Administrative information

Project Title: Randomized controlled trial comparing two different bladder instillation treatments for interstitial cystitis/bladder pain syndrome. (January 23, 2019)

Trial registration: ClinicalTrials.gov – NCT03463915

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Funding: None

Roles and responsibilities:

Principal Investigator: Dr. Kate Meriwether (Assistant Professor)
Department of Obstetrics, Gynecology & Women's Health
Division of Female Pelvic Medicine and Reconstructive Surgery
550 South Jackson Street
Louisville, KY 40202

Co-Investigators: Dr. Olivia Cardenas-Trowers (Fellow)
Dr. Sean Francis (Associate Professor)

Dr. James Ryan Stewart (Fellow)
Dr. Ankita Gupta (Fellow)

Department of Obstetrics, Gynecology & Women's Health
Division of Female Pelvic Medicine and Reconstructive Surgery
550 South Jackson Street
Louisville, KY 40202

Study Sites: Springs Reproductive Endocrinology and Female Pelvic Medicine Clinic
University Health Care Outpatient Center (HCOC)

Sub-investigators: None

Regulatory Coordinator: Heather Lange, APRN
University of Louisville, Division of FPMRS
Springs Clinic, 6420 Dutchman's Parkway, Suite 190

Research Protocol

Protocol Date: January 23, 2019

Introduction

Protocol Summary/Purpose:

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic pain disorder involving the genitourinary tract. IC/BPS disproportionately affects women with over 80% of patients with IC/BPS as female.[1] Like other chronic pain conditions, IC/BPS is physically and emotionally taxing on patients. IC/BPS costs the United States over $100 million annually due to direct healthcare costs and loss of worker productivity.[2] The exact pathophysiology of the disease is unknown, leading to a limitation in our ability to treat the disorder effectively. The current leading etiologic theory is that IC/BPS is a neurologically-derived chronic systemic pain syndrome due to its association with musculoskeletal pelvic pain, irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, and vulvodynia.[3-6] Although several options exist to treat IC/BPS, therapeutic effects are often transient.[7,8] Previous studies in chronic pain disorders have shown that multimodal treatment is more effective than single-agent treatment,[9,10] so future therapy should aim to augment rather than replace current treatments. Bladder instillation is a commonly used treatment in which a mixture of different agents are instilled into the bladder to improve IC/BPS symptoms. The data on the efficacy of bladder instillations as well as which ingredients in the mixture are effective is limited.[11,12] Small studies have shown the potential of steroids in decreasing IC/BPS; the mechanism of action is hypothesized to be due to decrease inflammation in the bladders of these patients.[13,14] The **knowledge gap** that exists is the necessity of a steroid in the bladder instillation treatment for IC/BPS symptoms especially since this tends to be the most expensive ingredient.

To evaluate the utility of a steroid in the bladder instillation treatment of IC/BPS, we propose a randomized, double blind, controlled trial that will compare the efficacy of bladder instillations with and without triamcinolone acetonide (Kenalog) on IC/BPS symptoms in women. We **hypothesize** that the addition of Kenalog in bladder instillation therapy will result in a more robust treatment response than bladder instillations without Kenalog. Our **rationale** is based on 1) the results of small studies that showed improvement of IC/BPS symptoms with use of a steroid and 2) the hypothesized mechanism of action of steroids decreasing inflammation in the bladder.

Objectives:

Primary objective:

1. To determine if IC/BPS patients will have a greater treatment response to bladder instillations with Kenalog plus oral than to bladder instillations without Kenalog.

Secondary objectives:

1. Cost-analysis of bladder instillations with versus without Kenalog.
2. Evaluate how a history of previous IC/BPS treatment or lack thereof correlates with treatment response.

3. Examine how patient-reported diagnoses of certain conditions (e.g., irritable bowel syndrome, fibromyalgia, chronic pain, chronic pelvic pain, vulvodynia, anxiety, depression, chronic fatigue syndrome) correlate with treatment response.
4. Determine treatment response of subgroups of patients with and without prominent overactive bladder (OAB) symptoms.

Hypothesis:
We hypothesize that patients with IC/BPS will have greater improvement in their general symptoms when treated with bladder instillations with Kenalog than IC/BPS patients treated with bladder instillations without Kenalog.

