AWARD NUMBER: W81XWH-16-1-0307

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

PRINCIPAL INVESTIGATOR: Kenneth M. Peters MD

RECIPIENT: WILLIAM BEAUMONT HOSPITAL INC
ROYAL OAK MI 48073-6712

REPORT DATE: September 2017

TYPE OF REPORT: Annual

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

DISTRIBUTION STATEMENT: Approved for public release; distribution is unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
September 2017	Annual	1 Sep 2016 - 31 Aug 2017

4. TITLE AND SUBTITLE

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

5a. CONTRACT NUMBER

5b. GRANT NUMBER W81XWH-16-1-0307

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Kenneth M. Peters

Kenneth.Peters@beaumont.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

WILLIAM BEAUMONT HOSPITAL INC
3601 W 13 MILE RD, ROYAL OAK MI
48073- 6212

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 actually 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. During Year 1, we finalized the study protocol, trained all investigators, built and tested the research database, obtained IRB and HRPO approval, and enrolled our first subject. However, enrollment during Year 1 was hampered by a national shortage of one of the medications that are used for bladder instillations (bladder focused therapy), thus we have only randomized 1 of 128 total women (64 in each treatment arm). Although the supply of medication is still not widely available, we have obtained a limited supply and as of August, 2017, have resumed study recruitment and enrollment.

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
U	U	**U**	UU	13	**19b. TELEPHONE NUMBER** *(include area code)*

TABLE OF CONTENTS

		Page No.
1.	Introduction……..	3
2.	Keywords……..	3
3.	Accomplishments……..	3
4.	Impact…….....	4
5.	Changes/Problems……	5
6.	Products…….....	6
7.	Participants & Other Collaborating Organizations…….	7
8.	Special Reporting Requirements…….....	12
9.	Appendices…….....	12

1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

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. 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. 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:** Provide a brief list of keywords (limit to 20 words).

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

Milestones to be achieved by 12 months:

- Study Start up (Final Protocol, Local IRB and HRPO approval, Research staff trained; all completed by 15-Mar-2017)

Major Task 2: Participant Recruitment, Therapy, Participant Evaluation

Milestones to be achieved by 12 months:

- First participant consented, screened and enrolled 28-April-2017
- Sixteen (16) participants consented, screened and enrolled: 1 patient enrolled and treated; currently in follow up (6% achieved)
- First enrolled participant completes primary assessment (completed 6-July-2017)
- First enrolled participant completes secondary assessment (completed 30-Aug-2017)

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

Milestone achieved:

- All study personnel have completed training 15-Mar-2017

We have completed all study start up activities. We have not been able to meet our enrollment goal of 16 participants (one patient enrolled/treated to date) because of a nationwide sodium bicarbonate shortage that has been in effect since May 2017 (needed to treat women randomized to bladder instillations). Even though we were not able to enroll, we continued recruitment and screening activities. As of 23-Aug-2017, bicarbonate became available through a compounding pharmacy and we have consented one more participant. In summary, during the first year, we conducted the following activities: monthly meetings; finalized the study protocol; obtained IRB and HRPO approval; completed an in-person training for study personnel; built, tested and launched the study database; screened several patients, enrolled/treated one and have consented another participant. We have also created a recruitment flier, disseminated study information to potential referral sources, and identified a list of other recruitment activities to support enrollment now that we are able to obtain bicarbonate through a compounding pharmacy.

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 recently identified a compounding pharmacy that can supply bicarbonate until the shortage is resolved (end of 2017). Thus, we have consented our second participant and are accelerating our marketing and recruitment efforts to achieve enrollment goals.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

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:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

.

During the third quarter of Year 1, we enrolled/randomized one patient but further enrollment was limited by the national shortage of sodium bicarbonate, which is needed for study treatment. The shortage was first expected to end in June, 2017, but may not be resolved until the end of 2017. As of 23-Aug-2017, the drug has become available through a compounding pharmacy and we have consented one new participant. Recruitment efforts have increased, and telephone screening has continued.
https://www.usatoday.com/story/money/2017/05/31/how-baking-soda-shortage-became-health-care-crisis/102320494/
https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Sodium%20Bi

Changes that had a significant impact on expenditures

As stated above, enrollment was limited by the national shortage of bicarbonate, so cumulative expenses are less than expected. There is a cost saving in salary, travel, patient care, subcontract and other misc. costs. As bicarbonate has just become available, we anticipate that expenditures will increase since budgeted funds will then 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

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 6-July-2017.

