The Efficacy and Cost-Effectiveness of a 24-hour course of Methenamine Hippurate For Preventing Post-Operative Urinary Tract Infection

NCT02358993

April 4, 2019

Protocol Details

Basic Info

Confirmation Number:	**cihdibib**
Protocol Number:	**820117**
Created By:	**CHU, CHRISTINE M**
Principal Investigator:	**ARYA, LILY A**
Protocol Title:	**The Efficacy and Cost-Effectiveness of a 24-hour course of Methenamine Hippurate For Preventing Post-Ope Urinary Tract Infection**
Short Title:	**Short-Course Methamine Hippurate for Prevention of Post-Operative UTI**
Protocol Description:	**We will determine the efficacy of an innovative short regimen of methenamine hippurate on prevention of post-operative UTI in patients requiring short-term catheterization after pelvic reconstructive surgery through a randomized, double-blinded, placebo-controlled trial. Primary outcome will be the rate of symptomatic UTI within 3 weeks of surgery. We will study cost-effectiveness, antibiotic resistance profiles, and adverse drug effects. Findings may reduce antibiotic use and nosocomial UTIs.**
Submission Type:	**Biomedical Research**
Application Type:	**FULL**

Resubmission*
Yes

Hospital Sites
Will any research activities and/or services be conducted at a Penn Medicine affiliated hospital site?
No

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Name of course completed:	**CITI Protection of Human Subjects Research Training - ORA**

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Disclosure of Significant Financial Interests*
Does any person who is responsible for the design, conduct, or reporting of this research protocol have a **FINANCIAL INTEREST**?
No

Penn Intellectual Property*
To the best of the Principal Investigator's knowledge, does this protocol involve the testing, development or evaluation of a drug, device, product, or other type of intellectual property (IP) that is owned by or assigned to the University of Pennsylvania?

Certification
I have reviewed the *Financial Disclosure and Presumptively Prohibited Conflicts for Faculty Participating in Clinical Trials* and the *Financial Disclosure Policy for Research and Sponsored Projects* with all persons who are responsible for the design, conduct, or reporting of this research; and all required Disclosures have been attached to this application.
Yes

Biomedical Research

Clinical Trial*
Is this a clinical trial?

Investigator Initiated Trial*
Is this an investigator initiated trial?
Yes

If Yes, please be aware that the investigator may be required to create and manage a record of this trial in https://clinicaltrials.gov.

Drugs or Devices*
Does this research study involve Drugs or Devices?
Yes: Drugs, products or devices are used in accordance with FDA approval.

IND Exemption

For studies that fall under an IND exemption, please provide the number below

For studies including IND or IDE's, please provide the number(s) below

IDE Review*
NOTE: For research involving investigational devices, you are required to review the guidance on Managing Research Device Inventory. Consult the Penn Manual for Clinical Research: https://www.med.upenn.edu/pennmanual/secure/investigational-product-management-at-sites-not-using-investigational-drug-services-(ids).html Please check the box Yes if you have reviewed the guidance.
Yes

Research Device Management*
Please indicate how research device(s) will be managed.
Not Applicable (no investigational devices)

Drug, Herbal Product or Other Chemical Element Management *
Please indicate how drugs, herbal products or other chemical entities will be managed.
The drug, herbal product or other chemical entity will be received, stored and dispensed by the research team (please provide information in the protocol summary as to how this will be conducted)

Radiation Exposure*
Are research subjects receiving any radiation exposure (e.g. X-rays, CT, Fluoroscopy, DEXA, pQCT, FDG, Tc-99m, etc.) that they would not receive if they were not enrolled in this protocol?
No

Gene Transfer*
Does this research involve gene transfer (including all vectors) to human subjects?
No

Human Source Material*
Does this research include collection or use of human source material (i.e., human blood, blood products, tissues or body fluids)?
Yes

CACTIS and CT Studies*
Does the research involve Center for Advanced Computed Tomography Imaging Services (CACTIS) and CT studies that research subjects would not receive if they were not part of this protocol?
No

CAMRIS and MRI Studies*
Does the research involve Center for Advanced Magnetic Resonance Imaging and Spectroscopy (CAMRIS) and MRI studies that research subjects would not receive if they were not part of this protocol?
No

Investigational Agent or Device within the Operating Room*
Does the research project involve the use of an investigational agent or device within the Operating Room?
No

Cancer Related research not being conducted by an NCI cooperative group*
Does this protocol involve cancer-related studies in any of the following categories?
No

Processing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
Yes

In-House Manufacturing of Materials*
Will the research involve processing (such as over encapsulating, or compounding)?
Yes

Medical Information Disclosure*
Does the research proposal involve the use and disclosure of research subject's medical information for research purposes?
Yes

If the answer is YES, indicate which items is is provided with this submission:

Modified research informed consent document that incorporates HIPAA requirements

CTRC Resources*
Does the research involve CTRC resources?
No

Pathology and Laboratory Medicine Resources*
Will samples be collected by hospital phlebotomy and/or processed or analyzed by any of the clinical laboratories of the University of Pennsylvania Health System?
Yes

Clinical Laboratory Services*
Will samples be collected by UPHS phlebotomy and/or analyzed by the hospital laboratory?
No

Anatomic Pathology Services*
Will tissue specimens (other than blood) be collected for clinical, diagnostic, or research purposes OR be processed through surgical pathology, cytopathology, neuropathology, or hematopathology?
No

Research Involves Apheresis, Cell Collection, and/or Blood Product Collection*
Does this research involve collection of blood products in the Penn Donor Center and/or the use of apheresis for treatment or collection of cells or other blood components?
No

Research involving blood transfusion or drug infusions*
Will your research involve blood transfusion or infusion of study drug in 3 Ravdin Apheresis Unit for research purposes?
No

Trial in Radiation Oncology
Is this research a prospective trial being done in Radiation Oncology, and if so, has this protocol been approved by the Radiation Oncology Protocol committee?
N/A

Study in Radiation Oncology
Is this research a retrospective study being done in Radiation Oncology, and if so, has this project been reviewed by the Radiation Oncology Clinical Research Group?
N/A

Use of UPHS services*
Does your study require the use of University of Pennsylvania Health System (UPHS) services, tests or procedures*, whether considered routine care or strictly for research purposes?
Yes

Primary Focus*
Clinical Trial (prospectively assigning subjects to health-related interventions to evaluate outcomes)

Protocol Interventions

	Sociobehavioral (i.e. cognitive or behavioral therapy)
x	**Drug**
	Device - therapeutic
	Device - diagnostic (assessing a device for sensitivity or specificity in disease diagnosis)
	Surgical
	Diagnostic test/procedure (research-related diagnostic test or procedure)
	Obtaining human tissue for basic research or biospecimen bank
	Survey instrument
	None of the above

The following documents are currently attached to this item:

There are no documents attached for this item.