Introduction and Background:
IC/BPS is not isolated to the genitourinary tract, but is likely a systemic disorder, based on IC/BPS patients' tendency to have other concurrent pain and inflammatory organ disorders.[3-6] The association of IC/BPS with other systemic, inflammatory syndromes is so strong that, in 2008, the National Institutes of Health initiated the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network to scientifically explore the connections between urological chronic pelvic pain and other physiological systems.[15]

Given the encouraging evidence, it is imperative to study the applicability of anti-inflammatory agents, such as steroids, in the treatment of IC/BPS symptoms. The **expected outcome** of this clinical trial is that Kenalog will be an efficacious agent in bladder instillations in treating IC/BPS symptoms in women. The **significance** of this outcome is that steroids as a drug class will be further supported as an important additive therapeutic agent in the treatment of IC/BPS, as they have already shown to be in other inflammatory disorders throughout the body. The **pay-off** of this study is not only decreasing the burden of IC/BPS, which costs the United States over $70 billion a year, but also paving the way for future studies to evaluate steroids as an adjuvant therapy in IC/BPS.

Small studies (<40 patients) have shown improvement of IC/BPS symptoms in patients with use of steroids. However, **no previously published studies** have evaluated the efficacy of Kenalog in bladder instillations using this larger size study design. The proposed research is **innovative**: (1) it builds upon the current evidence that IC/BPS is a systemic chronic pain condition that may respond to steroid medications and (2) it is a bigger and more rigorous study than previously published studies evaluating the role of steroids in bladder instillation treatment of IC/BPS in women. Based on the results of this study, new and improved therapeutic options will be attainable for IC/BPS and other pelvic floor disorders.

Trial design:
This will be a single center, randomized, double-blind, controlled trial. Women will be recruited from a subspecialty clinic at the University of Louisville and be eligible for participation if they have selected a course of bladder instillation treatments with their

physician as therapy for a diagnosis of IC/BPS. Eligible consenting participants will undergo randomization with equal probability of assignment to one of the two groups: (1) bladder instillation with Kenalog (2) bladder instillation without Kenalog. They will undergo weekly bladder instillations for 6 weeks. Patients and providers will be blinded to study allocation. Clinical outcomes will be assessed at 3 weeks into treatment (3 weeks into bladder instillations) and at the end of treatment (6 weeks).

Methods and Procedures: Participants, interventions, and outcomes

Study setting:
Subjects will be recruited from the ULP Female Pelvic Medicine and Reconstructive Surgery (FPMRS) practice at the University of Louisville Health Care Outpatient Center (HCOC) and the Springs Medical Center.

- **Study Sites**:
  - University Health Care Outpatient Center (HCOC)
  - Springs Medical Center

Eligibility criteria:
Eligible women will be offered participation in the trial by clinic providers and will sign an informed consent with the study investigators prior to completing further study materials or receiving any interventions for IC/BPS.

Inclusion Criteria:

- Age ≥ 18-years old
- Women with IC/BPS who have a score of ≥ 6 on either index (problem or symptom index) of the O'Leary-Sant questionnaire who have selected bladder instillations as part of their IC/BPS treatment
- Suitability for follow-up

Exclusion Criteria:

- Contraindications to the ingredients used in the bladder instillations
  - In particular: allergy to ingredients
  - Diagnosis of idiopathic thrombocytopenic purpura
- Does not desire to undergo bladder instillation therapy or unwilling to undergo bladder instillation therapy on schedule mandated by study
- Have a known alternative diagnosis explaining bladder pain symptoms that would preclude the diagnosis of IC/BPS (e.g. radiation cystitis, active urinary tract infection with bacteria or fungus treated within last 2 weeks or diagnosed at index visit, bladder injury or trauma within the last 30 days)
- Inability to speak or read English
- Bladder instillation within the past 4 weeks

Interventions:

Eligible patients will be randomized by a research statistician to one of two possible interventions:

1. Bladder instillation with Kenalog
2. Bladder instillation without Kenalog

The randomization sequence, generated by a statistician that is uninvolved in patient recruitment, will be in randomly alternating block sizes of 6-10 with a 1:1 distribution in each block. The sequence will be attached by a research medical assistant, also uninvolved in patient selection and recruitment, to the numbering of otherwise unmarked, identical syringes containing either a bladder instillation mixture with Kenalog or a mixture without Kenalog. The appearance of the syringes will be identical in every way except for the patient number on the labelling. The study investigators recruiting, treating, or assessing the patient during the study will not be aware of the patient's randomization, and the randomization sequence will not be opened until the last patient is through with the study unless an adverse event mandates.

