Vaginal Estrogen for the Prevention of Recurrent Urinary Tract Infection in Postmenopausal Women

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

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Version date: 05/11/2011

1. PROJECT TITLE

Vaginal Estrogen for the Prevention of Recurrent Urinary Tract Infection in Postmenopausal Women

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

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4. ESTIMATED DURATION OF THE STUDY

4 years

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

We would like to know if the use of vaginally applied estrogen can prevent the problem of repeated urinary tract infections (UTI) in women who have gone through menopause. We will use two forms of vaginal estrogen that are available by prescription (a ring and a cream) and compare their efficacy to that of a commercially available cream without any active ingredient. We are going to look at if the vaginal estrogen can prevent UTIs altogether and also the number of UTIs each group experiences over a 6 month period. After 6 months, all subjects will receive vaginal estrogen and the women will be able to choose which form of vaginal estrogen (ring or cream) they would like to use. We will then be able to compare the number of UTIs on and off active vaginal estrogen treatment within those subjects who started on the cream without estrogen. We are also going to look at quality of life before and during treatment using questionnaires and whether subjects stop using the treatments or do not use them as directed (compliance). Additionally, urine and vaginal swab specimens will be collected and processed for bacterial 16s rRNA characterization at baseline and after treatment.

6. SPECIFIC AIMS

Primary Objective
The primary purpose of this study is to assess the efficacy of vaginal estrogen versus placebo at 6 months on the prevention of urinary tract infections (UTI) in postmenopausal women with history of recurrent UTI.

Secondary Objectives
[1] a] To assess overall rates of UTI over 6 months in postmenopausal women with history of recurrent UTI receiving vaginal estrogen (ring or cream).
b] To compare rates of UTI between 6 and 12 months of those subjects initially randomized to placebo.
[2] To assess the impact of treatment of recurrent UTI with vaginal estrogen on quality of life at 6 and 12 months in postmenopausal women with history of recurrent UTI.
[3] To assess compliance with vaginal estrogen (ring or cream) treatment at 12 months in postmenopausal women with history of recurrent UTI.
[4] To assess efficacy of vaginal estrogen at 12 months in those compliant with treatment.

Primary Hypothesis
Vaginal estrogen (ring and cream) will be superior to placebo in the prevention of UTI at 6 months of treatment in postmenopausal women with a history of recurrent UTI.

Secondary Hypotheses
[1] a] Overall rates of UTI in the first 6 month period in those women receiving vaginal estrogen will be

lower compared to those receiving placebo.

b] Rates of UTI will decrease between 6 and 12 months for those initially on placebo and subsequently using estrogen.

[2] Vaginal estrogen will result in improved QOL in postmenopausal women with history of recurrent UTI.

a] compared to placebo at 6 months.

b] compared to baseline at 12 months.

[3] Adherence with vaginal ring will be superior to cream.

[4] At 6 and12 months, vaginal estrogen will be effective at preventing UTI in those adherent to therapy.

7. BACKGROUND AND SIGNIFICANCE

Recurrent Urinary Tract Infection

Recurrent urinary tract infection (UTI) in postmenopausal women is common, negatively affects the quality of life for millions and has significant impact on health care delivery [1]. The annual social cost of UTIs has been estimated at 1.6 billion dollars with 11.3 million prescriptions written for treatment [2]. Up to 15% of women over 60 will develop frequent UTIs [3]. This number increases to 20% over the age of 65 and between 25-50% of patients 80 years of age and older experience bacteruria [4]. Recurrent UTI is defined as three or more UTIs in 12 months or two UTIs in 6 months [5]. The pathogenesis of recurrent UTI in postmenopausal women may in part be related to the declining levels of systemic estrogen after menopause. This change causes differences in the bacterial flora of the vagina due to increasing vaginal pH, resulting in colonization by uropathogens (escherichia coli and enterococcus) as opposed to the normal lactobacillus flora seen in premenopausal women. While not entirely clear, the general consensus is that this vaginal colonization with enteric bacteria leads to more frequent UTIs [6]. Thus, a common therapy for prevention of recurrent UTI is topical vaginal estrogen. While commonly used in practice, there is a paucity of data on the efficacy of vaginal estrogen for the prevention of recurrent UTI in currently prescribed vehicles and doses.