Department budget code

None

Multi-Center Research

Penn as lead
1. Is this a multi-center study where Penn is serving as the Lead Site or the Penn PI is serving as the Lead Investigator?

Management of Information for Multi-Center Research
Not Applicable

Penn irb of record
2. Is this a multi-center study where the Penn IRB will be asked to serve as the IRB of Record for other external study sites?

Other Sites

No other sites

Protocol

Abstract
Catheter-associated urinary tract infection (UTI) is the most common post-operative nosocomial infection. An agent that prevents catheter-associated UTI but is not associated with antibiotic resistance is not known. Methenamine hippurate has similar pharmacokinetics as short-course antibiotics that prevent catheter-associated UTI, such as ciprofloxacin. Our aim is to compare the efficacy of an innovative short regimen of methenamine hippurate, an antiseptic that is converted into formaldehyde in urine, with the efficacy of short-course ciprofloxacin for preventing post-operative UTI in urogynecologic surgery. We propose a randomized, blinded non-inferiority trial to determine the efficacy of two doses of methenamine hippurate compared with the urology standard of fluoroquinolones at catheter withdrawal for reducing post-operative UTI in patients requiring short-term indwelling catheterization after pelvic reconstructive surgery. The primary outcome will be the rate of symptomatic UTI requiring treatment within three weeks of surgery. We will perform cost-effectiveness analysis comparing the cost of prophylaxis with methenamine to the cost of prophylaxis with ciprofloxacin. We plan to describe the resistance profile of positive urine cultures and adverse effects of methenamine. This study is innovative because it involves 1) a two-dose regimen of a non-antibiotic prophylactic and 2) cost-effectiveness analysis. The findings will help reduce the rate of antibiotic use and nosocomial UTIs, which are associated with morbidity and serve as important indicators of quality of care.

Objectives

Overall objectives
SPECIFIC AIMS Primary Aim: To determine if the efficacy of prophylaxis with a 24 hour course of methenamine hippurate (two doses) is non-inferior to the efficacy of a 24-hour course of fluoroquinolones in prevention of post-operative urinary tract infections after short-term indwelling catheterization following surgery for pelvic floor disorders. Secondary aim: - To determine if prophylaxis with methenamine hippurate is more cost-effective than prophylaxis with fluoroquinolones

in patients undergoing short-term indwelling catheterization. - To determine the antibiotic resistance profile of post-operative urinary tract infections that develop after short-term indwelling catheterization after surgery for pelvic floor disorders, with methenamine as compared to fluoroquinolones. - To determine the prevalence of side effects that may accompany use of methenamine hippurate prophylaxis. - To describe factors that influence patient medication compliance with short-term methenamine hippurate and ciprofloxacin prophylaxis.

Primary outcome variable(s)

PRIMARY OUTCOME: Treatment of clinically suspected UTI within three weeks of surgery. This is defined as any symptomatic UTI requiring treatment with antibiotics as determined by the development of 2 or more of the following symptoms, in the absence of vaginal symptoms: urinary frequency; urinary urgency; dysuria; fever over 38ºC/100.4ºF; suprapubic, flank, or back pain; and/or chills. Patients will be encouraged to undergo urine culture prior to empiric treatment, but a positive urine culture will not be required as part of the primary outcome. We feel that this more accurately reflects the diagnosis and treatment of UTI in the clinical setting as: 1) it may not always be possible to delay treatment until patients are able to undergo urine culture; 2) accuracy of self-reported symptoms for the diagnosis of UTI is high;28 3) the probability of UTI in patients with combinations of symptoms is very high.29

Secondary outcome variable(s)

SECONDARY OUTCOME: - cost-effectiveness of prophylaxis with methenamine hippurate for prevention of post-operative UTI compared to prophylaxis with fluoroquinolones - rate of culture-positive symptomatic UTI - prevalence of antibiotic resistance in positive post-operative cultures - prevalence of side effects following a 24-hour course of methenamine hippurate - factors that may influence patient compliance with short-course of chemoprophylaxis. Cost-effectiveness data: We plan to perform a cost-effectiveness analysis from a societal perspective, which will be expressed as incremental cost per UTI prevented. Routine costs of prevention of UTI with methenamine hippurate prophylaxis will be compared with costs of prevention of UTI with fluoroquinolone prophylaxis. We plan to capture incremental direct health care costs, which will be estimated using the resource costing method. Direct medical service standard of care use (such as number and types of physician visits, hospital admissions lengths, emergency transport and emergency room visits), and direct medical costs (such as antibiotic treatment of UTI, prophylaxis with methenamine or ciprofloxacin, urine laboratory tests, or treatment of complications like pyelonephritis) will be monetized by multiplying the number of units of each resource used per treatment arm by the average unit cost of these items in dollars. Detailed individual cost data will not be collected. This method allows a consistent capture of resource use when costs are incurred across multiple health systems or payers. Cost for each direct medical service use, direct non-medical items, and indirect items will be assigned based on national Medicare reimbursement rates or other standardized unit costs. Among patients who undergo urine culture as part of standard of care for UTI, the rate of positive cultures will be identified. As per standard of care, antibiotic resistance will be collected by sensitivity testing on all positive urine cultures identified from samples collected for evaluation of symptomatic UTI in post-operative patients. Bacterial species and sensitivities will be identified and recorded. To determine medication compliance rates, any unused medication will be returned to the office at their post-operative follow-up visit. As per routine care, investigators will also ask patients during the weekly routine post-operative call and routine post-operative visits about their compliance with the second dose of medication. Adverse effects from the administration of methenamine and fluoroquinolones will be collected. Patients will be asked to document any side effects, including nausea, vomiting, pruritis, and rash, that may occur within 24 hours of the administration of the last dose of methenamine or antibiotic.

Background

URINARY TRACT INFECTIONS ASSOCIATED WITH SHORT-TERM INDWELLING CATHETERIZATION: Catheter-associated urinary tract infection (UTI) is the most common nosocomial infection in the United States. The risk of UTI in women following pelvic reconstructive surgery is 9-48%.(1-4) Almost 50% women who undergo pelvic reconstructive surgery develop urinary retention that requires short-term catheterization. (2) In a recent study, over 80% women who required catheterization after pelvic reconstructive surgery used an indwelling catheter for at least 24 hours. (5) The risk of bacteriuria is estimated to be 5-10% for each day of indwelling catheterization. (6,7) UTIs occur frequently after catheter removal, (8,9) likely due to dislodgement of bacterial colonization in biofilms in the catheter. COMPLICATIONS AND COSTS ASSOCIATED WITH UTI: Prevention of post-operative UTI is important for both patient and health care systems. UTIs increase the economic