All study bladder instillation mixture will be drawn up in syringes, randomized, and dispensed (given to provider) by one of the medical assistants. The providers will be blinded to the study mixture and will perform the bladder instillations. The bladder instillation ingredients will be prepared in a standardized fashion by a trained medical assistant. The patients will undergo bladder instillations using a standardized technique by a physician or nurse practitioner. The medical practitioner will swab the external urethral meatus with betadine (or other appropriate cleansing agent if patient has an iodine allergy) and then instill approximately 5 mL of 1% viscous lidocaine in the urethra, letting the viscous lidocaine sit for 1 to 10 minutes. A pediatric (8 French) straight-tip catheter will be inserted to drain the bladder and collect a urine specimen for culture if indicated. After the bladder is drained, the bladder will be instilled with either a mixture of triamcinolone acetonide (1 vial, 40 milligrams (mg)/1 milliliters (mL)), heparin (10,000 units), 2% viscous lidocaine (10 mL), 8.4% sodium bicarbonate (15 mL of 1 mEq/mL), and 0.5% bupivacaine (10 mL of 5 mg/mL). After the instillation, the women will lay supine or move from supine to lateral positions intermittently for 20-30 minutes. They will then urinate the instillation. If a patient has previously demonstrated the ability to urinate without difficulty following an instillation, she may depart the office after 20-30 min and urinate the instillation in a more private, non-office setting.

If patients have a reaction to the bladder instillation or desire to stop the instillations, they may do so. Participants will be permitted to obtain any relevant concomitant care and interventions during the trial.

Outcomes

All outcome measures will be collected at 3 weeks into the bladder instillation schedule and again at the completion of the bladder instillations (6 weeks into study participation).

Primary Outcome:

1. Treatment response as measured by the score of the O'Leary-Sant questionnaire [16,17] as compared between study groups at completion of the bladder instillations.

Secondary Outcomes:

1. O'Leary-Sant subscores (problem and symptom index) at the completion of treatment
2. Change in O'Leary-Sant total scores and subscores (problem and symptom indices scores) from baseline to last collected measure
3. Pelvic pain and urgency/frequency (PUF) questionnaire [18]
4. Overactive Bladder Questionnaire (OABq) [19]
5. Pelvic floor distress inventory (PFDI) [20]
6. Sexual function measured by the Pelvic Organ Prolapse Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR) questionnaire [21-23]
7. Visual Analogue Scale (VAS) for pain as measured on marking on 10-centimeter (cm) ruler (measured in cm, 0= no pain and 10= most severe pain possible)
8. Prevalence and nature of adverse events related to study medications
9. The prevalence of notable OAB symptoms in the study population and in the different study groups, as defined by OABq score ≥ 8
10. The prevalence of concurrent pain or irritative organ disorders (irritable bowel syndrome, fibromyalgia, chronic pain, chronic pelvic pain, vulvodynia, anxiety, depression, chronic fatigue syndrome) in the study population and in the different study groups
11. Perform cost-analysis of two treatment groups

Participant timeline:

Upon recruitment, women will complete questionnaires (Figure 1) about their characteristics and health history, presence or absence and number of other pain syndromes related to IC/BPS (irritable bowel syndrome, fibromyalgia, chronic pain, chronic pelvic pain, vulvodynia, anxiety, depression, chronic fatigue syndrome), and complete the following reliable, validated questionnaires as follows:

(1) O'Leary-Sant questionnaire (problem and symptom index scores) [16,17]
(2) Pelvic pain and urgency/frequency (PUF) questionnaire [18]
(3) Overactive Bladder Questionnaire (OABq) [19]
(4) Pelvic floor distress inventory (PFDI) [20]
(5) Sexual function measured by the Pelvic Organ Prolapse Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR) questionnaire [21-23]
(6) Visual Analogue Scale (VAS) for pain as measured on marking on 10-centimeter (cm) ruler (measured in cm, 0= no pain and 10= most severe pain possible)

Bladder instillation will be performed weekly with the same mixture that the patient was randomized to (mixture with or without Kenalog) and for 6 weeks. Symptom questionnaires will be given at baseline, 3 weeks, and 6 weeks of treatment. If the patient misses a study appointment, she will be called by telephone and queried about side effects and if appropriate, re-scheduled for an appointment.