Vaginal Estrogen

There are a number of modes of delivery for vaginal estrogen (full and low dose) such as tablets (Vagifem™), creams (Estrace™ and Premarin™) and vaginal rings (Estring™ and Femring™). After safety concerns raised by the Women's Health Initiative, use of hormones is a concern for both patients and practitioners regarding the use of these compounds by any method. As such, the goals of treatment with hormones are to identify the minimum dose of therapy needed to achieve benefit. Given concerns regarding systemic hormone replacement therapy (HRT), topical dosing has become the mainstay of local therapy for vaginal atrophy/dyspareunia. Vagifem™, Estring™, Estrace™ and Premarin™ cream have been FDA approved for the treatment of atrophic vulva, atrophy of the vagina, urethral atrophy [7]. Circulating levels of estradiol have been shown to be minimal with low dose vaginal estrogen creams, tablets and the estrogen ring [6, 8]. Thus, systemic effects from these low dose topical therapies are felt to be extremely low. With the estrogen ring, serum estradiol increased from a baseline of 16+22 pmol/l to 49+64 pmol/l at week 24, then fell to 20+19 pmol/l by week 48 [10]. With administration of 0.5g twice weekly,serum estradiol increased from a baseline of 15+33 pmol/l to 36+51 pmol/l at week 24 and remained there at week 48 [10]. These levels are substantially than the upper limit of normal (130 pmol/l) for postmenopausal women. The other concern with any unopposed estrogen is endometrial safety. There have been several large studies that have established endometrial safety of various low-dose formulations of vaginal estrogen (Vagifem™, Estring™ and conjugated estrogen cream at a dose of 0.3mg) [9-11]. Controlled studies of more than 1,000 women on unopposed estrogen ring and estrogen cream at doses proposed in this study have not identified any endometrial cancers. With low systemic absorption and no significant increase in endometrial pathology with low dose vaginal estrogen, it is generally thought that the use of progestins is not necessary to protect the endometrium [12]. Additionally, because systemic absorption is minimal, it can be assumed that there should not be an effect on patients with breast cancer, however, the data is limited [13]. Topical, low dose vaginal estrogen is in general well tolerated, with dropout rates of 7 and 8% in prior studies with the ring and cream respectively. Only reported adverse events significantly higher than placebo was breast pain, however, the incidence of this is low [13]. Other reported adverse events in uncontrolled observational studies include vaginal bleeding, which occurred rarely in one study, however, endometrial sampling in those women with vaginal bleeding revealed no evidence of hyperplasia or malignancy[14].

While no formulation of vaginal estrogen is approved for prevention of UTIs, it is commonly used “off label”. The theory is that recurrent UTIs in postmenopausal women are directly a result of vaginal atrophy. The hypothesis behind its efficacy involves re-estrogenizing the vaginal mucosa, although it does not lead to premenopausal circulating levels of estradiol, leads to local effects on the balance of bacterial flora mimicking premenopausal states. In premenopausal women, the vagina is colonized by lactobacilli which result in a low vaginal pH and inhibits overgrowth of other bacteria. In postmenopausal states the vaginal pH is increased which allows overgrowth of pathogens. Previous trials with vaginal estrogen have shown that vaginal estrogen administration changes the pH of the vagina to premenopausal states, resulting in restoration of the bacterial balance [15]. However, this study examined higher doses of estrogen cream (0.5mg daily for 2 weeks followed by twice a week, as opposed to current dosing of 0.3125 mg twice a week) and only explored one preparation.

UTI definitions
There is debate over the optimal definition for recurrent UTI. In general, the most commonly accepted definition is the presence of 3 or more symptomatic UTI in 1 year or 2 in 6 months [16]. Symptomatic UTI has been defined by the Center for Disease Control (CDC) as a combination of signs, symptoms and laboratory measures. We will use this definition of UTI for our primary outcome: individuals experiencing at least one symptom (fever >38 degrees C, urgency, frequency, dysuria OR suprapubic tenderness) AND a positive urine culture that is ≥ 10 ^5 microorganisms per milliliter (mL) of urine with no more than 2 species of microorganisms. Alternatively, if the specimen is collected via catheterization, a culture as low as 10 ^3 microorganisms per mL of urine will be considered positive. Given that guidelines do not require primary care physicians to obtain urine cultures to diagnose a urinary tract infection, we will only require one positive urine culture and the other urinary tract infections may be diagnosed with urinalysis. From a practical and clinical standpoint, UTIs are generally diagnosed based on symptoms, urine analysis and/or culture and rarely are catheterized specimens collected in routine practice. Thus, presence of UTI will be determined using symptoms and a positive clean-catch culture as the primary outcome unless a patient cannot obtain a clean catch (in which case we will use a catheterized specimen). In order to minimize false positives, urine will be placed in preservative within 10 min of collection. Urine cultures are up to 95% sensitive and 99% specific at diagnosing UTI [17].

- **Innovation**

Given the high prevalence of recurrent UTI in the postmenopausal population, the growing elderly population and the increasing prevalence of multidrug resistant bacterial infections, prevention of UTI in this high-risk population is of utmost importance. Recurrent UTI does not currently have one accepted treatment and various regimens are used based on provider preference. One option is the use of cranberry, although a recent Cochrane review shows a smaller benefit than previously thought with cranberry performing similarly to placebo, water and no treatment (RR0.86, 95% CI 0.71 to 1.04) [18]. Other options include antibiotic suppression with daily treatment. Nitrofurantoin, cephalexin and trimethoprim/sulfamethoxazole have all been proven effective at preventing recurrent UTI when taken daily for prophylaxis with success rates ranging from 36-94% [19-22]. Patients who associate their UTIs with sexual intercourse have had 66-68% success with postcoital treatment with single dosing of antibiotic [23-25]. However, treating prophylactically with antibiotics has undesirable side effects such as promoting fungal infections, gastro intestinal flora upset, and resistance, making recurrent infections harder to treat. In addition, these antibiotics can have serious side effects including blood dyscrasias, pulmonary fibrosis, tendon rupture, peripheral neuropathy, hepato and renal toxicity.

