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

PRINCIPAL INVESTIGATOR: Kenneth M. Peters MD

CONTRACTING ORGANIZATION: WILLIAM BEAUMONT HOSPITAL RESEARCH INSTITUTE Royal Oak, MI 48073-6712

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

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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. During Year 3, our primary focus was 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 have been expanded to increase enrollment. 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

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TABLE OF CONTENTS

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 3, Actual: Thirty-six (36) women consented to study participation: 18 patients were enrolled, randomized and treated; 1 patient was enrolled, randomized and withdrew prior to treatment; and 17 patients consented and failed screening
- To date, fourteen (14) patients have completed all treatment visits; 12 and are in active follow-up, 1 patient withdrew from the study after the 1st follow-up visit was completed, and 1 patient was lost to follow-up after completing all the treatment visits.

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 (18 patients enrolled/treated through August 2019) 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 expand our marketing and recruitment efforts to achieve enrollment goals. For example, in Fall 2019, Urology Research will participate in several community events to increase the awareness of clinical trial opportunities, including participation in this study. Study materials will be provided to attendees and research staff will be available to discuss general research and study-specific questions.

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

Although approximately 208 potential study participants were contacted and pre-screened in Year 3, 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 Year 3 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 3. See the tables below for descriptions of each activity.

Urology Research Recruitment Activities *(includes this study)*

Activity	Description	Target Audience	Date(s)
Study Display	Urology Research presented study information at a Beaumont sponsored community event on Pain Management. Dr. Peters was a featured presenter	Community	April 30, 2019
Study Display	For Bladder Health Awareness month, Urology Research staff presented study information outside of the main cafeteria	Community, including Royal Oak employees	Nov 1, 2018
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

Study-Specific Recruitment Activities

Activity	Description	Target Audience	Date(s)
Educational Event	One hundred fifty five (155) local urology and/or gynecology providers were invited to attend a dinner and presentation on IC/BPS presented by Dr. Peters. The study was described and reference materials were provided to participants.	Advanced level providers; nurse practitioners, physician assistants	Jan 17, 2019

Patient Mailing	A letter from Dr. Peters and study brochure were sent to approximately 500 patients identified from Beaumont's electronic medical record	Beaumont IC/BPS patients	Oct 18, 2018
Beaumont Huddle Posting	Care teams "huddle" (meet) daily to discuss important news of the day. The study description was included in the items to share.	Beaumont employees; Troy and Royal Oak campuses	Sept 17, 2018
Beaumont's "In the Loop" Posting	Study description included in the daily e-news	Beaumont employees; all campuses	Sept 17, 2018
Beaumont Health Intranet Posting	The study was featured on the website's homepage	Beaumont employees; all campuses	Sept 17, 2018
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

Additionally, two protocol changes related to the eligibility criteria were implemented which may positively impact enrollment, while maintaining the scientific integrity of the study.

1. Previously, patients undergoing a prior pelvic floor physical therapy (PFPT) and/or bladder instillations within 12 months of screening were excluded or deferred. The required washout period was changed to 3 months.
2. Originally, the inclusion criteria included a history of clinical diagnosis of IC/BPS via patient self-report. This criterion was changed to read "a history of patient self-reported IC/BPS symptoms (urgency, frequency, pain) for at least 6 months". The rationale for this change is that we may reach more undiagnosed patients. These undiagnosed patients may be referred to a physician for evaluation and IC/BPS confirmation prior to study enrollment.

Changes that had a significant impact on expenditures

As stated previously, enrollment was initially limited by the national shortage of bicarbonate. Subsequently, the rate of enrollment has been slower than anticipated. 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 31-May-2018.

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
Jamie Bartley DO	Investigator	Left institution October 2018, removed from study personnel
Michael Chancellor MD	Investigator	No Change

Name	Role	Change from Previous Year
Laura Lamb PhD	Investigator	No Change
Christopher Smith MD	Investigator	No Change
Deborah Hasenau RN, MS	Project Manager	No Change
Lydia Kosovich RN, BSN	Lead Study Coordinator	No Change
Sandra McColley	Data 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 August 2018-September 2019; Key Personnel

Kenneth Peters MD

New:

Title:	Deployable Interstitial Cystitis Urine Diagnostic Technology Development
Effort:	N/A part of dedicated research time; Role: Investigator
Supporting Agency:	Department of Defense
Grants Officer:	Kathryn J. Argue Ph.D 1077 Patchel Street, Building 1054, Fort Detrick, MD 21701-5024
Performance period:	7/15/2019-7/14/2022
Funding Amount:	$3,860,821
Project Goals:	The *objective* of this grant is to develop a new diagnostic tool, the Interstitial Cystitis Risk Score (IC-RS), to identify and classify IC patients. The IC-RS is a machine learning classifier that will predict whether a patient has (or does not have) IC based on measured urinary cytokine levels and symptom scores already tested in a pilot study using clinically collected samples. If a patient has IC, it will also predict whether a patient has Hunner's lesions.
Specific Aims:	**Aim 1.** Refine and evaluate IC-RS in a large, crowdsourced collection of urine samples from IC patients and normal controls. **Aim 1b.** Refine and evaluate IC-RS in urine samples from men and women with IC and from normal controls within the military. **Aim 2.** Compare patient collected IC-RS from similar collected urine samples and demographic from three academic urology practices that will test civilian and military patients with and without IC and cohorts of patients with UTI, bladder cancer, and overactive bladder with incontinence to assess specificity of the IC-RS. **Aim 3.** Urine kit optimization. **Aim 3b**: Advance the technology to perform IC-RS in a small table-top system that can be run in any basic clinical laboratories regardless of location and without specialized expertise.
Overlap:	This project recruits from a similar patient population but there is no scientific, financial, or level of effort overlap.