burden on both patients and physicians, as each episode of UTI costs approximately $600. (10) Complications from short-term catheterization include pyelonephritis, perinephric abscesses, and bacteremia (UTIs are the cause of 15% of all nosocomial bloodstream infections). (11) Catheter-associated UTI (CAUTI) has become costly for hospitals as well; since October 1, 2008, the Centers for Medicare and Medicaid Services (CMS) have not provided hospitals compensation for CAUTIs. (10) As part of hospital quality measurement, the National Healthcare Safety Network monitors and reports CAUTIs, and prevention of CAUTI is one of the National Patient Safety Goals set by the Joint Commission. PROPHYLAXIS FOR PREVENTION OF POST-OPERATIVE UTI: Catheter-associated UTI likely occurs during catheter removal when bacteria colonized in the catheter are dislodged into the bladder. Chemoprevention with antibiotics or antiseptics such as methenamine can potentially decrease the chance of UTI after post-operative catheterisation. However, prophylaxis is not routinely used for prevention of urinary tract infections after catheterization. In a study by Wazait et al, 40% of providers involved in the management of indwelling catheters do not use prophylactic antibiotics for catheter removal.(12) A Cochrane review examining the use of prophylactic antibiotics for short-term catheterization showed weak and limited evidence that it reduced the rate of bacteriuria, and suggested caution in interpreting the results because of the limited literature.(13) American Urologic Association (AUA) and the American College of Obstetrics and Gynecology (ACOG) recommend consideration of prophylactic antibiotics for catheter removal, but does not require antibiotic use. AUA guidelines suggest that first-line antibiotics such as either fluoroquinolones (like ciprofloxacin or levofloxacin) or trimethoprim-sulfamethoxazole may be warranted at the time of catheter removal following urinary tract surgery, especially in patients with risk factors such as advanced age, anatomic anomalies, and immunodeficiencies; however, treatment may also be deferred and based on urine culture at catheter removal.(14) ACOG guidelines suggest that daily antibiotic prophylaxis should be considered in women discharged with an indwelling urinary catheter after urogynacologic surgery.(15) The above recommendations for chemoprophylaxis for short-term post-operative catheter use are mostly based on non-gynecologic populations and there are no specific recommendations on the choice and dose of the agent. However, several randomized controlled trials have explored the efficacy of short courses of antibiotic prophylaxis at catheter removal for preventing UTI. In a recent meta-analysis of 7 studies, Marschall et al concluded that antibiotic prophylaxis at catheter removal was beneficial in reducing symptomatic UTI, with subgroup analysis indicating significant benefit in post-surgical patients but not in general mixed hospital populations. (16) Of the four RCT or prospective cohort studies looking at gynecologic or urogynecologic populations solely, 3 showed some benefit to antibiotic prophylaxis, while 1 showed showed no benefit to antibiotic use. (17-20) COMPLICATIONS OF ANTIBIOTIC PROPHYLAXIS: Though a short course of antibiotic prophylaxis at catheter removal may be effective for preventing post-operative UTI, widespread adoption of antibiotic prophylaxis would increase the risk of antibiotic resistance. Multi-drug resistance is already prevalent in North America; in 2000, the SENTRY study reported that in nosocomial UTIs, rates of antibiotic resistance of four common uropathogens were 59, 31, 43 and 29% for ampicillin, amoxicillin/clavulanate, trimethoprim-sulfamethoxazole, and ciprofloxacin, respectively. (21) The rising cost of increased antibiotic use must also be considered, as well as the potential for adverse medication effects, which can be severe. METHENAMINE IS NOT AN ANTIBIOTIC: A possible alternative to antibiotics is methenamine hippurate, a urinary antiseptic currently used for prophylaxis for recurrent urinary tract infections. The mechanism of action of methenamine hippurate is through the formation of formaldehyde in the presence of acidic urine. Hippurate, also known as hippuric acid, acidifies the urine, which allows for greater production of formaldehyde. Methenamine hippurate is relatively inexpensive at about $2 per pill (22) (compared to $3-17 per pill for commonly used antibiotic prophylaxis). (23-25) While resistance to methenamine hippurate can be induced with some difficulty in vitro, it has not been reported in vivo. (26) Daily methenamine reduces UTI after gynecologic surgery: Daily methenamine hippurate throughout catheterization has been shown to be effective for decreasing post-operative UTI after gynecologic surgery .Three studies reported that daily methenamine decreases post-operative UTI as well as post-operative bacteriuria, (2,27,28) while one additional study showed significant difference in bacteriuria but did not report the rate of symptomatic UTI. (29) A Cochrane meta-analysis confirmed that methenamine reduces the risk of post-operative UTI. Two subgroup analysis in mixed surgical and non-surgical populations that excluded the presence of renal tract abnormalities and neurogenic bladder showed significant reduction in symptomatic bacteriuria (RR 0.24, CI 0.07-0.89) and bacteriuria (RR 0.56 CI 0.37-0.83).(30) Subgroup analysis of the effect of treatment less than 7 days, which essentially limited analysis to studies only involving patients with post-surgical short-term indwelling catheter, showed even greater benefits, with the risk ratio for bacteriuria and symptomatic bacteriuria be 0.48 (CI 0.23-0.99) and 0.14 (CI 0.05-0.38), respectively.(30) These studies used a wide variety of regimens of methenamine ranging from 1g to 4g