Prevention of recurrent urinary tract infection could greatly minimize the problems associated with chronic administration of antibiotics. While use of vaginal estrogen is often routine practice for prevention of UTI, only one study has ever explored using vaginal estrogen for this purpose in a randomized controlled trial and this study used a higher dose than currently used in clinical practice [15]. As such, there is no data on the efficacy of vaginal estrogen using modern doses and formulations. We hope that these results will help us better understand treatment for a disease where there is no ‘gold standard’. Using evidence from a randomized placebo controlled trial will allow us to definitively report on the efficacy of vaginal estrogen in the prevention of recurrent UTI and explore satisfaction, quality of life and efficacy between two commonly used preparations.

8. PROGRESS REPORT

We have completed enrollment.

9. RESEARCH DESIGN AND METHODS

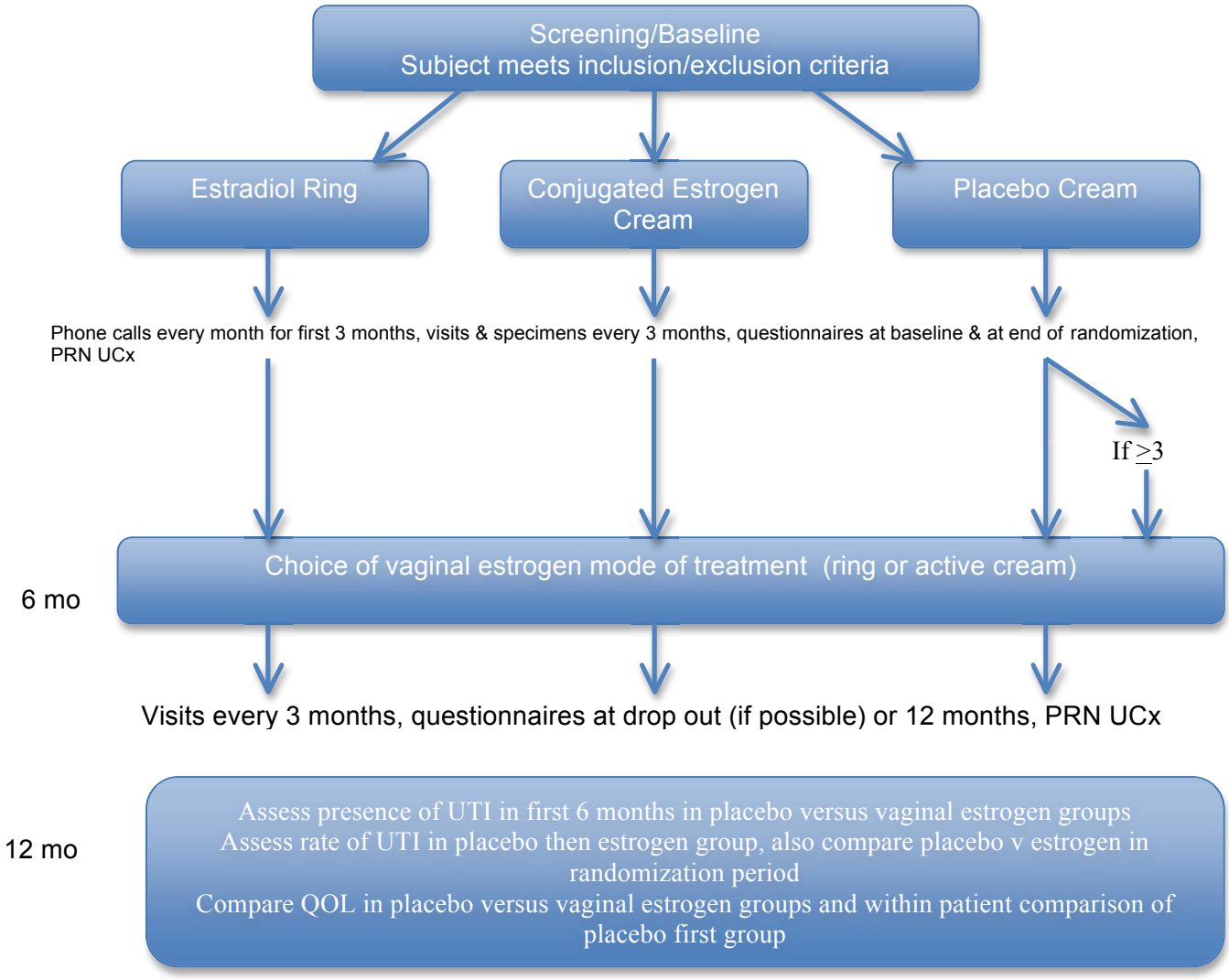
Overall Design

This is an investigator initiated, multicenter, single blind, randomized placebo controlled trial of vaginal estrogen (delivered by ring or cream) compared to placebo control. During the blinded portion, subjects will be randomized to either receive vaginal estrogen (via ring or cream), or receive a placebo cream. Conjugated estrogen cream at a strength of 0.625mg/g and a dose of 0.5g (0.312 mg) twice a week will be used, as will estradiol ring containing 2mg of estradiol placed vaginally every 3 months. These two doses are standard clinical dosing based on FDA approved treatment of vaginal atrophy and result in similar vaginal effects. The placebo cream will be a commercially available over the counter oil based vaginal lubricant which is semi-solid at room temperature and contains no active ingredients. Primary outcome will be assessed at 6 months with vaginal estrogen group compared to the placebo control. However, in order to improve recruitment and assess long term compliance, satisfaction and efficacy in the as treated groups, we will offer open label use of ring or active cream after 6 months of blinded treatment. Those on placebo at 6 months will be allowed to choose which vaginal estrogen form (ring or cream) she would like to use for another 6 months and secondary outcomes captured after their 6 months of active treatment will be combined with those 6 month measures collected from those originally randomized to active therapy. Vaginal estrogen group will also be allowed to choose which administration (ring or cream) they would like to continue with at 6 months. Subjects will not be told which preparation is the placebo in order for them to remain blinded to treatment. Providers, however, will not be blind to this. We chose not to use a placebo ring, as we felt this could be a nidus for infection skewing the results and unnecessarily placing subjects at risk. We will attempt to minimize bias by having providers blinded to outcome measures and questionnaire responses.

The primary outcome is occurrence of one or more symptomatic UTIs within 6 months of treatment. Subjects will perform a clean catch for a urine culture when they have symptoms of a UTI using the CDC definition of symptoms, as above. If the subject cannot perform a clean catch themselves, a provider may obtain a catheterized specimen as clinically indicated, in which case the threshold for bacterial count will decrease to 10 ^3 microorganisms per mL. Secondary outcomes include assessing rate of UTI over the course of the year in those women who received placebo and then vaginal estrogen, as well as comparing the rates of UTI in the placebo and vaginal estrogen group. Quality of life (QOL) questionnaires will be administered at baseline, at the end of randomization and at drop out or 12 months. There are no validated