We plan to recruit patients from January 2019 until July 2020. Patient follow up will be completed by September 2020. As bladder instillations are commonly performed and considered low risk, no interim analysis will be performed. Urinary tract infection will not be considered an adverse event related to study drug but will be monitored in data collection.

Sample size

Sample size calculation was based on the primary outcome, the O'Leary-Sant score on the final day of bladder instillation treatment as compared between the two treatment groups. Based on previous studies, patients have a baseline IC/BPS score following standard medical treatment of approximately 24 ± 5.6 points.[16,17] A 4.03 point decrease from baseline on the O'Leary-Sant questionnaire corresponds with at least a 50% perceived improvement in the patient's disease.[24] We believe this level of difference between the groups in the final O'Leary-Sant scores would be clinically significant. We want 80% power to detect a 4.03 point decrease from a baseline mean score of 24 (expected score in the bladder instillation without Kenalog group after treatment) with a standard deviation ≤ 5.6 points (alpha 0.05) with a 2-sided t-test. The G*Power sample size calculator was used for the power calculations (https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html) and these calculations were confirmed for accuracy by a University of Louisville biostatistician. The resulting sample size was n= 32 for each group for a total of 64 enrolled patients. Accounting for a 20% dropout in the study, this would translate to a sample size of 80 patients enrolled with a goal of 40 per group.

Recruitment

Participants will be enrolled from the FPMRS clinics as noted above, at the time when a diagnosis of ICBPS is established (score ≥6 on either the symptom or the problem index of the O'Leary-Sant questionnaire) and the patient has expressed desire for bladder instillations as a therapy for this disorder. Recruited subjects will be given a sequential study ID number (SIDN) at the time of their informed consent, which cannot be changed or altered throughout their course in the study.

Methods: Assignment of interventions

Allocation:

Sequence generation

The randomization schedule will be created by an uninvolved statistician (not involved with study enrollment or data collection) using a random permutated block design (randomly varying from 6-10 patients per block with a 1:1 distribution within each block) to reduce predictability of a random sequence. The statistician will provide the sequence to the medical assistant, who will correspond this to expected study ID numbers (SIDNs) of future subjects in the given sequence. Study medications and packaging in agreement with this preset sequence will be made prior to the recruitment of that subject.

Allocation concealment mechanism
The allocation concealment will be in the form of randomization, where only the biostatistician creating the allocation sequence and the medical assistant creating the study bladder instillation mixtures and are aware of the patient allocation. As both of these parties are uninvolved in patient eligibility determination, recruitment, and direct patient care and follow up, this will maintain allocation concealment from the investigators. Under no circumstances will the planned allocation for the patient be known at the time of recruitment.

Implementation
The investigators will enroll and consent eligible participants. The participants will be given their study number. This number will be tied to a bladder instillation mixture known to the medical assistant who will prepare the mixture but not to the study investigators or participants. This number serves as the participant's allocation.

Blinding (masking)
Patients and investigators will be blinded to treatment allocation, so this is a "double-blind" randomized, controlled trial.

The patients, once consented, will be randomly assign to a treatment group by using the randomization sequence that was created by an uninvolved statistician. The patients will use their SIDNs for the remainder of the study. They are blinded to treatment because the study medications all look the same except for the syringe labeling with the patient's SIDN. All patients will otherwise receive the same treatment and care.

The investigators are blinded because they are not privy to the bladder instillation mixture that the patient was assigned to and all patients are otherwise treated and assessed the same.

Unblinding (unmasking)
Should unblinding be warranted such as in exceptional circumstances when knowledge of the actual treatment is absolutely essential for further management of the patient, the ULH biotstatistician who has access to patient allocation, will be contacted to disclose to the principal investigator (PI) which treatment group the affected participant was assigned. The incident will be submitted on a case report form.

Methods: Data collection, management, and analysis

Data collection methods

All information will be obtained directly from questionnaires completed by the patient at the initial study visit, from contact points during study visits at which bladder instillations, are being performed, or at the end of the study at the 6th bladder instillation. The patients will undergo bladder instillations at the University of Louisville Female Pelvic Medicine clinics either at the Spring Clinic location or the HCOC building, and data from validated questionnaires and medication compliance worksheets will be collected on paper at the appropriate time point. Data will be extracted and entered into a RedCap or password-protected Excel spreadsheet as outlined below. No data will be extracted from the patient's medical record or HCOC AllScripts electronic medical record system for this study; all data will be collected directly via study questionnaires and data report sheets designed for use in this study.