daily in divided dosages.(30) Duration also ranged widely, generally initiated before catheterization to several days after catheterization, with treatment courses ranging from a minimum of five to as many as thirteen days.(30) INNOVATION Although catheter-associated UTI are an important indicator of quality of care, and health care systems are not reimbursed for these nosocomial infections, an effective agent that prevents catheter-associated UTI but does not increase antibiotic resistance has not been identified. We plan to investigate the efficacy of a short course of methenamine (two doses in a 24-hour period) for preventing UTI after short-term indwelling catheterization. Additionally, investigation of short course antibiotic prophylaxis at catheter removal in the urogynecologic population is innovative, since it is common practice in urology, but has not been studied significantly in the urogynecology population, where commonly daily prophylaxis is given. RATIONALE FOR A 24-HOUR DOSE OF METHENAMINE HIPPURATE: For several reasons, we anticipate that two doses of methenamine hippurate, with the first dose administered 2 hours prior to catheter removal, will reduce the rate of UTI following short-term catheterization, and will be non-inferior to antibiotic prophylaxis with fluoroquinolones. 1) Unlike antibiotics commonly used for UTI prophylaxis, methenamine becomes active only in the bladder, and thus concentrates its full antimicrobial effect in the area of choice. 2) Short courses of antibiotics administered 1-2 hours prior to catheter removal have been shown to reduce the rate of UTI post-catheterization.(9,16) 3) The pharmacokinetics of methenamine is similar to that of antibiotics used in short courses for prophylaxis, such as ciprofloxacin, trimethoprim-sulfamethoxazole (TMP-SMX), and nitrofurantoin. Methenamine hippurate has a half-life of 4.5 hours, and reaches the antimicrobial concentration (MIC of formaldehyde) of 13 microgram/mL 30 minutes to 1 hour after oral intake. A single 2 gram dose will yield 18-60 micrograms/mL (with typical daily doses as one dose every 12 hours). Methenamine is renally cleared, with 90% excreted within 24 hours. (26) Comparable antibiotics have half-lives ranging from 3 - 5 hours (ciprofloxacin), 8-10 hours (TMP-SMX), and 20 minutes-1 hour (nitrofurantoin), with serum drug levels peaking at 20 minutes to 4 hours. (31-33) Elimination is also comparable, ranging from 30-40% in urine (nitrofurantoin), (31) 40-50% in urine (and 20-50% in feces within 5 days for ciprofloxacin), (32) 80%/67% in urine (sulfamethoxazole and trimethoprim, respectively, within 72 hours). (33) 4) Prior studies suggest that acidification of urine by additional acidifying agents is not required for effectiveness of methenamine hippurate. (34) This suggests that two doses of methenamine hippurate, with the first dose initiated 2 hours prior to catheter removal is reasonable and potentially effective for preventing post-operative UTI. Benefits of a 24-hour dose of methenamine: A short course of methenamine hippurate for preventing post-operative UTI will decrease the cost and complications of post-operative UTI; minimize drug resistance, adverse effects and cost of treatment; and likely increase medication compliance. There are currently no studies to demonstrate the effectiveness of a short-course of methenamine hippurate as chemoprophylaxis for post-operative UTI. If successful, a short course of methenamine hippurate would be a revolutionary and attractive non-antibiotic chemoprophylaxis alternative to a short-course of a commonly used antibiotics such as the fluoroquinolones or a longer course of methenamine. Justification for Non-Inferiority Trial We believe that a non-inferiority trial between two active arms would be more clinically useful than a placebo-controlled trial. As stated above, both methenamine and fluoroquinolones (such as ciprofloxacin or levofloxacin) are accepted to be effective in reducing the rate of bacteriuria. Additionally, current urology practice is to give a first-line antibiotic (either the fluoroquinolones or trimethoprim-sulfoxazole) at catheter withdrawal at prophylaxis. Our study is innovative in that this Is not current standard practice in urogynecology; having two active arms would change antibiotic use in urogynecology by showing the effectiveness of a lower dose of antibiotic prophylaxis for catheter removal, as well as comparing this to the effectiveness of an antibiotic alternative for catheter removal prophylaxis in the urogynecologic population. Both of the results from these active arms would help to decrease use of antibiotics in current urogynecology practice. References [1] Sutkin G, Alperin M, Meyn L, Wiesenfeld HC, Ellison R, Zyczynski HM. Symptomatic urinary tract infections after surgery for prolapse and/or incontinence. Int.Urogynecol.J. 2010;21 955-61. [2] Schiotz HA. Comparison of 1 and 3 days' transurethral Foley catheterization after retropubic incontinence surgery. Int.Urogynecol. J. Pelvic Floor Dysfunct. 1996;7 98-101. [3] Schiotz HA, Guttu K. Value of urinary prophylaxis with methenamine in gynecologic surgery. Acta Obstet.Gynecol.Scand. 2002;81 743-6. [4] Anger JT, Litwin MS, Wang Q, Pashos CL, Rodriguez LV. Complications of sling surgery among female Medicare beneficiaries. Obstet.Gynecol. 2007;109 707-14. [5] Dieter AA, Amundsen CL, Edenfield AL, Kawasaki A, Levin PJ, Visco AG, et al. Oral antibiotics to prevent postoperative urinary tract infection: a randomized controlled trial. 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Study Design

Phase*
Not applicable

Design
This study will be conducted as a randomized, blinded study among patients requiring short-term indwelling transurethral catheterization following pelvic reconstructive surgery.

Study duration
RECRUITMENT We plan to recruit women from 5 sites in 3 departments in the University of Pennsylvania Health System: 1) Urogynecology at Hospital of University of Pennsylvania (HUP), 2) Urogynecology at Pennsylvania Hospital (PAH) and 3) Urology at Pennsylvania Hospital (PAH). Last year, the combined surgical volume of these cases at our three clinics was 532 subjects; thus, we anticipate we will be able to easily recruit and collect data from the proposed sample size of 144 (72 participants per arm) in about eight months. FOLLOW UP VISITS: Patients will follow up for a total of 6 weeks after surgery through three weekly follow-up calls and one 6-week postoperative visit. Urogynecology nurses will contact study participants once a week for the first three weeks following surgery per routine practice in our offices. Six weeks following surgery, patients will return to the office for a routine post-operative assessment with the investigating physicians. PROJECT DATES Research Proposal March 2014 IRB Approval August/September 2014 Data Collection September 2014 - September 2015 Data Entry November 2014 - October 2015 Data Analysis November 2015 Abstract Submission December 2015

Resources necessary for human research protection
Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.
Key Personnel: Primary Investigator: Christine Chu, MD Co-Investigator, Mentor: Lily Arya, MD, MS Co-Investigator, Mentor: Heidi Harvie, MD, MBA, MSCE (Cost-effectiveness analysis) Co-Investigator, Mentor: Darren Linkin, MD, MSCE (Infectious Diseases) Co-Investigator: Ariana Smith, MD Co-Investigator: Pamela Levin, MD Co-Investigator: Uduak Andy, MD Co-Investigator: Avita Pahwa, MD The above investigators, as well as the urogynecologic nurses who help with routine clinical care and will be in touch per routine care with post-operative patients, will be made informed of protocol and research-related duties through reading material as well as research meetings after the protocol is approved. Additionally, the primary investigator will be in touch with each of the support staff and co-investigators weekly to help coordinate duties, provide updates, and to answer any questions that may occur through the course of this study. The proposed clinical study is a multi-disciplinary collaboration between the Divisions of Urogynecology (OB/GYN), Urology (Surgery) and Infectious Diseases (Internal Medicine). We will recruit patients from five sites, including: the Division of Urogynecology (OB/GYN) at the Hospital of University of Pennsylvania (HUP) the Division of Urogynecology (OB/GYN) at Pennsylvania Hospital (PAH) the Division of Urogynecology (OB/GYN) at Chestnut Hill Hospital (CHH) the Division of Urology (Surgery) at Pennsylvania Hospital (PAH). the Division of Urology (Surgery) at the Hospital of University of Pennsylvania (HUP) Last year, the combined surgical volume of these cases at our three clinics was 532 subjects; thus, we anticipate we will be able to easily recruit the proposed sample size in eight months. Therefore, there should be enough time to recruit, as well as conduct and complete research, within the next year. The University of Pennsylvania Health System (UPHS) is an academic tertiary care referral center that draws patients from a wide geographic area. The four urogynecology clinics are located at the Hospital of the University of Pennsylvania, an inner city teaching hospital; Pennsylvania Hospital, a largely private urban hospital; and Chestnut Hill Hospital, a suburban community hospital. The Division of Urogynecology offices cares for the full spectrum of pelvic organ prolapse, urinary incontinence, fecal incontinence, and other pelvic floor dysfunction related disorders. The Division of Urology has female urology clinics at both the Hospital of the University of Pennsylvania and Pennsylvania Hospital, as well as inpatient services at Pennsylvania Hospital. The clinical and research infrastructure of these two hospitals are completely integrated with electronic inpatient and outpatient medical records, shared clinical responsibilities, on-call schedule. Additionally, we have a staff of clinical and research nurses to help coordinate with patient follow-up visits and routine post-operative care. No radiologic or