questionnaires that assess UTI specifically, therefore we have chosen questionnaires which relate to general QOL, as well as those which include symptoms similar to that of UTI. In addition, we know that vaginal estrogen can treat dyspareunia, so we will capture sexual function. We will be using the SF 12, as well as the overactive bladder satisfaction questionnaire (OAB-SAT-q), the medical, epidemiological and social aspects of aging questionnaire (MESA), the urogenital distress inventory (UDI-6) and the female sexual function index (FSFI) along with the patient satisfaction global ratings: patient satisfaction question (PSQ), estimated percent improvement (EPI) and global perception of improvement (GPI). The SF 12 is a general quality of life questionnaire initially used to survey health status [26]. The OAB-SAT-q is a questionnaire evaluating satisfaction pertaining to overactive bladder symptom treatment, symptoms which are similar to those of a UTI [27]. The MESA questionnaire explores lower urinary tract symptoms [28]. The UDI-6 is the short form of the urogenital distress inventory which surveys life impact and symptom distress of urinary incontinence and related issues in women [29]. The FSFI is a validated questionnaire assessing female sexual function [30]. The PSQ, EPI and GPI are patient global ratings, satisfaction, perception of improvement and estimated percent improvement validated previously in the treatment of urinary incontinence [31]. These questionnaires will allow us to assess whether general quality of life, irritative urinary symptoms, as well as sexual function are improved by vaginal estrogen, which could occur secondary to the correction of atrophic vaginitis alone. We will also assess whether QOL changes when UTIs occur with less frequency and will assess overall patient satisfaction with treatment. We will also be evaluating adherence in each treatment arm. Adherence with creams will be assessed by medication diary and weighing the tubes at each 3 month visit and vaginal rings will be accounted for by confirming that the ring is still in place in the vagina and then exchanging it for the new ring. Adherence is defined as $\geq$80% usage.

The open label portion of the study will start at month 6. All of those women using placebo cream will be allowed to choose a vaginal estrogen preparation to use for the remainder of the study (ring or cream). Those women initially randomized to vaginal estrogen will be allowed to choose which vaginal estrogen preparation they want to continue with. The rationale behind an open label portion of the study is an incentive to participate. Vaginal estrogen is available to patients via prescription, as an off label indication, but coverage for this therapy can be limited and treatment costly (up to $300 per prescription refill). The open label portion of the study should provide incentive for women to enroll when the study drug is already available, as will modest reimbursement for study visits. We will also be able to compare the rates of UTI in those women who received placebo initially to their rate of UTI on drug.

Eligible women will be consented and block randomized using preset, opaque and sealed envelopes. These cards will either say “study drug 1, 2 or 3“ and will be placed in numbered envelopes in a random order and selected by study staff and dispensed to the subject. These drugs will be stored in a locked cabinet in the Female Pelvic Medicine clinic. After the subject receives her study drug, she will receive administration instructions. If the assigned treatment is a ring, the subject will have it placed by the provider, if it is a cream, the cream will be weighed at baseline and she will be shown how to place it vaginally herself and instructed on bringing the remaining study drug to each 3 month visit for weighing.



