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TITLE: Comparison of Bladder-Directed and Pelvic Floor Therapy in Women with Interstitial Cystitis/Bladder Pain Syndrome

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14. ABSTRACT

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating constellation of symptoms including urinary urgency, frequency, and pain related to the bladder, which predominantly affects women. Although symptoms appear to be bladder related, there has been little solid evidence linking IC/BPS with a dysfunctional bladder epithelium unless ulcers are present. There is growing evidence that the bladder may be an innocent bystander in a more diffuse syndrome with a complex interplay of various systems/factors. It is our *objective* to assess the role of the pelvic floor muscles as a major contributor to pelvic pain and voiding dysfunction in adult women with IC/BPS symptoms. Our primary focus has been on study recruitment and enrollment. Due to the national shortage of one of the medications that are used for bladder instillations (bladder focused therapy), we only enrolled 1 of 128 total women (64 in each treatment arm) in the first project year. In August 2017 we obtained a limited supply of the medication, and study recruitment and enrollment resumed. In Years 2 and 3, recruitment activities expanded to increase enrollment. In mid-March of Year 4 all in-person research visits, and enrollment and screening activities were halted due to COVID-19. In year 6, Although our targeted enrollment goals are not met, enrollment has been steadily growing.

15. SUBJECT TERMS

Cystitis, Interstitial; Pelvic pain; Lower Urinary Tract Symptoms; Pelvic Floor Disorders; Pain, Chronic; Biomarkers

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1. INTRODUCTION:

Although severe urinary urgency, frequency, and pelvic pain symptoms are present in interstitial cystitis/bladder pain syndrome (IC/BPS), there has been little solid evidence linking symptoms with a dysfunctional bladder epithelium unless ulcers are present. Our *objective* is to assess the role of the pelvic floor muscles as a major contributor to pelvic pain and voiding dysfunction in adult women with IC/BPS symptoms. The project aims to randomize 128 women (64 in each arm) with IC/BPS to bladder instillations (bladder focused therapy) or pelvic floor physical therapy. Participants will be followed with symptom and biomarker assessments for up to 3 years.

2. KEYWORDS:

Cystitis, Interstitial; Pelvic pain; Lower Urinary Tract Symptoms; Pelvic Floor Disorders; Pain, Chronic; Biomarkers

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: **Evaluate the effects of bladder directed therapy twice weekly (bladder instillation) and twice weekly PFPT on IC/BPS symptoms.**

Major Task 1: Study Start Up

Completed, all milestones achieved by 12 months:

- Research protocol finalized, Local IRB and HRPO approval obtained, Research staff trained, Flow chart implemented for all study activities, data collection and database requirements

Major Task 2: Participant Recruitment, Therapy, Participant Evaluation

Milestones to be achieved by 36 months:

- One hundred twenty-eight (128) participants consented, screened and enrolled.
- Year 7, Actual: Eighty-three (83) women consented to study participation. Thirty-eight (38) patients were enrolled, randomized, and treated; Four (4) patients were enrolled, randomized, and withdrew prior to treatment; and forty-one (41) patients consented and failed screening. Note: One patient initially screened and failed. When she was re-screened, she failed again. She was only counted as one potential participant.
- To date, thirty (30) patients have completed all treatment visits of which 10 are in active follow-up, nine (9) patients withdrew from the study, and eight (8) patients were lost to follow-up. One additional patient is in active follow-up, but this patient did not complete all 16 treatment visits. Twelve (12) subjects completed all study activities and exited the study.
- In mid-March of Year 4 (2020) all in-person research visits, including enrollment and screening activities were halted due to COVID-19. Consequently, one patient had a break in their treatment delivery schedule, which was re-started in July 2020 when research activities commenced.

Major Task 3: Data analysis

- 15% achieved: In the 4th quarter of year 6 we performed an interim data analysis of data collected through 3-day voiding diary and various questionnaires. From this data we

gathered that both treatments are effective in improving symptoms, though treatments differed in the type of symptom that it was superior in improving. As this is an ongoing study, we are not including the actual data in this report to maintain the integrity of the study. Results from interim data analysis were presented in a podium presentation at the 2023 Society of Urodynamics, Female pelvic medicine and Urogenital reconstruction (SUFU) annual meeting and at the 2023 American Urological Association annual meeting.

Specific Aim 2: **Improve clinician assessment of IC/BPS**

Major Task 1: Evaluate pelvic floor assessment between multiple clinicians

- 20% achieved – data analysis to compare pelvic floor assessment between pelvic floor physical therapist and urologist is ongoing.