laboratory facilities will be used in this study. The Division of Infectious Diseases (Internal Medicine) has over 20 academic and research faculty who offer consultative services to departments conducting clinical trials and/or translation research, including extensive expertise in hospital-acquired infections and antibiotic resistance research. Clinical research facilities of the Division of Urogynecology are located in close proximity to all patient activity. Fellows have their own dedicated desk stations and a state-of-the-art computer and printer. The PC has word-processing, spreadsheet, and statistical database analysis programs (STATA). The fellows have full access to secretarial support, information services, slide preparation and poster presentations assistance, and videotaping/editing services. Each fellows computer is connected to the main hospital network, which allows for easy and rapid retrieval of inpatient data, biomedical library access, and free access to the Internet. Literature searches may be conducted from the fellows office through these means. Additionally, the Biomedical Library is in close proximity and has extensive facilities for literature searches, journals, and inter-library loan. The library periodically holds courses on updated methods of database searches, and experienced medical librarians are always on staff. The Clinical Center for Epidemiology and Biostatistics (CCEB) provides a Clinical Research Certificate Program for clinicians associated with the university and provides a foundation in biostatistics, research methodology, epidemiology and grant writing to allow those completing to coursework to have the tools to pursue a career as an independent researcher. CCEB will provide biostatistics support for this project. The CCEB has been actively involved in clinically- and pharmacologically-oriented research since 1978. As a Type II Center, it is the primary home for epidemiology and biostatistics at the University of Pennsylvania. It is an interdisciplinary and interdepartmental program of more than 275 individuals and includes clinical and non-clinical faculty, fellows, research staff, biostatisticians, and clerical staff. Many studies in the CCEB have focused exclusively on women's health issues. Additionally, should patients require additional medical services as a consequence of the research, such as adverse reactions to medications, patients will have 24-hour access to the on-call physician or to the medical offices of the co-investigators, where the patients can be examined and referred to additional medical services if necessary.

Characteristics of the Study Population

Target population
Adult patients requiring short-term indwelling transurethral catheterization for at least 24 hours following pelvic reconstructive surgery for pelvic organ prolapse, incontinence, or both.

Subjects enrolled by Penn Researchers
370

Subjects enrolled by Collaborating Researchers
0

Accrual
This trial will be an non-inferiority trial, intended to determine if a short course of methenamine hippurate is no worse than a short course of fluroquinolones (ciprofloxacin at Pennsylvania Hospital, levofloxacin at HUP, based on current practice and fluoroquinolone availability at each site) in prevention of post-operative UTI in short-term indwelling catheterization. Our primary outcome is the treatment of UTI by symptoms, a clinically relevant outcome. In the only study to look at this primary outcome after treatment with prophylactic antibiotics during short-term catheterization in urogynecologic surgery, the percentage of patients requiring treatment for UTIs after prophylactic antibiotics was 22%. If we assume a non-inferiority margin of 15%, a clinically relevant margin and commonly used in non-inferiority/equivalence trials for studies examining antibiotic use for urinary tract infections, as well as 80% power and a one-sided alpha of 0.025, 120 participants in each arm (total of 240 patients) will be required. Of all patients that undergo pelvic reconstructive surgery at our institution, approximately 75% are discharged home with an indwelling catheter. With a potential 15% drop-out rate, we therefore anticipate that we will need to recruit about 370 eligible patients in our clinics. As listed before, review of the surgeons logs over the last 12 months shows that this study is feasible due to the large volume of pelvic reconstructive surgery procedures in Urogynecology and Urology. Last year, the combined surgical volume of these cases at our three clinics was 532 subjects; thus, we anticipate we will be able to easily recruit the proposed sample size in one year. We plan to

recruit women from 4 sites in 3 departments in the University of Pennsylvania Health System: 1) Urogynecology at Hospital of University of Pennsylvania (HUP), 2) Urogynecology at Pennsylvania Hospital (PAH) and 3) Urology at Pennsylvania Hospital (PAH). Physician investigators are present at all three sites, and will have opportunity to screen patients planning for surgery for pelvic organ prolapse, urinary incontinence, or both, for participation.

Key inclusion criteria
Inclusion criteria: female; patients who are able to read and write English; 18 years of age or older; underwent surgery for pelvic organ prolapse, urinary incontinence, or both; require post-operative short-term transurethral catheterization for greater than 24 hours.

Key exclusion criteria
Exclusion criteria: patients undergoing surgical intervention for sacral neuromodulation, or mesh excision; patients requiring long-term catheterization secondary to injury to the urinary tract; patients who pass their post-operative trial void and thus, do not require additional catheterization; patients requiring catheterization for less than 24 hours; pregnant patients; patients who are breast-feeding; allergy to methenamine hippurate or fluroquinolones (either ciprofloxacin or levofloxacin); impaired renal or hepatic function; pre-operative urinary retention; patients who are currently using sulfonamides; patients who have severe dehydration; patients using tizanidine; patients sensitive to quinolones class; patients using theophylline; patients with myasthenia gravis; patients with prolongation of QT interval.

Vulnerable Populations

	Children Form
	Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form
	Fetuses and/or Neonates Form
	Prisoners Form
	Other
x	**None of the above populations are included in the research study**

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion
All patients will be advised that participation in the study is completely voluntary, and does not involve any monetary compensation, which will minimize the risk of coercion for the economically disadvantaged. Patients will also be assured that their participation will not affect their care or treatment. Also, each person will be provided the opportunity to decline or participate in the study through the process of thorough informed consent. Penn employees and students who may be approached during their evaluation in the urogynecology clinics will be told that their decision to participate will not impact their standing with the University.

Subject recruitment
We plan to recruit women from 3 departments in the University of Pennsylvania Health System: 1) Urogynecology at Hospital of University of Pennsylvania (HUP), 2) Urogynecology at Pennsylvania Hospital (PAH) and 3) Urology at Pennsylvania Hospital (PAH). Physician investigators, who are present at all clinics associated with these departments, will screen patients planning for surgery for pelvic organ prolapse, urinary incontinence, or both, for participation. Patients may also be pre-screened for eligibility using the electronic medical record. Following confirmation of eligibility, the physicians will obtain informed consent preoperatively prior to surgery.

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?
No

The following documents are currently attached to this item:

There are no documents attached for this item.

Subject compensation*
Will subjects be financially compensated for their participation?
No

The following documents are currently attached to this item:

There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

None.