Methodology
Details of the Intervention

Women will be randomized to one of the two vaginal estrogen arms or placebo in a 1:1:2 fashion. For those randomized to the ring, the ring will be placed by the provider in 3 month intervals at their visits. Subjects randomized to cream arm will receive 0.5g (0.312 mg) conjugated estrogen vaginal cream per vagina at bedtime two times per week. The placebo cream will be administered in a similar fashion. These cream tubes will be weighed at baseline and again at the every 3 month office visits to assess adherence. They will also be given diaries to keep track of their medication administration. Subjects will be called once a month for the first 3 months by study personnel to assess for adverse events as well as UTI symptoms. After the first 3 months, a relationship will be established with study personnel and the participants will be encouraged to call with symptoms.

Written quality of life questionnaires will be administered at baseline, at the end of randomization or 6 months and at drop out (if possible) or 12 months. The questionnaires include the OAB-SAT-q, MESA, UDI-6, FSFI and PSQ, GPI and EPI rating scales and are previously validated questionnaires referenced above in *Overall Design* [26-31]. These will assess global QOL, as well as irritative bladder symptoms and sexual function. We will also collect baseline data with respect to medical history and concomitant pelvic medicine diagnoses.

Safety and Toxicity Measures
If subjects in any arm develop 3 UTIs in the 6 month treatment period, they will be unblinded. If on placebo, they will be provided active study drug as would have been done at the 6 month visit or if they are on study drug, they will be treated according to the provider's clinical practice and their outcomes recorded for the remainder of the study. Six month outcome assessments will be administered early to capture QOL data for the secondary analyses. We will also be monitoring for adverse events monthly with phone calls for the first 3 months, specifically querying symptoms of pain, bleeding or abnormal discharge which would prompt evaluation for relatedness to study participation. Events related to participation will not be billed to insurance, however, any events which are part of routine clinical care (ie. UTI or other pelvic floor disorder treatment such as urinary incontinence) will be billed according to standard clinical care. After that subjects will be encouraged to call with any adverse reactions. Attribution of these events to study participation will be assigned by the investigator and reported to the IRB according to local policy.

Outcomes
The primary outcome will be the occurrence of symptomatic UTI within the 6 month treatment period. Clean catch urine culture will be collected whenever subjects report symptoms of a UTI: fever (>38 degrees C), urgency, frequency, dysuria or suprapubic tenderness. Standing orders for urine analysis and culture will be present at the local institution's lab and women will be asked to have all urine labs done at the parent site as per standard clinical practice. If subjects are not able to submit a specimen to the local site, lab orders will be faxed to a local laboratory for collection and results sent to parent institution as per clinical care standards. Treatment will be up to the discretion of the treating physician. If they are unable to perform a clean catch, they may come in to the office for a catheterized specimen according to the treating physician's clinical recommendations. As these cultures would be obtained regardless of study participation, they will be obtained and billed according to standard of care. The presence of a UTI in the 6 month window will be the primary outcome of the study, but secondarily we will assess the rate of UTIs over the course of the year that occur in order to assess efficacy.

Other secondary outcomes include QOL questionnaires mentioned above. These will help us to look at changes in general QOL, as well as irritative bladder symptoms and sexual function, impacted by study drug. Adherence will also be assessed. We will weigh tubes of cream to determine adherence with creams, as well as collect medication diaries (adherence will be defined as $\geq$80% use as measured by weight of the vaginal cream tubes). For the ring, compliance will be assessed based on presence of the ring vaginally at 3 month visits.

Analysis
Sample Size Consideration
The primary outcome is whether there is any occurrence of symptomatic UTI at the end of the randomized

treatment period. Based on the literature [15] we assume that the rate of at least one UTI in the placebo group is 63%. With 20 subjects at the end of the randomized treatment period in each of the two treatment groups, we will have 80% power to detect a difference using Fisher's exact test if the corresponding rate in an active treatment group is 16% [15] under a two-sided significance level of 0.05. A total sample size of 48 (24 subjects per group) will be needed allowing for 20% attrition seen to date in the study.

Data Analysis

Subject characteristics including baseline measures will be compared across the randomized groups using t-test or chi-squared test (or their nonparametric / small sample counterparts) as appropriate, and will be adjusted in a regression model in addition to the primary comparisons above. It is known that even if the characteristics are balanced across the groups, such adjust can improve the efficiency of the comparisons [32]. For the secondary outcomes, frequencies (counts) of UTIs in the randomized period as well as the additional follow-up period will be compared between groups using a Poisson model; the QOL outcomes will be compared between groups using t-tests, and between baseline and 12 months within an active treatment group using paired t-test; adherence will be compared between the ring group and the active cream group as a dichotomous variable, with adherence for the latter group defined as $\geq$80%. While the primary comparisons are intent-to-treat, secondary comparisons will be carried out among those subjects who have adhered. In addition, for the variables that are collected at three or more time points, longitudinal data analysis will be performed using random effects models. As the attrition rate is expected to be as high as 20%, whether the missing data mechanism might be informative will be checking using methods such as those described by Ridout et al. [33] in case of informative (non-ignorable) missingness, sensitivity analysis will be carried out.

10. HUMAN SUBJECTS

Our total subject recruitment will be 48 subjects (assuming 20% drop out). However, if we do not such a drop out rate, once we reach 40 subjects total who have completed 6 months (achievement of the primary outcome), we will stop study enrollment.