Title:	CELLEBRATE: An Adaptive, Two-Stage, Double-Blind, Stratified, Randomized, Controlled Trial Comparing the Safety and Efficacy of AMDC-USR with Placebo in Female Subjects with Stress Urinary Incontinence (SUI)
Effort:	N/A part of dedicated research time; Role: Investigator
Supporting Agency:	Cook Myosite, Inc. (Commercial Sponsor)
Grants Officer:	N/A
Performance period:	March 2019 – March 2022
Funding Amount:	$ 273,945
Project Goals:	To evaluate the safety and efficacy of AMDC-USR

Specific Aims:	1. To evaluate the efficacy of a single dose of 150 x 106 AMDC-USR in the reduction of stress incontinence episode frequency (IEF) in adult female subjects at 12 months post-treatment. 2. To evaluate improvement in incontinence quality of life (I-QOL) and the extent of reduction of stress IEF after a single dose of 150 x 106 AMDC-USR in adult female subjects at 12 months. 3. To determine the safety of a single dose of 150 x 106 AMDC-USR in the treatment of SUI in adult female subjects at 12 months and 2 years post-treatment.
Overlap:	None

Closed:

Title:	Double-Blind, Placebo-Controlled, Parallel Design, Phase 2 Study to Assess Clinical Activity and Safety of Enobosarm (GTx-024) in Postmenopausal Women with Stress Urinary Incontinence
Effort:	N/A part of dedicated research time; Role: Principal Investigator
Supporting Agency:	GTx, Inc. (commercial sponsor)
Grants Officer:	N/A
Performance period:	September 2017 – October 2018
Funding Amount:	$98,504
Project Goals:	To evaluate the efficacy and safety of GTx-024 (1 mg and 3 mg) compared to placebo in the treatment of postmenopausal women with stress urinary incontinence
Specific Aims:	To evaluate the safety and efficacy of GTx-024
Overlap:	None

Larry Sirls MD

New:

Title:	CELLEBRATE: An Adaptive, Two-Stage, Double-Blind, Stratified, Randomized, Controlled Trial Comparing the Safety and Efficacy of AMDC-USR with Placebo in Female Subjects with Stress Urinary Incontinence (SUI)
Effort:	N/A part of dedicated research time; Role: Principal Investigator
Supporting Agency:	Cook Myosite, Inc. (Commercial Sponsor)
Grants Officer:	N/A
Performance period:	March 2019 – March 2022
Funding Amount:	$ 273,945
Project Goals:	To evaluate the safety and efficacy of AMDC-USR
Specific Aims:	1. To evaluate the efficacy of a single dose of 150 x 106 AMDC-USR in the reduction of stress incontinence episode frequency (IEF) in adult female subjects at 12 months post-treatment. 2. To evaluate improvement in incontinence quality of life (I-QOL) and the extent of reduction of stress IEF after a single dose of 150 x 106 AMDC-USR in adult female subjects at 12 months. 3. To determine the safety of a single dose of 150 x 106 AMDC-USR in the treatment of SUI in adult female subjects at 12 months and 2 years post-treatment.
Overlap:	None

Closed:

Title:	Double-Blind, Placebo-Controlled, Parallel Design, Phase 2 Study to Assess Clinical Activity and Safety of Enobosarm (GTx-024) in Postmenopausal Women with Stress Urinary Incontinence
Effort:	N/A part of dedicated research time; Role: Co-Investigator
Supporting Agency:	GTx, Inc. (commercial sponsor)
Grants Officer:	N/A

Performance period:	September 2017 – October 2018
Funding Amount:	$98,504
Project Goals:	To evaluate the efficacy and safety of GTx-024 (1 mg and 3 mg) compared to placebo in the treatment of postmenopausal women with stress urinary incontinence
Specific Aims:	To evaluate the safety and efficacy of GTx-024
Overlap:	None

Michael Chancellor MD
Laura Lamb PhD
Christopher Smith MD

New: *No additional changes*

Title:	Deployable Interstitial Cystitis Urine Diagnostic Technology Development
Effort:	Michael Chancellor MD, Role: Investigator (15%) Laura Lamb PhD, Role: Principal Investigator (50%) Christopher Smith MD, Role: Investigator (10%)
Supporting Agency:	Department of Defense
Grants Officer:	Kathyrn J Argue PhD 1077 Patchel Street, Building.1054, Fort Detrick, MD 21701-5024
Performance period:	7/15/2019-9/29/2022
Funding Amount:	$3,860,821
Project Goals:	The *objective* of this grant is to develop a new diagnostic tool, the Interstitial Cystitis Risk Score (IC-RS), to identify and classify IC patients. The IC-RS is a machine learning classifier that will predict whether a patient has (or does not have) IC based on measured urinary cytokine levels and symptom scores already tested in a pilot study using clinically collected samples. If a patient has IC, it will also predict whether a patient has Hunner's lesions.
Specific Aims:	**Aim 1.** Refine and evaluate IC-RS in a large, crowdsourced collection of urine samples from IC patients and normal controls. **Aim 1b.** Refine and evaluate IC-RS in urine samples from men and women with IC and from normal controls within the military. **Aim 2.** Compare patient collected IC-RS from similar collected urine samples and demographic from three academic urology practices that will test civilian and military patients with and without IC and cohorts of patients with UTI, bladder cancer, and overactive bladder with incontinence to assess specificity of the IC-RS. **Aim 3.** Urine kit optimization. **Aim 3b:** Advance the technology to perform IC-RS in a small table-top system that can be run in any basic clinical laboratories regardless of location and without specialized expertise.
Overlap:	This project recruits from a similar patient population but there is no scientific, financial, or level of effort overlap.

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