intravesical evaluation: Cystoscopy to evaluate for hunner ulcers or variant (treat with Kenalog injection alone if Hunner ulcers or variant with or without hydrodistention if no hunner ulcers)

11) Bladder instillations x 6 weeks (lidocaine, heparin, sodium bicarb, available glucocorticoid (dexamethasone, etc), gentamicin[48])

-Invasive interventions to be repeated as needed per patient.

Data will be stored and managed in a RedCap database[37]

Measures to reduce loss to follow up:
Phone calls and email from study coordinators.

Potential confounding variables: patients frequently have overlapping pain syndromes; likely many different CPP phenotypes. Patients will be enrolled sequentially.

Demographic data:

Age, self-identified race, BMI, menopausal status, past medical history, past surgical history, psychiatric history, tobacco, sexual assault/abuse history, history of prior interventions for their chronic pain condition, internal vs. external referral

Study Size/Power Calculation: based on the primary outcome, the primary outcomes is defined as the change in the total OLS score from baseline to 12 weeks compared between the groups. Based on previous studies, patients with IC/BPS have a baseline OLS score following standard medical treatment of 24 ± 5.6 190 points. [3849]. A 4.03-point

decrease from baseline on the OLS-ICSI corresponds with at least a 50% perceived improvement in symptoms[25], we have chosen to use 6 points, to represent 75% improvement. We desired 90% power to detect a 6-point or larger difference in the mean score change between the groups with a 2-sided t-test at a significance level of alpha=0.05. Accounting for 20% dropout, the target sample size was 40 for each group (80 total).

Ethical Concerns:

Pain patients are a vulnerable population.

Strengths/Weaknesses; patients cannot be blindly randomized, interventions are evidence-based but not being studied separately. There are likely differing phenotypes of pain patients (endometriosis vs. infectious vs. trauma) making for a heterogenous population.

Timeline: 12 month enrollment and 12 month follow up.

Budget:

Research Manager (1-2 years)-$10K
Research Operations Coordinator (1-2 years) $25K
Data Collection Tools (RedCap, database management, tablets for surveys, statistics, analytics)-$5K
Patient Incentives: 5 time points
$25 for each first 4 visits, $50 for final visit ($12K)
Promotional Materials/Design/Publicity -$1K
General Materials (Office supplies including file folders, printing supplies)$1K
Mail supplies (postage)$1K

Estimated Total: $50K

References:

1. Ahangari A. Prevalence of chronic pelvic pain among women: an updated review. *Pain Physician*. 2014;17(2):E141-147.

2. Chronic Pelvic Pain: ACOG Practice Bulletin Summary, Number 218. *Obstet Gynecol*. 2020;135(3):744-746. doi:10.1097/AOG.0000000000003717

3. Armour M, Lawson K, Wood A, Smith CA, Abbott J. The cost of illness and economic burden of endometriosis and chronic pelvic pain in Australia: A national online survey. *PloS One*. 2019;14(10):e0223316. doi:10.1371/journal.pone.0223316

4. Fall M, Baranowski AP, Elneil S, et al. EAU Guidelines on Chronic Pelvic Pain. *Eur Urol*. 2010;57(1):35-48. doi:10.1016/j.eururo.2009.08.020

5. Professionals SO. EAU Guidelines: Chronic Pelvic Pain. Uroweb. Accessed May 5, 2021. https://uroweb.org/guideline/chronic-pelvic-pain/#note_33

6. Lampe A, Sölder E, Ennemoser A, Schubert C, Rumpold G, Söllner W. Chronic Pelvic Pain and Previous Sexual Abuse. *Obstet Gynecol*. 2000;96(6):929-933.

7. Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. *Hum Reprod*. 2002;17(10):2715-2724. doi:10.1093/humrep/17.10.2715

8. Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. *Am J Obstet Gynecol*. 2019;220(4):354.e1-354.e12. doi:10.1016/j.ajog.2018.12.039

9. Intertitial Cystitis (IC/BPS) Guideline - American Urological Association. Accessed January 20, 2021. https://www.auanet.org/guidelines/interstitial-cystitis-(ic/bps)-guideline

10. Hanno Philip M., Erickson Deborah, Moldwin Robert, Faraday Martha M. Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome: AUA Guideline Amendment. *J Urol*. 2015;193(5):1545-1553. doi:10.1016/j.juro.2015.01.086

11. Clemens JQ, Erickson DR, Varela NP, Lai HH. Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome. *J Urol*. 2022;208(1):34-42. doi:10.1097/JU.0000000000002756

12. Nickel JC, Downey J, Ardern D, Clark J, Nickel K. FAILURE OF A MONOTHERAPY STRATEGY FOR DIFFICULT CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME. *J Urol*. 2004;172(2):551-554. doi:10.1097/01.ju.0000131592.98562.16