Target and Study Population

The target population is postmenopausal women with the diagnosis of recurrent UTI as defined by 3 or more symptomatic UTIs within 1 year or 2 UTIs within 6 months. For purposes of this study, we will use the CDC definition of symptomatic UTI as defined above. Our study population will be selected from patients seen at the UCSD Women's Pelvic Medicine clinic as well as those referred from primary care offices at UCSD and those subjects recruited from Researchmatch, Craigslist and approved flyers. In addition, New York University Pelvic Medicine Center will also be recruiting patients from their clinic once IRB approved. A total of 184 new patients were seen with a diagnosis of recurrent UTI between July 2011 to June 2012 at the Women's Pelvic Medicine Clinic.

Inclusion Criteria

1. Postmenopausal status as defined by amenorrhea for $\geq$12 months, OR history of bilateral salpingoophrectomy, OR if the patient has had a hysterectomy defined by menopausal symptoms for >1 year OR age >55
2. Recurrent UTIs (3 or more in the last year or 2 or more in the last 6 months). Patients must have one culture documented UTI, but the others may be documented by urinalysis.
3. Ability to provide informed consent

Exclusion Criteria

1. Use of any investigational drug or device within thirty days of screening
2. Urologic surgery within the past 3 months of screening or plan for surgery within one year of screening
3. Diagnosis of Interstitial Cystitis/painful bladder syndrome
4. History of urinary tract infections which require the use of IV antibiotics or where only one oral antibiotic is available for treatment, or where the risk of treatment with vaginal estrogen only is deemed unacceptable by the principle investigator secondary to the severity of prior urinary tract infections
5. Known etiology of infection such as, but not limited to: kidney or bladder stones, enterovaginal/vesical fistula, fecal incontinence, intermittent catheterization, indwelling catheter, poorly controlled diabetes
6. Urothelial cancer
7. Actively treated estrogen sensitive tumor (breast or endometrial cancer)

8. Undiagnosed vaginal bleeding
9. Inability to use a vaginal ring (secondary to advanced prolapse or shortened vaginal length)
10. Any medical reason the investigator deems incompatible with treatment with vaginal estrogen
11. Prolapse requiring pessary use

Deferral Criteria

1. Undiagnosed hematuria – may enroll after malignancy is ruled out
2. Use of a progestin containing intrauterine device or use of any vaginal androgens, estrogens or progestins within 3 months of enrollment – may enroll after wash out
3. Use of drugs/supplements known to prevent UTIs (ie cranberry products, prophylactic antibiotics, methenamine hippurate) 1 month prior to enrollment – may enroll after wash out if still meets inclusion criteria.

History of estrogen sensitive tumor (breast or endometrial cancer) – requires approval by the subject's primary oncologist or primary care physician

11. RECRUITMENT

The subjects will be recruited from those patients referred to the Women's Pelvic Medicine clinic at UCSD, Thornton campus. Patients are frequently referred to this clinic by primary care physicians when they have repeated UTIs We will also send out an email to primary care physicians to inform them of the study and post flyers in primary care offices. We will also place an advertisement on Craigslist (see separate document) and we will use ResearchMatch for recruitment (please see separate document for recruitment message).

In addition, we will perform a search of the EPIC system to identify patients with the CPT code diagnosis of recurrent UTI and will contact their primary care physicians to inform them that their patient may be eligible for the study, allowing the primary care physicians to contact their own patients. This presents minimal risk to the patients as the diagnosis of recurrent urinary tract infection carries no stigma and their own physician would contact them about the study should they qualify. There will be no direct contact between the patients and the study staff, just between the study staff and the patients' physicians. We are requesting a waiver of consent for recruitment purposes as a consent form would be the only document linking these patients to the study and would therefore subject them to more risk than the waiver of consent as there is a risk of breech of confidentiality by having the consent document. Because of the large number of patients seen in the UCSD Health System, it would not be practical to try to consent them all to look at their charts for the diagnosis of recurrent urinary tract infection.

We are also requesting a partial waiver of HIPAA authorization. We will request a list of medical record numbers and names of patients with a diagnosis of recurrent urinary tract infections from EPIC. In addition, we will ask for the names of these patient's listed primary care providers. This list will be sent electronically over encrypted mail and will be downloaded onto a secure password protected computer. The primary care physicians will then be sent an email with the name of the patient (again over secure, encrypted email) along with the already approved text informing them about the study, letting them know that their patient may qualify. As soon as these emails are sent out, we will destroy the electronic document. We anticipate this process will take about one week. Again, because of the large number of patients seen in the UCSD Health System, it would not be practical to try to obtain HIPAA authorization to look at their charts for the diagnosis of recurrent urinary tract infection. In addition, this could not be done without the use of PHI as we need to inform the primary care physicians the names and medical record numbers of the patients so that they can contact them should they feel it is appropriate. The contacted patients may greatly benefit from receiving potential treatment for their recurrent urinary tract infections through this study. The privacy risk to these patients is minimal given that only EPIC and study staff will see the list and this part of recruitment will be complete and the list destroyed within a week. Amendment was submitted in July 2013 to add recruitment flyers to UCSD primary care and gynecology clinics.