Major Task 2: Explore methods for improving clinician assessment in military and other health care settings

- 0% achieved

Specific Aim 3: **Improve biomarker-based evaluation of IC/BPS before, during and after therapy**

Major Task 1: Collect biological sample for testing

25% achieved:

- All study personnel have completed training
- Preliminary analysis of collected samples was completed in quarter 4 of year 5 (2021). This data was reported in the annual technical report of year 5. Urine collection is ongoing.

What was accomplished under these goals?

All study start-up activities are completed. Although enrollment has been steadily increasing, our enrollment goal of 128 participants (42 patients enrolled/treated through August 2023) has not been met. A major reason for this shortfall, was due to the initial delay in enrollment due to the nationwide sodium bicarbonate shortage, which has since been resolved, and the subsequent COVID 19 pandemic. To increase enrollment, numerous and varied recruitment initiatives have been implemented and efforts are being made to restore the disruption in study activities due to the pandemic. These activities are specifically described in Section 5.

Additionally, quarterly research meetings and intradepartmental study audits are conducted to support and enhance research performance.

What opportunities for training and professional development has the project provided?

Nothing to Report.

How were the results disseminated to communities of interest?

The results from the interim analysis were presented at the SUFU 2023 and AUA 2023 annual meetings. An abstract was also accepted for a podium presentation at the ICS 2023 annual meeting.

What do you plan to do during the next reporting period to accomplish the goals?

We will continue to work towards our enrollment goal by continuing marketing and recruitment efforts. We have worked with PatientWing to modernize and simplify patient recruitment (e.g. providing opportunity for potential study candidates to schedule first screening phone call with Clinical Research coordinator on PatientWing study website). We have increased patient stipends to help cover the cost of travel. In addition, we are partnering with a second online recruitment company (HoneyBee Trials) to help boost enrollment. We will continue to raise awareness for urological conditions and clinical trial opportunities at community events. Study investigators will be available to discuss general research and study-specific questions. Finally, we continue to work with Beaumont marketing to aid in recruitment efforts. Despite the halting of research activities, we continue to receive study referrals from various sources resulting in study visits being scheduled.
We aim to perform an interim analysis of biomarker data and assess the impact of treatment on urinary biomarker levels (Aim 3). Finally, we will perform an interim evaluation of pelvic floor assessment between multiple clinicians (Aim 2).

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
Nothing to Report

What was the impact on other disciplines?
Nothing to Report

What was the impact on technology transfer?
Nothing to Report

What was the impact on society beyond science and technology?
Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
The number and availability of pelvic floor physical therapists (PFPT) at the Women's Urology and Pelvic Health Center (WUPHC) has stabilized and we have returned to having three therapists available (2 are Beaumont employees who provide PT treatments as well as conduct assessments) and the third is contracted with the study to complete assessments only (retired former Beaumont employee).

We received 367 referrals during this reporting period, of which 191 contacts were made. Of the contacts made, 81 women were prescreened. However, despite the high number of referrals **(over 1,100 women since the start of enrollment)**, the study enrollment rate remains lower than anticipated. Therefore, study staff will continue to review the reasons for non-participation, including screen failures and logistics, to determine methods to improve enrollment. Recruitment

initiatives will also continue to be reviewed by study staff and new opportunities will be explored and initiated, if deemed potentially worthwhile.

Recruitment efforts have been negatively impacted by the COVID-19 pandemic. We continue with online recruitment efforts to maintain exposure to the study. Research staff continuously explore and implement possible recruitment activities to support enrollment. Various general Urology Research and study-specific recruitment efforts have taken place over the study period. See the tables below for descriptions of each activity.