Study Procedures

Suicidal Ideation and Behavior
Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?
No

Procedures
RECRUITMENT We plan to recruit women from 3 clinical sites associated with 3 departments in the University of Pennsylvania Health System: 1) Urogynecology at Hospital of University of Pennsylvania (HUP), 2) Urogynecology at Pennsylvania Hospital (PAH) and 3) Urology at Pennsylvania Hospital (PAH). Physician investigators, who are present at all sites, will screen patients planning for surgery for pelvic organ prolapse, urinary incontinence, or both, for participation. Following confirmation of eligibility, the physicians will obtain informed consent prior to surgery at the planned preoperative visit. Last year, the combined surgical volume of these cases at our three clinics was 532 subjects; thus, we anticipate we will be able to easily recruit the proposed sample size in twelve months. ENROLLMENT AND BASELINE VISIT: Patients who are being discharged home with an indwelling catheter following pelvic reconstructive surgery will be enrolled into the study. With regards to outpatient surgery (such as a suburethral sling), this will occur within a few hours after surgery for patients who fail their trial of void. Following inpatient surgery (such as sacrocolpopexy, uterosacral or sacrospinous ligament fixation, or colpocleisis), patients who are being discharged from the hospital with an indwelling catheter will be enrolled into the study. As per standard of care, all subjects will be scheduled for an office visit for catheter removal 24 to 72 hours after placement of the indwelling catheter per surgeon preference. Demographic information will be collected from the patients medical record (age, menopausal status, concurrent estrogen use, ethnicity, level of education, medical comorbidities, history of recurrent UTIs, and duration of hospitalization). Data regarding the patients surgical intervention (procedure type, surgical complications, operative time) will be collected from the operative record. At the time of catheter removal, subjects will be randomized to either methenamine hippurate or fluoroquinolones, using sealed, opaque, sequentially numbered envelopes. All patients, and all physicians and nurses directly involved in patient calls and clinical interaction, will be masked to treatment allocation. Only the nurses involved in catheter removal, but not decisions on the primary outcome, will open the envelope, and distribute the allocated medication to the patient, who will take one dose at the office. A 24-hour course of fluoroquinolones, as per AUA guidelines, are the first-line antibiotics for catheter removal, and will be one of the active arms of the study. Due to differences of office practice and formulary availability, the fluroquinolone of choice at each site will be different; this is clinically relevant as different urology practices across the country use different fluoroquinolones for prophylaxis. At HUP and Radnor, the 24 hour course of fluoroquinolone used will be one dose of 500 mg of levofloxacin, as per office practice and formulary availability. At the other sites (Pennsylvania Hospital, Chestnut Hill Hospital), the 24 hour course of fluoroquinolone as per office practice will be two doses of 500 mg of ciprofloxacin, 12 hours apart. Methenamine hippurate will be given as two doses of 1g of methenamine hippurate, taken 12 hours apart. The patient will not be told which

medication they are taking. The methenamine, ciprofloxacin, and levofloxacin used in this study are all similar in shape, although not in color. Following catheter removal one to two hours after the first dose of medication, patients will be given a white vial or bag with the second dose of medication (if given methenamine or ciprofloxacin) and will be instructed to take second dose of the study medication at home about 12 hour later. As part of standard of care, nurses perform void trials per practice guidelines by backfilling the bladder with 300 cc normal saline, removing the catheter, and prompting the patient to void immediately. If a patient fails her trial of void, majority of the patients at our site are taught intermittent self-catheterization. If an indwelling catheter is replaced, the allocated treatment (drug or placebo) will be re-administered at repeat trial of void/repeat catheter withdrawal. No further drug will be given if the patient performs intermittent self-catheterization after the failed trial of void. FOLLOW UP VISITS: Three weekly follow-up calls and one postoperative visit are planned. It is standard of care of our clinical practices in the office for a clinical urogynecology nurses to routinely contact patients post-surgery to ask about any symptoms or complications from the procedures they underwent. In this study, per routine office practice, urogynecology nurses will call study participants once a week for the first three weeks following surgery. As per routine, using a structured form, patients will be asked about symptoms of UTI, any treatment for UTI, any urine laboratory testing, visits, and treatment for suspected UTI from other providers other than the urogynecology clinic (e.g. ER, primary care doctor), treatment of complications secondary to UTI (such as pyelonephritis and sepsis), and any additional use of antibiotic for infections other than UTI. Questions related solely to the study medication will include compliance with medications given, and side effects within 24 hours of taking medication. At any time during the study, as per standard of care of all urogynecology patients, patients who feel that they may have UTIs will be encouraged to call the urogynecology clinical nurses or the on-call physician with their symptoms. These encounters, any testing, and any empiric treatment are documented in the electronic medical system. If the diagnosis of UTI is unclear at any time, per standard of care, the patient will be asked to come into the office for physical examination and further diagnostic testing. If patients are suspected of having UTI, treatment for UTI will be initiated. As per routine office care for treatment of UTI, if possible, all patients will be asked to give a specimen for urinalysis and urine culture prior to beginning empiric treatment. Four to eight weeks following surgery, as per standard of care, patients will return to the office for a routine post-operative assessment with the investigating physicians. The patients will undergo routine post-operative physical examination and answer the above questions. Any methenamine or ciprofloxacin that has not been taken as instructed will be returned at this time. At their post-operative visit, the patient will be asked if they were aware of which medication they were taking to assess blinding.

The following documents are currently attached to this item:

There are no documents attached for this item.

Deception
Does your project use deception?
No

International Research
Are you conducting research outside of the United States?
No

Analysis Plan
Categorical variables will be analyzed using chi-squared or Fishers exact test and parametric or non-parametric t-tests for continuous variables. Bivariable analysis will be used to determine variables (risk factors) that are independently associated with post-operative UTI. Duration of catheterization between groups will be compared using the Mann-Whitney test to compare difference in medians. The primary outcome will be the rate of clinically suspected UTI requiring treatment within the first three weeks following surgery. Comparison with fluoroquinolones will be performed using relative risk ratio. Analysis will be performed by intention to treat. If imbalances in baseline demographics are identified, multivariate analyses for post-operative UTI will be performed to control the inequality. Cost-effectiveness analysis will be performed by monetizing the collected resource utilization data in each treatment arm, including use of intervention resources, UTI treatment resources, as well as primary and secondary care resources. Incremental cost-effectiveness ratios will be calculated to compare difference in costs between prophylaxis with methenamine and prophylaxis with fluroquinolones to the difference in effect on the incidence of post-operative UTI. Prevalence of adverse effects will be measured as

percentages. Rate of urine cultures performed by patients treated for symptomatic UTI, as well as the rate of culture-positive UTI will be noted; comparison with fluoroquinolones will be performed using relative risk ratio, with analysis by intention to treat. Positive cultures will be analyzed for percentage of uropathogen type, type of uropathogen showing resistance, and overall percentage of cultures showing resistance.

The following documents are currently attached to this item:

There are no documents attached for this item.