Subjects will also be recruited at the NYU Pelvic Medicine Center where four collaborative board certified Female Pelvic Medicine and Reconstructive Surgery attendings see their patients (similar to the Women's Pelvic Medicine clinic at UCSD). Only deidentified data will be shared between the principal investigators at the sites.

12. INFORMED CONSENT

Women with recurrent UTI will be introduced to the study opportunity and referred to the physician investigator to be counseled about risks and benefits of enrollment in the study. Patients are typically approached for study participation in the context of their clinic visit and thus consent and study procedures are performed in a private setting as their clinic visit would be. The physician/investigator will explain in detail about the risks and benefits associated with participation in this study. Patients will specifically be consented to randomization to a vaginal ring or one of two vaginal preparations. We will also request that they sign a separate authorization for the use of personal health information as this research is subject to HIPAA privacy rule provisions. Patients who are recruited from outside institutions must provide documentation of UTIs at their recruitment visit and must sign an authorization for the transfer of urine culture and urinalysis results from their healthcare center.

13. ALTERNATIVES TO STUDY PARTICIPATION

The patient may receive vaginal estrogen by prescription. Other therapies in the prevention of recurrent UTI include antibiotic prophylaxis, either postcoital or daily dosing. They may also use cranberry, such as the FDA approved drug Elura, or cranberry supplements along with probiotics. Alternatively, they may take methenamine hippurate daily which is a bactericidal turning urine to formaldehyde and ammonia. Notably, none of these alternative approaches have proven more effective than vaginal estrogen.

14. POTENTIAL RISKS

The potential risk to all subjects is continued UTI. However, if a subject has 3 UTIs in a 6 month period, we will unblind them and if they are on placebo, we will place them on study drug. If they are already on study drug, they will be treated according to the attending physician's clinical practice and observed for the study.

Risks of vaginal estrogen are not separated from oral hormone replacement therapy (HRT) estrogen on the package insert and state that the risks include thromboembolism, retinal thrombosis, heart attack, stroke, hypertension, breast cancer, ovarian cancer, endometrial cancer, endometrial hyperplasia, uterine fibroid enlargement, hypercalcemia, cholestatic jaundice, pancreatitis, hepatic hemangioma enlargement, depression, dementia, migraine, chorea exacerbation, seizure exacerbation, asthma exacerbation, porphyria aggravation, systemic lupus erythematous exacerbation, anaphylaxis, erythema multiforme, erythema nodosum, ischemic colitis, intestinal obstruction, vaginal ulceration/erosion, toxic shock syndrome. However, numerous studies of transvaginal dosing with significantly lower (less than 1/7) doses than typically administered for oral hormone therapy have failed to identify any of the risks associated with full strength oral HRT. As discussed in the background section above, there have been no reported cases of endometrial hyperplasia, breast or endometrial cancer and systemic levels after 3 months of therapy are no different than those prior to initiation of therapy [9-14].

Reactions reported in randomized controlled trials of vaginal estrogen include application site reaction, vaginal bleeding/spotting, breast changes/pain, abdominal bloating/cramps, nausea/vomiting, cervical secretion changes, headache/migraine, fluid retention, elevated blood pressure, mood changes, candidiasis, glucose intolerance, weight changes, libido changes, contact lens intolerance, vision changes, rash, melasma/choasma, hair loss and hirsutism. These were significantly different from placebo.

There is also the risk of loss of confidentiality, as with any study. Specimens will be labeled only with the subject's unique identifying study number and no PHI will be transferred to Loyola University.

The risks associated with specimen collection are minimal and mostly related to inconvenience of providing a urine specimen and discomfort associated with a pelvic examination, however most of these subjects will be having a pelvic examination as part of their clinical care or with placement of the vaginal estrogen ring. Subjects may opt out of having specimens collected at any time.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Monitoring Plans for Safety
Data safety and monitoring for adverse events will be overseen by a committee composed of the PI, the study statistician and research mentor. The study staff will conduct monthly telephone interviews with the subjects during the first 3 months of the study to ascertain any adverse events in the treatment arms. The subjects will then be encouraged to call should they experience any adverse reactions. The PI will be notified of any adverse events, which will be reviewed on a case-by-case basis. Any serious adverse events requiring hospitalization and/or surgical intervention will be reported to the institutional IRB within 24 hours of identification of the event. Data will be reviewed on a quarterly basis to assess for completeness, accuracy, or any trends that may require alteration of study protocol, including number of UTIs in each subject. Any errors, omissions or adverse events will be brought to the attention of the PI.

Adequacy of Resources
Statistical support for this project will be provided under the direction of Dr. Xu together with the UCSD Clinical and Translational Institute (CTRI). A team approach will be used with biostatistics, faculty member (Xu, Director of CTRI Design, Biostatistics and Ethics) partnered with an experienced staff statistician. This team approach provides a number of advantages. The faculty member brings knowledge and skill in the application and interpretation of contemporary biostatistical tools, while the trained staff statistician can efficiently implement any required data analysis. The budget for this project covers a 100 hour commitment of a staff statistician to carry out the data analysis under Dr. Xu's supervision.