13. Westbay LC, Adams W, Kistner M, et al. Clinical Outcomes of a Multidisciplinary Female Chronic Pelvic Pain Program. *Female Pelvic Med Reconstr Surg*. 2021;Publish Ahead of Print. doi:10.1097/SPV.0000000000001045

14. Jochum SB, Legator H, Abraham RR, et al. It Takes a Village: The First 100 Patients Seen in a Multidisciplinary Pelvic Floor Clinic. *Female Pelvic Med Reconstr Surg*. 2021;27(4):e505. doi:10.1097/SPV.0000000000000884

15. Brown HW, Barnes HC, Lim A, Giles DL, McAchran SE. Better together: multidisciplinary approach improves adherence to pelvic floor physical therapy. *Int Urogynecology J*. 2020;31(5):887-893. doi:10.1007/s00192-019-04090-w

16. Fullerton ME, Mwesigwa PJ, Tandel MD, Kwan L, Grisales T, Tarnay CM. Comparison of Pelvic Floor Physical Therapy Attendance Based on Referring Provider Specialty. *Female Pelvic Med Reconstr Surg*. 2021;Publish Ahead of Print. doi:10.1097/SPV.0000000000001061

17. Woodburn KL, Tran MC, Casas-Puig V, Ninivaggio CS, Ferrando CA. Compliance With Pelvic Floor Physical Therapy in Patients Diagnosed With High-Tone Pelvic Floor Disorders. *Female Pelvic Med Reconstr Surg*. 2021;27(2):94-97. doi:10.1097/SPV.0000000000000732

18. Lavallée JF, Gray TA, Dumville J, Russell W, Cullum N. The effects of care bundles on patient outcomes: a systematic review and meta-analysis. *Implement Sci*. 2017;12(1):142. doi:10.1186/s13012-017-0670-0

19. Rice KL, Castex J, Redmond M, Burton J, Guo JW, Beck SL. Bundling Interventions to Enhance Pain Care Quality (BITE Pain) in Medical Surgical Patients. *Ochsner J*. 2019;19(2):77-95. doi:10.31486/toj.18.0164

20. Jhang JF, Kuo HC. Pathomechanism of Interstitial Cystitis/Bladder Pain Syndrome and Mapping the Heterogeneity of Disease. *Int Neurourol J*. 2016;20(Suppl 2):S95-104. doi:10.5213/inj.1632712.356

21. Foster HE, Hanno PM, Nickel JC, et al. Effect of amitriptyline on symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome. *J Urol*. 2010;183(5):1853-1858. doi:10.1016/j.juro.2009.12.106

22. Giannantoni A, Porena M, Gubbiotti M, Maddonni S, Di Stasi SM. The efficacy and safety of duloxetine in a multidrug regimen for chronic prostatitis/chronic pelvic pain syndrome. *Urology*. 2014;83(2):400-405. doi:10.1016/j.urology.2013.09.024

23. Abernethy MG, Rosenfeld A, White JR, Mueller MG, Lewicky-Gaupp C, Kenton K. Urinary Microbiome and Cytokine Levels in Women With Interstitial Cystitis. *Obstet Gynecol*. 2017;129(3):500-506. doi:10.1097/AOG.0000000000001892

24. Lewis AL, Gilbert NM. Roles of the vagina and the vaginal microbiota in urinary tract infection: evidence from clinical correlations and experimental models. *GMS Infect Dis*. 2020;8. doi:10.3205/id000046

25. Meriwether KV, Lei Z, Singh R, Gaskins J, Hobson DTG, Jala V. The Vaginal and Urinary Microbiomes in Premenopausal Women With Interstitial Cystitis/Bladder Pain Syndrome as Compared to Unaffected Controls: A Pilot Cross-Sectional Study. *Front Cell Infect Microbiol*. 2019;9:92. doi:10.3389/fcimb.2019.00092

26. Dessie SG, Von Bargen E, Hacker MR, Haviland MJ, Elkadry E. A randomized, double-blind, placebo-controlled trial of onabotulinumtoxin A trigger point injections for myofascial pelvic pain. *Am J Obstet Gynecol*. 2019;221(5):517.e1-517.e9. doi:10.1016/j.ajog.2019.06.044

27. Olson LE, Dyer JE, Haq A, Ockrim J, Greenwell TJ. A systematic review of the literature on cystodistension in bladder pain syndrome. *Int Urogynecology J*. 2018;29(2):251-257. doi:10.1007/s00192-017-3355-y

28. FitzGerald MP, Payne CK, Lukacz ES, et al. Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. *J Urol*. 2012;187(6):2113-2118. doi:10.1016/j.juro.2012.01.123