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: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  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: Kenneth Peters, MD
Project Role: Principal Investigator
ORCID ID: 0000-0002-1430-1168
Nearest person month worked: 1 person month
Contribution to Project: provided leadership in all aspects of clinical trial, including administrative and scientific oversight, leading the study team, and patient referral and recruitment
Funding Support: N/A

Name: Larry Sirls, MD
Project Role: Investigator
ORCID ID: 0000-0003-0138-3026
Nearest person month worked: 1 person month
Contribution to Project: provided input into protocol review/evaluation, study recruitment, patient referrals, study logistics
Funding Support: N/A

Name: Kim Killinger RN, MSN
Project Role: Project Manager
ORCID ID: 0000-0001-9228-8758
Nearest person month worked: 2 person months
Contribution to Project: Coordinated team meetings, communications between team members, guided database development, completed required reports
Funding Support: N/A

Name: Lydia Kosovich RN, BSN
Project Role: Lead study coordinator
ORCID ID: None
Nearest person month worked: 5 person months
Contribution to Project: subject recruitment, screening, consenting/enrollment, study visits/treatments; trained additional study coordinators; provided input into data base development; lead recruitment efforts
Funding Support: N/A

Name: Sandra McColley
Project Role: Data Manager
ORCID ID: None
Nearest person month worked: 3 person months
Contribution to Project: built and tested study database in RedCAP; input study data; run reports
Funding Support: N/A

Kenneth M. Peters

Closed:

Title:	A Multicenter, Randomized, Double-blind, Placebo-controlled Study, Evaluating Safety and Efficacy of LiRIS® 400 mg in Females With Interstitial Cystitis/Bladder Pain Syndrome
Effort:	N/A part of dedicated research time; Role: PI
Supporting Agency:	Allergan (commercial sponsor)
Grants Officer:	N/A
Performance period:	9/1/2015-3/31/2018
Funding Amount:	$69,760
Project Goals:	To evaluate the safety and efficacy of the lidocaine releasing LiRIS device inserted into the bladder compared to placebo in women with IC/BPS without Hunner's Lesions. Safety is evaluated by the number/type of adverse events. The average daily bladder pain score patients experience over the previous 24-hour period as measured on a scale of 0 to 10 will assess efficacy.
Overlap:	This project recruits from a similar patient population but there is no scientific, financial, or level of effort overlap.

Title:	Optimizing Sacral Neuromodulation Reprogramming with EMG
Effort:	N/A part of dedicated research time; Role: PI
Supporting Agency:	SUFU (Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction)
Grants Officer:	N/A
Performance period:	February 2014-July 2016
Funding Amount:	$25,000
Project Goals:	To evaluate the effectiveness of Interstim reprogramming with electromyography (EMG) vs. reprogramming based on sensory response alone.
Overlap:	None

New:

Title:	A prospective, multi-center, open-label study of trospium delivered intravesically by TAR-302-5018 to subjects with idiopathic overactive bladder (iOAB) and urinary incontinence.
Effort:	N/A part of dedicated research time; Role: sub investigator
Supporting Agency:	Taris Biomedical LLC (commercial sponsor)
Grants Officer:	N/A
Performance period:	May 2017-December 2018
Funding Amount:	$23,046.95
Project Goals:	Evaluate the safety and tolerability of 1 dosing cycle of trospium-releasing intravesical system TAR-302-5018 for up to 42 days

Overlap:	None.

Title:	The LEADERSHIP 301 Trial: A 12-Week, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Phase 3 Trial to Evaluate the Efficacy and Safety of 2 Doses of AQX-1125 Targeting the SHIP1 Pathway in Subjects with Interstitial Cystitis/Bladder Pain Syndrome Followed by an Extension Period
Effort:	N/A part of dedicated research time; Role: PI
Supporting Agency:	Aquinox Pharmaceuticals (commercial sponsor)
Grants Officer:	N/A
Performance period:	8/1/2016 to 8/1/2018
Funding Amount:	$16,236.35
Project Goals:	The primary objective of this study is to evaluate the effect of 12 weeks of treatment with 2 different doses of oral AQX-1125 (100 mg or 200 mg) administered once daily compared to placebo on the change in maximum daily bladder pain in subjects with interstitial cystitis/bladder pain syndrome (IC/BPS)
Overlap:	This project recruits from a similar patient population but there is no scientific, financial, or level of effort overlap.

Title:	Multi-center, Prospective, Randomized, Controlled Clinical Trial Study of Chronic Afferent Nerve Stimulation (CAN-Stim) to demonstrate Non-Inferiority in the treatment of Urinary Urgency Incontinence resulting from Refractory Overactive Bladder (OAB) with Wireless Neuromodulation Technology as compared to Percutaneous Tibial Nerve Stimulation (PTNS) - "PROTECT" Study
Effort:	N/A part of dedicated research time; Role: coinvestigator
Supporting Agency:	StimGuard LLC (commercial sponsor)
Grants Officer:	N/A
Performance period:	June 2016-June 2018 (tentative)
Funding Amount:	$273,250.00
Project Goals:	The purpose of this pivotal study is to illustrate the safety and effectiveness of the StimGuard Sacral Nerve Stimulation (SNS) System in the treatment of refractory urgency incontinence.
Overlap:	None

Larry Sirls MD

Closed:

Title:	A Prospective, Safety and Efficacy Cohort Study of Elevate® Anterior and Apical Prolapse Repair System Compared to Native Tissue Repair for Pelvic Organ Prolapse Repair
Effort:	N/A; part of dedicated research time; Role: PI

