AWARD NUMBER: W81XWH-16-1-0307

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

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REPORT DATE: September 2020

TYPE OF REPORT: Annual Progress Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
SEPTEMBER 2020	Annual	1 Sept 2019-31 Aug 2020

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER
W81XWH-16-1-0307

5b. GRANT NUMBER
PR151889

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited

13. SUPPLEMENTARY NOTES

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. Identification of enrollment barriers and possible resolutions are ongoing. 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

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	10	**19b. TELEPHONE NUMBER** *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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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 4, Actual: Forty-six (46) women consented to study participation. Twenty-two (22) patients were enrolled, randomized and treated; 1 patient was enrolled, randomized and withdrew prior to treatment; and 23 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, seventeen (17) patients have completed all treatment visits; 11 and are in active follow-up, 4 patients withdrew from the study, and 5 patients were lost to follow-up. One subject completed all study activities and exited the study.
- In mid-March of Year 4 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 when research activities commenced.

Major Task 3: Data analysis

- 0% achieved

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

Major Task 1: Evaluate pelvic floor assessment between multiple clinicians

- 0% achieved

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

Milestones achieved:

- All study personnel have completed training
- Preliminary analysis of samples completed. No significant findings with the small number of samples collected thus far. Will repeat analyses later in the study period.

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 (21 patients enrolled/treated through August 2020) 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. To increase enrollment, numerous and varied recruitment initiatives were implemented during this reporting period. 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?

Nothing to Report.

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 re-initiating marketing and recruitment efforts that were temporarily discontinued due to COVID-19. For example, in Fall 2020, Urology Research will participate in an on-line community event to increase the awareness of clinical trial opportunities, including participation in this study. Study investigators will be available to discuss general research and study-specific questions. Despite the halting of research activities, we continued to receive study referrals from various sources throughout the Spring and early Summer. Now that screening activities are resumed; study visits are being scheduled.

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 steadily decreased over the course of the study period. At the start of the study three therapists were actively involved in the study. Currently there is one available therapist.

PFPT services are an integral component of the study. Therapists perform pelvic floor assessments and provide PFPT to study participants randomized to this treatment arm. We are currently exploring options to rectify this situation, including establishing an independent contractor agreement with one of the therapists that chose to retire while services were placed on hold due to COVID-19.

Although approximately 145 potential study participants were contacted and pre-screened in Year 4 **(over 550 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 significantly increased in to boost study enrollment. Research staff continuously explore and implement possible recruitment activities to support enrollment. Various general Urology Research and study-specific recruitment efforts occurred in Year 4. 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

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-Present

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
Local Radio Ads	Study ad run on Pandora to a local audience.	Women with IC/BPS	March 9-20, 2020

An additional no-cost extension period was requested and granted by the funding agency. Therefore, study activities will continue from September 1, 2020 – August 30, 2020. 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 17-Apr-2020.

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
Larry Sirls MD	Investigator	No Change
Jason Gilleran MD	Investigator	No Change
Michael Chancellor MD	Investigator	No Change
Laura Lamb PhD	Investigator	No Change
Christopher Smith MD	Investigator	No Change
Deborah Hasenau RN, MS	Project Manager	Study time and effort decreased from mid-March through July 2020 due to COVID-19.
Lydia Kosovich RN, BSN	Lead Study Coordinator	
Sandra McColley	Data Manager	
Elijah Ward	Research Assistant	
Teresa McCartney	Clinical Research Nurse	

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 August 2019-September 2020; Key Personnel

Kenneth Peters MD, Larry Sirls MD and Jason Gilleran MD

New:

Title:	**An Exploratory Phase 2a Study Evaluating the Efficacy and Safety of URO-902 in Subjects with Overactive Bladder and Urge Urinary Incontinence**
Effort:	N/A part of dedicated research time; Role: PI
Supporting Agency:	Urovant Sciences GmH. (commercial sponsor)
Grants Officer:	N/A
Performance period:	June 2020 – June 2022

Funding Amount:	$155,186.40
Project Goals:	Evaluate the efficacy, safety, and tolerability of a single dose of URO-902.
Specific Aims:	Evaluate the safety and efficacy of URO-902 compared to placebo with OAB and UUI up to 48 weeks post dose.
Overlap:	None

Title:	**A Phase 3 Double-Blind, Randomized, Placebo Controlled, Multi-Center Study to Evaluate the Efficacy, Safety and Tolerability of Vibegron in Men with Overactive Bladder (OAB) Symptoms on Pharmacological Therapy for Benign Prostatic Hyperplasia (BPH)**
Effort:	N/A part of dedicated research time; Role: PI
Supporting Agency:	Urovant Sciences GmbH. (commercial sponsor)
Grants Officer:	N/A
Performance period:	December 2019 – December 2021
Funding Amount:	$193,622.68
Project Goals:	Assess the efficacy, safety, and tolerability of vibegron vs. placebo in men.
Specific Aims:	Evaluate the safety and efficacy of vibergon vs. placebo in men with OAB and BPH.
Overlap:	None

Closed: *None*

Michael Chancellor MD
Laura Lamb PhD
Christopher Smith MD
No changes

Mireya Diaz, PhD: No Changes

What other organizations were involved as partners?

Baylor College of Medicine
Houston, Texas
Contribution: Dr. Smith continues to actively participate in quarterly teleconferences along with other key study personnel. He assists in protocol review and the contributes to the development of the patient recruitment plan. Dr. Smith also helps to design strategies to troubleshoot anticipated and unanticipated issues as the study progresses. Finally, he remains engaged with military and Veteran's Affair communities in anticipation of eventual transition of study findings to their IC/BPS patient populations.

8. SPECIAL REPORTING REQUIREMENT COLLABORATIVE AWARDS:
Not Applicable

QUAD CHARTS:
Not Applicable

9. APPENDICES:
None