Data confidentiality

x **Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**

x **Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**

Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.

x **Wherever feasible, identifiers will be removed from study-related information.**

A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.

A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)

Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

Subject Confidentiality
Extensive efforts will be made to ensure and maintain participant confidentiality. Data from patients will be recorded on data collection forms, which will be associated with a Subject ID number only. The patient name, medical record numbers, or other identifiers will not be present on the data collection forms themselves. The 6-digit Participant ID number will be composed by the sequential ordering of participants. At each site, a log book will be kept in for data management purposes to match Subject ID number with patient medical record numbers if chart review is needed for missing data. This will also be maintained in a secure and locked filing system at all times. Any additional source documentation that may associate the patient and PHI to data (such as consent forms) will also be kept in a secure and locked filing system at all times. Additionally, any data collection forms will also be kept in a separate secure and locked filing system at all times. At the University of Pennsylvania, the participant will be logged in the Excel spread sheet using their assigned Subject ID number. The Excel spreadsheet form will be stored in a password-secured file and a physical backup copy of this file will be made at the end of every other week and the copy stored in a separate, secure area/filing system.

Sensitive Research Information*
Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?
No

Subject Privacy
Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).

Patients will be identified and screened by physician investigators at each site involved in patient care in their offices. The patient will be located in a private room prior to surgery before discussing the study and enrollment with the patient. Consent, which will be given prior to surgery in the pre-operative holding area, will also be conducted in a private room. During the study, interactions with the patient will involve routine post-operative care by the physician investigators and urogynecologic nurses, which is conducted in physicians' offices. It will also involve routine post-operative telephone calls, done in a private manner in the office setting, in the usual manner. Patients may also interact through telephone calls with the on-call physician in the cases of after hour question, care, or emergency, as per routine post-operative care.

Data Disclosure
Will the data be disclosed to anyone who is not listed under Personnel?
No.

*Data Protection**

- x **Name**
- x **Street address, city, county, precinct, zip code, and equivalent geocodes**
- x **All elements of dates (except year) for dates directly related to an individual and all ages over 89**
- x **Telephone and fax number**
- x **Electronic mail addresses**
- **Social security numbers**
- x **Medical record numbers**
- **Health plan ID numbers**
- **Account numbers**
- **Certificate/license numbers**
- **Vehicle identifiers and serial numbers, including license plate numbers**
- **Device identifiers/serial numbers**
- **Web addresses (URLs)**
- **Internet IP addresses**
- **Biometric identifiers, incl. finger and voice prints**
- **Full face photographic images and any comparable images**
- **Any other unique identifying number, characteristic, or code**
- **None**

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?
No

Tissue Specimens Obtained as Part of Research*
Are Tissue Specimens being obtained for research?
No

Tissue Specimens - Collected during regular care*
Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?
No

Tissue Specimens - otherwise discarded*
Would specimens otherwise be discarded?
No

Tissue Specimens - publicly available*
Will tissue specimens be publicly available?
No

Tissue Specimens - Collected as part of research protocol*
Will tissue specimens be collected as part of the research protocol?
No

Tissue Specimens - Banking of blood, tissue etc. for future use*
Does research involve banking of blood, tissue, etc. for future use?
No

Genetic testing
If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."
Not applicable.

Consent

1. Consent Process

Overview
Informed consent will be obtained by the investigator in the preoperative area, although the patient will be identified and recruited in the clinic as a potential participant for the study. The subjects will have as much time between the initial recruitment and the consent as needed to consider participation. Additionally, at any time from the time of recruitment to the time of hospital discharge with an indwelling catheter, the patient may choose to consent and participate in the study. The patient may also choose to withdraw from the study at any time. Investigators will emphasize that participation (or lack of participation) in the study: 1) not influence their evaluation, care, or treatment 2) is completely voluntary 3) does not involve any financial compensation 4) may be terminated at any time. Layman terms will be used by those obtaining the consent. The consent will be written at a 6th grade reading level. All questions will be answered to the patient's satisfaction and understanding before informed consent is obtained.

Children and Adolescents
Not applicable.

Adult Subjects Not Competent to Give Consent
Yes, all adult subjects who meet inclusion criteria will be able to give informed consent.

2. Waiver of Consent

Waiver or Alteration of Informed Consent*
No Waiver Requested

Minimal Risk*

Impact on Subject Rights and Welfare*

Waiver Essential to Research*

Additional Information to Subjects

Written Statement of Research*
No

If no written statement will be provided, please provide justificiation

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study Risks

Physical Risks: Because this is a clinical trial of methenamine, there are possible physical risks to the patients secondary to the medication in use and the clinical outcome. However, this is minimal since methenamine is 1) a FDA-approved medication available in the United States and regularly used for prevention of UTIs, and 2) has relatively few and mild side effects. Methenamine hippurate is a medication that exhibits antibacterial activity by converting to formaldehyde in the presence of acidic urine. It is currently FDA approved for the prophylaxis of recurrent urinary tract infections. The most common side effects are rash (3.5% or less), nausea (3.5% or less), upset stomach (3.5% or less), and dysuria (3.5% or less). Serious side effects include immune hypersensitivity reaction and pneumonia.(1) In the studies which examined the use of methenamine for prophylaxis for UTI after gynecologic surgery, only 6 patients treated with methenamine out of a total of 6 studies displayed mild dermatologic and gastrointestinal side effects. No patients displayed any serious side effects. Additionally, there was no significant difference in presentation of side effects between placebo and treatment groups. The doses used in this study is significantly less than the doses used in the studies above, which further decreases the risk of physical harm. Methenamine is contraindicated in severe renal and hepatic impairment, which are exclusion criteria in this study. (1) The second risk is from the potential development of urinary tract infection after short-term indwelling catheter use. However, patient eligible for participation in this study would be at risk of urinary tract infection even if they were not participating in this study because they have opted to undergo pelvic reconstructive surgery. Additionally, the methenamine hippurate may be preventative for urinary tract infection, so participation in this study may be beneficial. Additionally, there may be risk with use of fluroquinolones, though the dose will be minimal and patients will be unlikely to undergo side effects. Oral ciprofloxacin is commonly used in clinical practice with minimal problems, for urinary tract infections as well as other infections. The most common side effects of ciprofloxacin in adults include: Rash (up to 1.8%), diarrhea (1.6% to 4.8%); nausea (2.5% to 4%), vomiting (1% to 4.8%), headache (oral extended-release tablets, 3%). Life-threatening adverse effects are rare, but diverse, and include: Cardiovascular: Cardiorespiratory arrest (up to 1%), Myocardial infarction (up to 1%), Prolonged QT interval, Syncope (up to 1%), Torsades de pointes Dermatologic: Photosensitivity (up to 1%), Stevens-Johnson syndrome (up to 1%), Toxic epidermal necrolysis (up to 1%) Gastrointestinal: Clostridium difficile diarrhea (up to 1%), Gastrointestinal hemorrhage (up to 1%), Pancreatitis (up to 1%), Pseudomembranous enterocolitis Hematologic: Agranulocytosis, Aplastic anemia, Bone marrow depression, Hemolytic anemia, Leukopenia (0.4%), Pancytopenia (0.1%), Thrombocytopenia Hepatic: Hepatic necrosis (up to 1%), Hepatitis (up to 1%), Hepatotoxicity, Liver failure Immunologic: Immune hypersensitivity reaction (up to 1%) Musculoskeletal: Myasthenia gravis, Exacerbation, Rupture of tendon, Tendinitis Neurologic: Raised intracranial pressure, Seizure (up to 1%) Ophthalmic: Retinal detachment Psychiatric: Depression (up to 1%), Psychotic disorder (up to 1%) Renal: Acute renal failure (up to 1%), Hemorrhagic cystitis (up to 1%) [2] Levofloxacin is also commonly used in practice for the treatment of infections including urinary tract infections. Common side effects include: Diarrhea (5%), Nausea (7%); Dizziness (3%), Headache (6%), Insomnia (4%). Life-threatening side effects are uncommon, but include: Cardiovascular: Cardiac arrest (0.1% to 1%), Prolonged QT interval, Torsades de pointes, Ventricular tachycardia (0.1% to 1%) Dermatologic: Erythema multiforme, Stevens-Johnson syndrome Endocrine metabolic: Hypoglycemia (0.1% to 1%) Hematologic: Aplastic anemia, Pancytopenia, Thrombocytopenic purpura Hepatic: Hepatitis, Liver failure Immunologic: Anaphylactoid reaction, Immune hypersensitivity reaction (0.1% to 1%) Musculoskeletal: Myasthenia gravis, Exacerbation, Rupture of tendon, Tendinitis (0.1% to 1%) Neurologic: Peripheral neuropathy, Seizure (0.1% to 1%) Ophthalmic: Retinal detachment Renal: Acute renal failure (0.1% to 1%) [3] However, risk will be minimized by the short course of fluroquinolones, as well as exclusion of patient with allergies to either ciprofloxacin or levofloxacin, or hepatic and renal issues. Again, both antibiotics are commonly used in inpatient and outpatient settings for treatment of infections with minimal risk, so risk to the patient (compared with benefit) should be