Supporting Agency:	American Medical Systems (AMS) now Aphrodite (commercial)
Grants Officer:	N/A
Performance period:	5/7/14-4/28/2016
Funding Amount:	$58,000
Project Goals:	This is a prospective, multi-center, post-market cohort study designed to evaluate the long-term efficacy and safety of the Elevate® Anterior and Apical Prolapse Repair System compared to Native Tissue Repair in the treatment of anterior or anterior/apical vaginal prolapse in females at least 18 years of age
Overlap:	None

New:

Title:	Multi-center, Prospective, Randomized, Controlled Clinical Trial Study of Chronic Afferent Nerve Stimulation (CAN-Stim) to demonstrate Non-Inferiority in the treatment of Urinary Urgency Incontinence resulting from Refractory Overactive Bladder (OAB) with Wireless Neuromodulation Technology as compared to Percutaneous Tibial Nerve Stimulation (PTNS) - "PROTECT" Study
Effort:	N/A part of dedicated research time; Role: PI
Supporting Agency:	StimGuard LLC (commercial sponsor)
Grants Officer:	N/A
Performance period:	June 2016-June 2018 (tentative)
Funding Amount:	$273,250.00
Project Goals:	The purpose of this pivotal study is to illustrate the safety and effectiveness of the StimGuard Sacral Nerve Stimulation (SNS) System in the treatment of refractory urgency incontinence.
Overlap:	None

Title:	A prospective, multi-center, open-label study of trospium delivered intravesically by TAR-302-5018 to subjects with idiopathic overactive bladder (iOAB) and urinary incontinence.
Effort:	N/A part of dedicated research time; Role: sub investigator
Supporting Agency:	Taris Biomedical LLC (commercial sponsor)
Grants Officer:	N/A
Performance period:	May 2017-December 2018
Funding Amount:	$23,046.95
Project Goals:	Evaluate the safety and tolerability of 1 dosing cycle of trospium-releasing intravesical system TAR-302-5018 for up to 42 days
Overlap:	None

Title:	The LEADERSHIP 301 Trial: A 12-Week, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-

	Group, Phase 3 Trial to Evaluate the Efficacy and Safety of 2 Doses of AQX-1125 Targeting the SHIP1 Pathway in Subjects with Interstitial Cystitis/Bladder Pain Syndrome Followed by an Extension Period
Effort:	N/A part of dedicated research time; Role: subinvestigator
Supporting Agency:	Aquinox Pharmaceuticals (commercial sponsor)
Grants Officer:	N/A
Performance period:	8/1/2016 to 8/1/2018
Funding Amount:	$16,236.35
Project Goals:	The primary objective of this study is to evaluate the effect of 12 weeks of treatment with 2 different doses of oral AQX-1125 (100 mg or 200 mg) administered once daily compared to placebo on the change in maximum daily bladder pain in subjects with interstitial cystitis/bladder pain syndrome (IC/BPS)
Overlap:	This project recruits from a similar patient population but there is no scientific, financial, or level of effort overlap.

Michael Chancellor, MD

Closed:

Title:	Urinary Biomarkers for Objective Measurement of InterStim Response in OAB Patient
Effort:	0.01 Calendar Months (1%); Role: PI
Supporting Agency:	Medtronic, Inc (commercial)
Grants Officer:	N/A
Performance period:	9/1/2012-12/31/2016
Funding Amount:	$100,000
Project Goals:	To identify urinary biomarkers in patients with overactive bladder before and after InterStim and determine if inflammatory chemokines or growth factors can be used to objectively measure InterStim efficacy in patients with overactive bladder
Overlap:	None

New:

Title: A Double-Blind, Randomized Study of Safety and Efficacy of OnabotulinumtoxinA	Analysis Of Urine Specimens From A Double-Blind, Randomized Study Of The Safety And Efficacy Of Onabotulinumtoxin A (Onabont-T) Versus Oral Oxybutynin In Spinal Cord Injured Patients With Neurogenic Detrusor Overactivity
Effort:	1 Calendar Months (5%); Role: PI
Supporting Agency:	Baylor College of Medicine/DOD

Grants Officer:	N/A
Performance period:	4/26/2016-9/29/2017 (tentative)
Funding Amount:	$83,698
Project Goals:	The main purpose of this proposal that incorporates novel urine biomarker testing into existing clinical methodologies is to: 1) evaluate the efficacy of 200 U BoNT-A injected into the detrusor versus oral oxybutynin for the treatment of urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) in spinal cord injured patients and 2) to determine the potential role of urine biomarkers in guiding the process of patient selection and
Overlap:	None

Christopher Smith, MD: no changes
Mireya Diaz PhD: no changes
Laura Lamb PhD: no changes

What other organizations were involved as partners?

Baylor College of Medicine
Houston, Texas
Contribution: During the past year, Dr. Smith actively participated in monthly teleconferences along with other key study personnel. He assisted in protocol design and implementation to allow for patient recruitment to begin. Dr. Smith also helped to design strategies to troubleshoot anticipated and unanticipated issues as the study became active. Finally, he remained engaged with military and Veteran's Affair communities in anticipation of eventual transition of study findings to their IC patient populations.

8. SPECIAL REPORTING REQUIREMENT

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

None