Other resources include an administrative assistant, library facilities and office space with workstations with computers, internet, printer, copier, fax, as well as secure filing cabinet and basic supplies needed to conduct research for data analysis and writing.

Patients with pelvic floor disorders are seen at the UCSD Women's Pelvic Medicine Center, housed at Chancellor Park. This clinic is equipped to see patients with pelvic floor disorders and has the ability to perform the spectrum of diagnostic tests and therapeutic procedures. In addition, they offer a full range of therapies from behavioral and medical to minimally invasive surgeries and total pelvic floor reconstruction. Annually, UCSD Women's Pelvic Medicine physicians see over 830 new patients with 4900 patient encounters. One hundred and eighty four of these new patients had a diagnosis of recurrent UTI in the last year from July 2011 to June 2012.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

There is also a risk of loss of confidentiality, however, the data obtained from this study will be identified with a subject identifier that does not contain identifiable information. The key which links the subject identifiers to protected health information will be kept in a binder in a locked cabinet in a locked physician's office within the Women's Pelvic Medicine Center clinic in Chancellor Park. All subject paper forms for the study and any paper data collected will also be kept in a binder separate from identifiable information in the locked cabinet. Only the study staff (co-investigators) will have access to the records. In terms of the electronic data captured, the database will be encrypted and placed on a password protected secure server provided by UCSD. Select study staff will have access to the database, including the PI and those entering data, as well as those study staff who are on the Data Safety Monitoring Committee. This database will not include the subjects' names, or medical record numbers as they will be identified by a subject identifier. The key linking the subject's name and medical record number to the identifier will be kept on the same password protected secure server as a separate file, as well as paper copy kept in a locked cabinet in the clinic discussed previously. This will not be destroyed until all data analyses have been completed. PHI will be coded only to subject identifiers and will be kept in a separate file. The statisticians at UCSD will also have access to de-identified data. HIPAA authorization will be obtained in order to collect clinical outcomes of interest for this study (ie UTIs, clinic visits), however all of this data will be transferred to a case report form using subject identifier.

All women evaluated in the Women's Pelvic Medicine Clinic for recurrent UTIs, as well as other pelvic floor disorders, are seen, evaluated an counseled in private examination rooms as part of routine clinical care. Estrogen ring changes for clinical care are always done in a private exam room setting and will be performed

in the same way for this study.

17. POTENTIAL BENEFITS

Potential benefits include prevention of recurrent UTIs. Vaginal estrogen is also known to relieve vulvovaginal atrophy and associated symptoms including dyspareunia. Data from this study will help to inform appropriate treatment protocols and options for millions of women who suffer from recurrent UTI.

18. RISK/BENEFIT RATIO

The risks of systemic effects from vaginal estrogen are low. In clinical practice, vaginal estrogen is routinely prescribed for vaginal atrophy. Currently in our clinics, we also use it to treat recurrent UTI, although there is only one randomized trial to support this practice, which used higher doses of estrogen and only the cream form. Recurrent UTIs can seriously affect the day to day quality of life of patients. Thus, we feel that the benefit to the subjects is greater than the risks of rare serious adverse reactions. Also, since we already use this in clinical practice, knowing whether vaginal estrogen truly does prevent recurrent UTI is a benefit to current and future patients. Thus the overall risk benefit ratio favors study participation.

19. EXPENSE TO PARTICIPANT

There will be no expense to the subject over and above standard clinical care other than the cost of time, gas and parking for 4 extra visits. We plan to compensate the participants for these costs (see below).

20. COMPENSATION FOR PARTICIPATION

The subjects will receive $40 for their 3 month and 6 month visits in the study. They will then be paid $20/visit at their 9 and 12 month visits. The change monetary compensation is to incentivize follow up for the primary outcomes in the first 6 months. In general, subjects will be compensated for visits because they are visits which would not be occurring without participation in the study and the compensation is designed to cover the costs of time, gas and parking.

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22. FUNDING SUPPORT FOR THIS STUDY

This study will be funded by a 2 year grant awarded by the American Urogynecologic Society (AUGS). The dates of the funding are March 1, 2013 to February 28, 2017. This is an investigator initiated trial. Pfizer is donating drug for the trial only and is not participating in the trial in any other way. The company will provide no coverage for any adverse events associated with the study.

23. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

N/A

24. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Drug inserts for Estring and Premarin will be provided (see 2 separate attached files).

We will not be seeking an IND as we qualify for exemption per the FDA requirements: 1) The studies are not intended to support FDA approval of a new indication or a significant change in the product labeling. 2) The studies are not intended to support a significant change in the advertising for the product. 3) Investigators and their IRBs determine that based on the scientific literature and generally known clinical experience, there is no significant increase in the risk associated with the use of the drug product. 4) The studies are to be conducted in compliance with IRB and informed consent regulations.5) The studies will not be used to promote unapproved indications.

While we are looking at vaginal estrogen to prevent recurrent UTI, the mechanism by which vaginal estrogen cream and the estradiol ring will do so is by treating vaginal atrophy, an indication for which both drugs are already FDA approved. In essence we are looking at if the treatment of atrophic vaginitis by vaginal estrogen will prevent recurrent UTI.