Retention and follow-up

We plan to query adverse events or side effects at each study visit. We offer appointments three days a week to allow for optimal scheduling and will call patients if they are unable to make their follow up visit to ask about medication side effects as well as reschedule them for another appointment time. They will be given written and verbal instructions on what to do in the event of side effects or adverse events to increase the likelihood of them presenting in person and communicating with their physician and/or study investigators about any issues. Patients will be allowed to submit their interval and end-of-study questionnaires during their appointment visits.

Data Management

Data collection form: See below and Appendix A

The following information will be collected directly from study questionnaires and entered into an encrypted excel spreadsheet:

- Study ID number (SIDN)
- Name
- Date of birth
- Age
- Race/ethnicity
- Contact information
- Emergency contact information (if patient willing to provide)
- Social security number (SSN)
- Weight
- Body mass index (BMI)
- Smoking status
- Gravidity
- Parity

- Reason for visit
- Prior pelvic reconstructive surgery
- Medical history, specifically history of: irritable bowel syndrome, fibromyalgia, chronic pain, chronic pelvic pain, vulvodynia, anxiety, depression, chronic fatigue syndrome
- Charleston comorbidity index[25]
- O'Leary-Sant questionnaire (problem and symptom index scores)[16,17]
- Pelvic pain and urgency/frequency (PUF) questionnaire[18]
- Overactive Bladder Questionnaire (OABq)[19]
- Pelvic floor distress inventory (PFDI)[20]
- Sexual function measured by the Pelvic Organ Prolapse Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR) questionnaire[21-23]
- Visual Analogue Scale (VAS) for pain
- Timing and nature of adverse events during the study, regardless of suspected or known relationship to study medication

Data Handling/Storage:
All identifying information and data collected during the course of this study will be kept secure and strictly confidential. All data will be stored electronically on a password protected, encrypted laptop in the possession of the study investigator. Risks for breaches of confidentiality will be minimized by entering data from the medical record to a password protected, encrypted computer database which will have limited access to the PI.

The patient's unique study ID will be used for storage, analysis and publication.

Paper data collections forms will be utilized and data will be entered from the paper data form by a study investigator into either a RedCap database or an encrypted, password protected laptop or computer Excel database. These data forms will be housed in a locked file cabinet in the Division of Female Pelvic Medicine and Reconstruction office in a locked cabinet with restricted access.

Data Analysis and Statistical Methods:
The data will be analyzed in consultation with a department-committed biostatistician utilizing SPSS statistical software. Categorical variables (e.g. 'yes" to certain questions on the PFDI) will be compared using chi-square tests (or Fisher's exact test when appropriate). Continuous variables (such as primary outcome) will be compared using t-tests, and changes in continuous outcomes over time (e.g. change from baseline to 8-week O'Leary-Sant score) will be compared with paired t-tests. A regression analysis will be performed to determine the impact of various relevant cofactors (e.g. patient age, presence of other chronic disorders, level of OAB symptoms) on the relationship between group assignment and treatment outcomes.

We will perform an intention-to-treat analysis by the assigned study groups for the initial analysis, comparing women who followed up at the completion of the study (6-week outcomes) between the study groups (bladder instillations with and without Kenalog) as

assigned. We will also perform a per-protocol analysis, comparing women in the bladder instillation with Kenalog who had at least 4 bladder instillation treatments to the group that had bladder instillations without Kenalog. Lastly, we will perform two types of sensitivity analysis:

(1) Imputation of missing data with assumption of treatment non-response (baseline O'Leary-Sant and other outcomes scores carried forward as the final outcome)
(2) Imputation of missing data with assumption of "best last known" response (final outcomes assumed to be the best value for that outcome during the study course that was available)
(3) Imputation of missing data with "most recent last known" response (final outcomes assumed to be the most recent value for that outcome during the study course that was available)

Planned secondary analyses will include: (1) treatment response of subgroups of patients with and without prominent OAB symptoms (OABq score ≥ 8); (2) treatment response in patients with and without a history of prior IC/BPS treatment; and (3) the relationship between known coexisting pain and irritative organ disorders (irritable bowel syndrome, fibromyalgia, chronic pain, chronic pelvic pain, vulvodynia, anxiety, depression, chronic fatigue syndrome) and response to treatment; (4) Treatment cost-analysis. The interaction of these factors (prominent OAB symptoms, prior IC/BPS treatment, coexisting pain or irritative organ disorders) with the relationship between randomization and treatment response will be determined.