29. Keenan JE, Speicher PJ, Thacker JKM, Walter M, Kuchibhatla M, Mantyh CR. The Preventive Surgical Site Infection Bundle in Colorectal Surgery: An Effective Approach to Surgical Site Infection Reduction and Health Care Cost Savings. *JAMA Surg*. 2014;149(10):1045-1052. doi:10.1001/jamasurg.2014.346

30. Albert H, Bataller W, Masroor N, et al. Infection prevention and enhanced recovery after surgery: A partnership for implementation of an evidence-based bundle to reduce colorectal surgical site infections. *Am J Infect Control*. 2019;47(6):718-719. doi:10.1016/j.ajic.2018.11.004

31. Stone R, Carey E, Fader AN, et al. Enhanced Recovery and Surgical Optimization Protocol for Minimally Invasive Gynecologic Surgery: An AAGL White Paper. *J Minim Invasive Gynecol*. Published online August 20, 2020. doi:10.1016/j.jmig.2020.08.006

32. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev*. 2012;(7):CD008943. doi:10.1002/14651858.CD008943.pub2

33. Thiese MS. Observational and interventional study design types; an overview. *Biochem Medica*. 2014;24(2):199-210. doi:10.11613/BM.2014.022

34. STROBE Statement: Available checklists. Accessed February 2, 2021. https://www.strobe-statement.org/index.php?id=available-checklists

35. Brown O, Siddique M, Mou T, et al. Disparity of Racial/Ethnic Representation in Publications Contributing to Overactive Bladder Diagnosis and Treatment Guidelines. *Female Pelvic Med Reconstr Surg*. 2021;Publish Ahead of Print. doi:10.1097/SPV.0000000000000992

36. Suresh K. An overview of randomization techniques: An unbiased assessment of outcome in clinical research. *J Hum Reprod Sci*. 2011;4(1):8-11. doi:10.4103/0974-1208.82352

37. REDCap. Accessed February 2, 2021. https://www.project-redcap.org/

38. O'Leary MP, Sant GR, Fowler FJ, Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. *Urology*. 1997;49(5A Suppl):58-63. doi:10.1016/s0090-4295(99)80333-1

39. Melzack R. The short-form McGill Pain Questionnaire. *Pain*. 1987;30(2):191-197. doi:10.1016/0304-3959(87)91074-8

40. detpdi.pdf. Accessed May 4, 2021. https://www.med.umich.edu/1info/FHP/practiceguides/pain/detpdi.pdf

41. Parsons CL, Dell J, Stanford EJ, et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology*. 2002;60(4):573-578. doi:10.1016/s0090-4295(02)01829-0

42. Barber MD, Chen Z, Lukacz E, et al. Further validation of the short form versions of the Pelvic Floor Distress Inventory (PFDI) and Pelvic Floor Impact Questionnaire (PFIQ). *Neurourol Urodyn*. 2011;30(4):541-546. doi:10.1002/nau.20934

43. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000;26(2):191-208. doi:10.1080/009262300278597

44. Pain Catastrophizing Scale. Physiopedia. Accessed March 21, 2021. https://www.physio-pedia.com/Pain_Catastrophizing_Scale

45. Tincello DG, Owen RK, Slack MC, Abrams KR. Validation of the Patient Global Impression scales for use in detrusor overactivity: secondary analysis of the RELAX study. *BJOG Int J Obstet Gynaecol*. 2013;120(2):212-216. doi:https://doi.org/10.1111/1471-0528.12069

46. Gillman A, Zhang D, Jarquin S, Karp JF, Jeong JH, Wasan AD. Comparative Effectiveness of Embedded Mental Health Services in Pain Management Clinics vs Standard Care. *Pain Med Malden Mass*. 2020;21(5):978-991. doi:10.1093/pm/pnz294

47. Chwa A, Kavanagh K, Linnebur SA, Fixen DR. Evaluation of methenamine for urinary tract infection prevention in older adults: a review of the evidence. *Ther Adv Drug Saf*. 2019;10. doi:10.1177/2042098619876749

48. Cardenas-Trowers O, Abraham A, Dotson, Thomas, Houlette, Brooke, Gaskins J, Francis S. Effect of Bladder Instillations with versus without Triamcinolone Acetonide on Symptoms of Interstitial Cystitis/Bladder Pain Syndrome in Women: A Randomized Controlled Trial. *2021 Ahead Print*.

49. Lubeck DP, Whitmore K, Sant GR, Alvarez-Horine S, Lai C. Psychometric validation of the O'leary-Sant interstitial cystitis symptom index in a clinical trial of pentosan polysulfate sodium. *Urology*. 2001;57(6 Suppl 1):62-66. doi:10.1016/s0090-4295(01)01126-8