Urology Research Recruitment Activities *(includes this study)*

Activity	Description	Target Audience	Date(s)
Urology Research Banner Display	Stand-up and table-top Urology Research banners are stationed around the hospital campus. A flier describing the active studies is also available.	Community, including Royal Oak employees	Jan 2018-Present
Current Study Mailing	Each quarter, as a reminder of studies that are seeking patients, providers are e-mailed a study flier briefly describing each of the department's active studies, eligibility criteria and referral information.	Beaumont and non-Beaumont physicians and advanced level providers	Oct 2017-Present
Posting to Beaumont's public research website	Clinical trial opportunities are posted on the Beaumont's public website at https://www.beaumont.org/research/clinical-trials	Community, including employees	Sept 2016-Present
Community Education Event	Participation at the Annual Men's Health Event, held in downtown Detroit and sponsored by Michigan Institute of Urology (MIU). Discussed Urology Research opportunities with attendees as they visited the event table.	Community	Sept 21, 2019
Educational Event	Participation at the Beaumont Urology Neuromodulation Conference. Discussed Urology Research opportunities with attendees as they visited the event table.	Health care providers; local and national	Oct 4, 2019
Health Promotion and Awareness	Women's Health/Breast Care table, outside the hospital's cafeteria. Discussed Urology Research opportunities with attendees as they visited the information table.	Community, including employees	Oct 10, 2019
Educational Event	Beaumont Primary Care Symposium. Discussed Urology Research opportunities with attendees as they visited the information table.	Health care providers	Nov 1, 2019
Health Promotion and Awareness	Bladder health month table, outside the hospitals' cafeteria. Discussed Urology Research opportunities with attendees as they visited the information table.	Community, including employees	Nov 2019
Community Education Event	Senior Coffee Talk with a Beaumont Urologist, featuring Dr. Sirls. Urology Research opportunities discussed. A research nurse clinician was present to address questions.	(Beaumont) Botsford Commons, Seniors	Nov 20, 2019
Community Education Event	Bladder health presentation with a Beaumont Urologist, featuring Dr. Gilleran. Urology Research opportunities discussed. A research nurse clinician was present to address questions.	NEXT Birmingham, Seniors	Jan 16, 2020

Community Education Event	Webinar on common urologic conditions (OAB, SUI), sponsored by Beaumont Comprehensive Urology, and presented by Drs. Peters, Sirls, Gilleran and Padmanabhan.	Community	Jul 29, 2020 May 3, 2021

Study-Specific Recruitment Activities

Activity	Description	Target Audience	Date(s)
Beaumont's "In the Loop" Posting	Study description included in the daily e-news	Beaumont employees; all campuses	Sept 2019
Beaumont Health Face Book Posting	The study was featured on Face Book	Community, including IC/BPS	November 2019
Interstitial Cystitis Network (ICN) Posting	The study is posted on the ICN website at https://www.ic-network.com/beaumont-study-seeks-women-ic-bps-royal-oak-mi/	IC/BPS Community	March 2018-Present
Patient Wing; Web-based Recruitment Initiatives	Study ads are targeted at persons with IC/BPS. Potential subjects are directed to a website for study information and undergo initial screening.	On-line community	April 2018 - Present
Local Radio Ads	Study ad runs for 2 consecutive weeks on a quarterly basis.	Community	Sept 2018-2021
Clinicaltrials.gov Posting	Per Federal requirements, the study is posted and available to the community (NCT02870738)	Community	Sept 2016 - Present
Health Promotion and Awareness	Newsletter article on IC/BPS, including a description of the study.	Generations Newsletter, Local Seniors	November 2019
Targeted Mailing	Approximately 150 letters were sent to Beaumont patients prescribed Elmiron for IC/BPS. The mailing provided an overview of the study and information on participation.	Beaumont Elmiron users	February 2020
CARDS review of study flyer	Community advisors on research design and strategies (CARDS), a stakeholder engagement group at University of Wisconsin-Madison, reviewed study flyer, and we updated the flyer based on stakeholder input.	Women with IC/BPS	April – June, 2022
PatientWing review	Worked with PatientWing to review target area, renew study website, and add online scheduler.	Women with IC/BPS	July – September, 2022
HoneyBee trails	Study ads are targeted at persons with IC/BPS. Potential subjects are directed to a website for study information and undergo initial screening.	Women with IC/BPS	In development

An additional 2-year no-cost extension period was granted by the funding agency. Therefore, study activities will continue from September 1, 2023 – August 31, 2025. The study team will continue to evaluate the status of study activities and available funding, and work towards achieving the research goals.

Changes that had a significant impact on expenditures

Despite numerous and varied recruitment initiatives, enrollment continues to be slower than anticipated. COVID-19 also impacted expenditures temporarily halting recruitment, and in-

person study activities, including screening and enrollment. Therefore, cumulative expenses are less than expected, despite increased spending related to recruitment initiatives. There is a cost saving in salary, travel, patient care, subcontract, and other miscellaneous costs. We anticipate that expenditures will increase, as study enrollment increases. Budgeted funds will be needed to cover patient care costs and achieve the aims of the study.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
None

Significant changes in use or care of human subjects
There have been no changes in the use or care of human subjects. IRB continuing review and approval was obtained for an additional 12 months on JAN-20-2023.