Potential Benefits:
Participants may benefit from the multiple agents in the bladder instillation, including Kenalog, a steroid. Steroids have been shown to be helpful in patients with IC/BPS. Bladder instillation therapy is a well-tolerated and commonly used treatment of IC/BPS.

Potential Risks:
This research study cannot practically be conducted without access and use of protected health information. Thus, the principle risk to patients involved in the study is a potential breach of confidentiality and misuse or exposure of this information. With this in mind, the investigators will conduct all research activities in such a way that maximizes data security and minimizes any risk of potential data breaches.

Patients may have risk of embarrassment or offense due to the private and personal nature of some of the study questions (e.g. such as questions about urinary incontinence or sexual activity). This risk will be minimized by accurate description of the nature of the study and the study outcomes to the patient prior to informed consent, and communication with the patient regarding the right to decline to answer any given study question.

Prior to offering enrollment in the study, the patient must desire bladder instillation therapy for treatment of her IC/BPS symptoms. The standard practice of bladder instillations is to cleanse the external urethral meatus with betadine or another appropriate cleansing solution. This, as well as the insertion of a small bladder catheter, can sometimes be uncomfortable for patients. Sometimes the instillation solution can be uncomfortable for

patients due their IC/BPS symptoms and the expansion of their bladders. These potential risks and discomforts are not over and above that experienced in a standard visit to this clinical service. That being said, there may be ways to reduce the occasional discomfort of undergoing a bladder instillations, such as using topical lidocaine gel for insertion of the bladder catheter and instilling the solution into the bladder slowly. Another potential risk is an allergic reaction to the ingredients in the bladder instillations. Although women with known hypersensitivity will be excluded, women may have unknown or new sensitivity to the medications. These are highly unlikely to be serious and are reversible on stopping use of medication. Patients will have the study personnel's contact information should they develop any adverse events prior to their weekly visit and need medical attention.

Methods: Monitoring

Data monitoring:
As this study has minimal risk, a Data Safety Monitoring Board (DSMB) is not required. However, the study participants will be given numbers to reach the principal investigator, clinic, or after-hours answering service should they experience any side effects or adverse events related to the study. They will be advised to seek care from their doctor for medical advice related or unrelated to the study, and the study investigators will alert the University of Louisville IRB apprised of all adverse events experienced by trial patients, regardless of severity or clinical belief of relation to the study drug. If an adverse event is sufficiently severe enough to merit stopping the study drug temporarily or permanently, we will work in collaboration with the IRB to determine if patient randomization should be revealed. This determination will come after the drug has been stopped and appropriate medical attention given to the patient. Serious, drug-related adverse events will be those that require intravenous medication, hospital admission, or procedural intervention and are considered to be directly associated with study treatment. If $\geq 25\%$ of patients have experienced an adverse event thought to be related to the study drug or if $\geq 10\%$ of patients have experienced a serious adverse event related to the study drug, the study will be terminated early.

Harms:
Adverse event and unintended effects of trial interventions or trial conduct with be managed by a Research Nurse, and the investigators. Such information will be both solicited and participants will be encouraged to spontaneously report such effects. The research team will closely monitor data collection and assure confidentiality at every point during this study. The IRB and appropriate hospital research office will be notified immediately of any adverse events, including security breaches of the data, or UPIRTSOs, whether expected or unexpected. Participants will discontinue the products if they have an allergic reaction to the medication or any of its components. The worse anticipated adverse reaction is discomfort with bladder instillation which would be monitored, recorded, and responded to by either our Research Nurse or the patient's chosen provider.

The individual stopping criteria are severe allergic reactions and events that require intravenous medication, hospital admission, or procedural intervention and are considered to be directly associated with the bladder instillations. Allergic reactions will be skin

reactions such as ulcers; rashes; and swelling and anaphylactic reaction to the bladder instillations. As noted above, monitoring of adverse events via study investigators and the IRB will be performed.