minimal. Any patients with any side effects will be told to discontinue use of the medications and be evaluated by a physician, and any serious adverse events will be reported to the IRB. There are no psychological, social, economic, monetary, or legal risks to this study. Loss of confidentiality: Any study in which personal health information (PHI) is collected has the potential risk of loss of confidentiality. However, extensive efforts will be made to ensure and maintain security of PHI and maintain participant confidentiality. Patients will be identified and screened by physician investigators at each site involved in patient care in their offices. The patient will be brought into a private room before discussing the study and enrollment with the patient in the privacy of a private room. During the study, interactions patient will involve routine post-operative care by the physician investigators and urogynecologic nurses, which is conducted in physicians' offices. It will also involve routine post-operative telephone calls, done in a private manner in the office setting, in the usual manner. Data from patients will be recorded on data collection forms, which will be associated with a Subject ID number only. The patient name, medical record numbers, or other identifiers will not be present on the data collection forms themselves. The Participant ID number will be composed by the sequential ordering of participants. At each site, a log book will be kept in for data management purposes to match Subject ID number with patient medical record numbers if chart review is needed for missing data. This will also be maintained in a secure and locked ling system at all times. Any additional source documentation that may associate the patient and PHI to data (such as consent forms) will also be kept in a secure and locked ling system at all times. Additionally, any data collection forms will also be kept in a separate secure and locked ling system at all times. One year after the study has been completed, any forms with patient identifiers (such as logs and consents) will be destroyed. At the University of Pennsylvania, the participant will be logged in the Excel spread sheet using their assigned Subject ID number. The Excel spreadsheet form will be stored in a password-secured file and a physical backup copy of this file will be made at the end of every other week and the copy stored in a separate, secure area/filing system. [1] Methenamine. In: Micromedex 2.0. Martindale - The Complete Drug Reference. Ann Arbor, MI: Truven Health Analytics. [updated 8/20/2010; accessed 2/21/14]. http://www.micromedexsolutions.com/micromedex2/librarian/. [2] Ciprofloxacin. In: Micromedex 2.0. Martindale - The Complete Drug Reference. Ann Arbor, MI: Truven Health Analytics. [updated 8/20/2010; accessed 2/21/14]. http://www.micromedexsolutions.com/micromedex2/librarian/. [3] Levofloxacin. In: Micromedex 2.0. Martindale - The Complete Drug Reference. Ann Arbor, MI: Truven Health Analytics. [updated 8/20/2010; accessed 2/21/14]. http://www.micromedexsolutions.com/micromedex2/librarian/.

Potential Study Benefits

Potential benefits to the individual subject include prevention of urinary tract infection, or a decreased risk of urinary tract infection, after short-term indwelling catheterization. Additionally, if a short course of methenamine hippurate is effective in decreasing the risk of UTIs, it would be an exciting and attractive chemoprophylaxis alternative to antibiotics, potentially decreasing the cost and complications of post-operative UTI; minimizing drug resistance, adverse effects and cost of treatment; and potentially increasing medication compliance. This would potentially decreased economic burdens on patients and health systems. Additionally, catheter-associated UTIs are measures of quality monitored by the National Healthcare Safety Network.

Alternatives to Participation (optional)

Patients are not required to participate in the study. Patients who require short-term indwelling catheters after pelvic reconstructive surgery may or may not be given prophylactic antibiotics based on their physicians routine practice. They will participate in routine post-operative care.

Data and Safety Monitoring

This study contains low risks, as both of these medications are already used in clinical practice for prophylaxis of urinary tract infections. Study progress and safety will be reviewed by the PI. Review of the rate of subject accrual, adherence to inclusion/exclusion criteria will occur to assure that participants meet the eligibility criteria. There will be ongoing collection of data on adverse events and compliance to the treatment protocol throughout the study by research staff.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment

The benefits of this treatment outweigh the risks. As discussed before, there is risk of physical harm and

loss of confidentiality as part of participation in this study. However, the risk of physical harm is minimal secondary to rarity and minor adverse effects of methenamine and fluoroquinolones, and minimization of the dose administered in this study. Additionally, these medications are already being used for prophylaxis of urinary tract infections in the urogynecology/urology practice. The loss of confidentiality will be minimized by careful and secure management of all paper and electronic documentation of patient data. Additionally, all patients undergoing pelvic reconstructive surgery are at risk of urinary tract infection. Participation in this study would not increase this risk, but could potentially benefit the patient by decreasing this risk. If this trial is successful, benefits to society and health care systems could result in decreased antibiotic resistance, decreased health-care associated infections, and decreased cost secondary to these infections.

General Attachments

The following documents are currently attached to this item:

There are no documents attached for this item.