Significant changes in use or care of vertebrate animals.
N/A

Significant changes in use of biohazards and/or select agents
N/A

6. PRODUCTS:
Publications, conference papers, and presentations

Journal publications.
Nothing to Report

Books or other non-periodical, one-time publications.
Nothing to Report

Other publications, conference papers, and presentations.
Nothing to Report

Website(s) or other Internet site(s)
Nothing to Report

Technologies or techniques
Nothing to Report

Inventions, patent applications, and/or licenses
Nothing to Report

Other Products
Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	Role	Change from Previous Year
Kenneth Peters MD	Principal Investigator	No Change
Jason Gilleran MD	Investigator	No Change
Priya Padmanabhan, MD	Investigator	No Change
Michael Chancellor MD	Investigator	No Change
Christopher Smith MD	Investigator	No Change
Bernadette Zwaans, PhD	Project Manager; Investigator	No Change
Lydia Kosovich RN, BSN	Lead Study Coordinator	No Change
Sandra McColley	Data Manager	No Change
Sarah Bartolone	Research Assistant	No longer working on this project
Elijah Ward	Research Assistant	No Change
Jennifer Giordano	Clinical Research Nurse Manager	No Change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Updated Other Support September 2022-August 2023; Key Personnel

Kenneth Peters MD – no change
Jason Gilleran MD – no change
Priya Padmanabhan – no change

Michael Chancellor, MD
New:

Title:	**The role of Amphiregulin in mediating radiation cystitis in cancer survivors (R01 DK135986)**
Role	Investigator
Effort:	5%
Supporting Agency:	National Institutes of Health - NIDDK
Performance period:	April 2023 – March 2028
Funding Amount:	(including direct costs)
Project Goals:	1. Determine the expression pattern of AREG and its importance in maintaining urothelial integrity in normal and irradiated bladder; 2. Determine the role of AREG in mediating radiation-induced fibrosis; 3. Assess AREG as a predictive biomarker for RC.
Overlap:	None

Change to existing:

Title:	**Michigan Interdisciplinary Center for Urology Research and Education (MI-CURE) (1P20 DK127554-01)**
Role	Co-PI
Effort:	5%
Supporting Agency:	National Institutes of Health - NIDDK
Performance period:	August 2021 – July 2024 (currently in NCE)
Funding Amount:	(including indirect costs)
Project Goals:	To understand the effect of changes in mechanical characteristics of urinary bladder tissue, due to fibrosis, on the development of bladder dysfunction.
Overlap:	None

Title:	**Deployable Interstitial Cystitis Urine Diagnostic Technology Development (W81XWH1910288)**
Role	PI
Effort:	15%
Supporting Agency:	Department of Defense
Performance period:	July 15, 2019 – July 14, 2024 (currently in NCE)
Funding Amount:	(including indirect costs)
Project Goals:	The primary goal of this grant is to develop a clinically relevant and validated tool to classify interstitial cystitis patients. This is not a clinical trial.
Overlap:	None

Bernadette Zwaans, PhD

New:

Title:	**The role of Amphiregulin in mediating radiation cystitis in cancer survivors (R01 DK135986)**
Role	PI
Effort:	30%
Supporting Agency:	National Institutes of Health - NIDDK
Performance period:	April 2023 – March 2028
Funding Amount:	(including direct costs)
Project Goals:	1. Determine the expression pattern of AREG and its importance in maintaining urothelial integrity in normal and irradiated bladder; 2. Determine the role of AREG in mediating radiation-induced fibrosis; 3. Assess AREG as a predictive biomarker for RC.
Overlap:	None

Change to existing:

Title:	**Michigan Interdisciplinary Center for Urology Research and Education (MI-CURE) (1P20 DK127554-01)**

Role	Co-PI
Effort:	10%
Supporting Agency:	National Institutes of Health - NIDDK
Performance period:	August 2021 – July 2024 (currently in NCE)
Funding Amount:	(including indirect costs)
Project Goals:	To understand the effect of changes in mechanical characteristics of urinary bladder tissue, due to fibrosis, on the development of bladder dysfunction.
Overlap:	None

Title:	**Deployable Interstitial Cystitis Urine Diagnostic Technology Development (W81XWH1910288)**
Role	PI
Effort:	35%
Supporting Agency:	Department of Defense
Performance period:	July 15, 2019 – July 14, 2023
Funding Amount:	(including indirect costs)
Project Goals:	The primary goal of this grant is to develop a clinically relevant and validated tool to classify interstitial cystitis patients. This is not a clinical trial.
Overlap:	None

Mireya Diaz, PhD: No Changes

What other organizations were involved as partners?
Nothing to report

8. SPECIAL REPORTING REQUIREMENT COLLABORATIVE AWARDS:
Not Applicable

QUAD CHARTS:
Not Applicable

9. APPENDICES:
None