The investigators will be responsible for ensuring participants' safety on a weekly basis. The investigators will monitor participant safety, evaluate the progress of the study, to review procedure for maintaining the confidentiality of data, quality of data collection, management, participant safety, and analyses on a monthly basis at our research meetings. The PI will be informed of serious adverse events as soon as they occur and will notify the research nurse or the other investigators within 24 hours of notification. The participants will be given a number to call the office or the answering service to contact the PI in the event of an adverse reaction. Adverse reactions will be documented according the guidelines set forth by the US Dept. of Health and Human Services.

Auditing:
Auditing will be at the discretion of the IRB.

Ethics and dissemination

Research ethics approval:
This study will be reviewed and approved by the University of Louisville Institutional Review Board.

Protocol amendments:
Important protocol modifications, such as, changes eligibility criteria, outcomes, analysis, to relevant parties (investigators, trial participants, clinicaltrial.gov). The research personnel involved in this study Dr. Kate Meriwether, Dr. Sean Francis, Dr. Olivia Cardenas-Trowers, Dr. James R. Stewart, and Dr. Ankita Gupta are CITI and HIPAA trained. No additional personnel are involved at this time. If new research personnel are added to the study, an amendment will be submitted to and approved by the IRB before being allowed to participate in the study.

Consent or assent:
Informed consent from potential trial participants or authorized surrogates will be obtained before enrollment. There is a possibility that the participants' data could be used in an ancillary study, and this will be disclosed to patients and part of the informed consent language.

Confidentiality:
The investigators will take great care to protect and secure all study data collected for this study. Risks for breaches of confidentiality will be minimized by entering data from the medical record or paper data collection forms to a password protected, encrypted computer database which will have limited access to the PI, Co-PIs, and sub-investigators.

Personal identifiers (name, DOB, contact information for patient and an emergency contact person, and social security number) will be collected and retained in the event of need to contact patients with clarification of questionnaire responses, urgent study alerts, or early termination of the study by the investigators. However, all study information will be completely de-identified by using a study code or number instead of identifiers for the purposes of data analysis and reporting.

Data will be de-identified as soon as is feasible without compromising the study. Data will be stored as an encrypted file on a password protected laptop computer or password protected shared U of L drives, ULP share point server or secure hospital database. Data will NOT be stored on a 'cloud' type server per HIPAA regulations.

A de-identified Excel spreadsheet will be provided to the statistician for statistical analysis. Statistical consultants on this study will only work with totally de-identified data and will never see patient identifying information, patient images, or patient medical records.

The protected health information gathered for this study will be destroyed as soon as is feasible and will not be reused or disclosed to any other person or entity, except as required by law. The Excel "key" spreadsheet listing Research ID #, name, DOB, contact information for patient and emergency contact, and SSN will be kept distinct from the remainder of the study information as a means to contact patients or identify the patient as needed for safety, medical care, or study-wide alerts. As soon as all data have been collected and there is no further need to return to a subject's contact information and identifying information, the Excel key(s) linking name, DOB, contact information, and SSN to study ID numbers (SIDNs) will be destroyed.

Declaration of interests:
The PI does not have any financial disclosures or competing interests for the overall trial.

Access to data:
The PI and co-investigators will have access to the de-identified final trial dataset. Only the investigator, Olivia Cardenas-Trowers, who is performing data entry and management for this study, will have access to the password-protected key that allows identification or contact of the individual patient as related to their SIDN.

Ancillary and post-trial care:
We do not anticipate any major harm or complications due to use of the products. We do not foresee any long-term sequelae from the bladder instillations.

Dissemination policy:
The investigators intend to publish the results obtained from this trial. All the investigators are eligible for authorship. No professional writers will be used for the publication.

Appendices

1. Informed consent

2. Data collection spread sheet (Microsoft Excel)
3. Contact information and patient identification sheet (Appendix A)
4. Patient health history and characteristics questionnaire (Appendix B)
5. O'Leary-Sant questionnaire (problem and symptom index scores)[16,17] (Appendix C)
6. Pelvic pain and urgency/frequency (PUF) questionnaire[18] (Appendix D)
7. Overactive Bladder Questionnaire (OABq)[19] (Appendix E)
8. Pelvic floor distress inventory (PFDI)[20] (Appendix F)
9. Pelvic Organ Prolapse Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR) questionnaire[21-23] (Appendix G)
10. Visual Analogue Scale (VAS) for pain (Appendix H)
11. Medication compliance/pill count, adverse event, and medical event reporting worksheet (Appendix I)

References:

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