Does antibiotic prophylaxis reduce wound complications after vulvar excision of premalignant lesions: A Double-Blinded Randomized Controlled Trial

Washington University School of Medicine
Division of Gynecologic Oncology
4911 Barnes Jewish Plaza
Campus Box 8064
St. Louis, MO 63110

Protocol#: 201804136
Version Date: September 10, 2020

Principal Investigator:** **Mary M. Mullen, M.D.**
4911 Barnes Jewish Plaza
Campus Box 8064
St. Louis, MO 63110
Phone: (314) 655-8750
Fax: (314) 362-2893
E-mail: marymullen@wustl.edu

Sub-Investigators*		
	Lindsay M. Kuroki, M.D.	**Gynecologic Oncology**
	Katherine C. Fuh, M.D.	**Gynecologic Oncology**
	Andrea R. Hagemann, M.D.	**Gynecologic Oncology**
	L. Stewart Massad, M.D.	**Gynecologic Oncology**
	Carolyn K. McCourt, M.D.	**Gynecologic Oncology**
	David G. Mutch, M.D.	**Gynecologic Oncology**
	Matthew A. Powell, M.D.	**Gynecologic Oncology**
	Premal H. Thaker, M.D., M.S.	**Gynecologic Oncology**
	David Eisenberg, M.D., MPH	**Gynecologic Oncology**
	Dineo Khabele, M.D.	**Gynecologic Oncology**
	Jerry Lowder, M.D.	**Gynecologic Oncology**
	Tessa Madden, M.D., MPH	**Gynecologic Oncology**
	Gillian Schivone, M.D., MS	**Gynecologic Oncology**
	Tammy Sonn, MD	**Gynecologic Oncology**
	Eric Strand, MD	**Gynecologic Oncology**
	Denise Willers, MD	**Gynecologic Oncology**

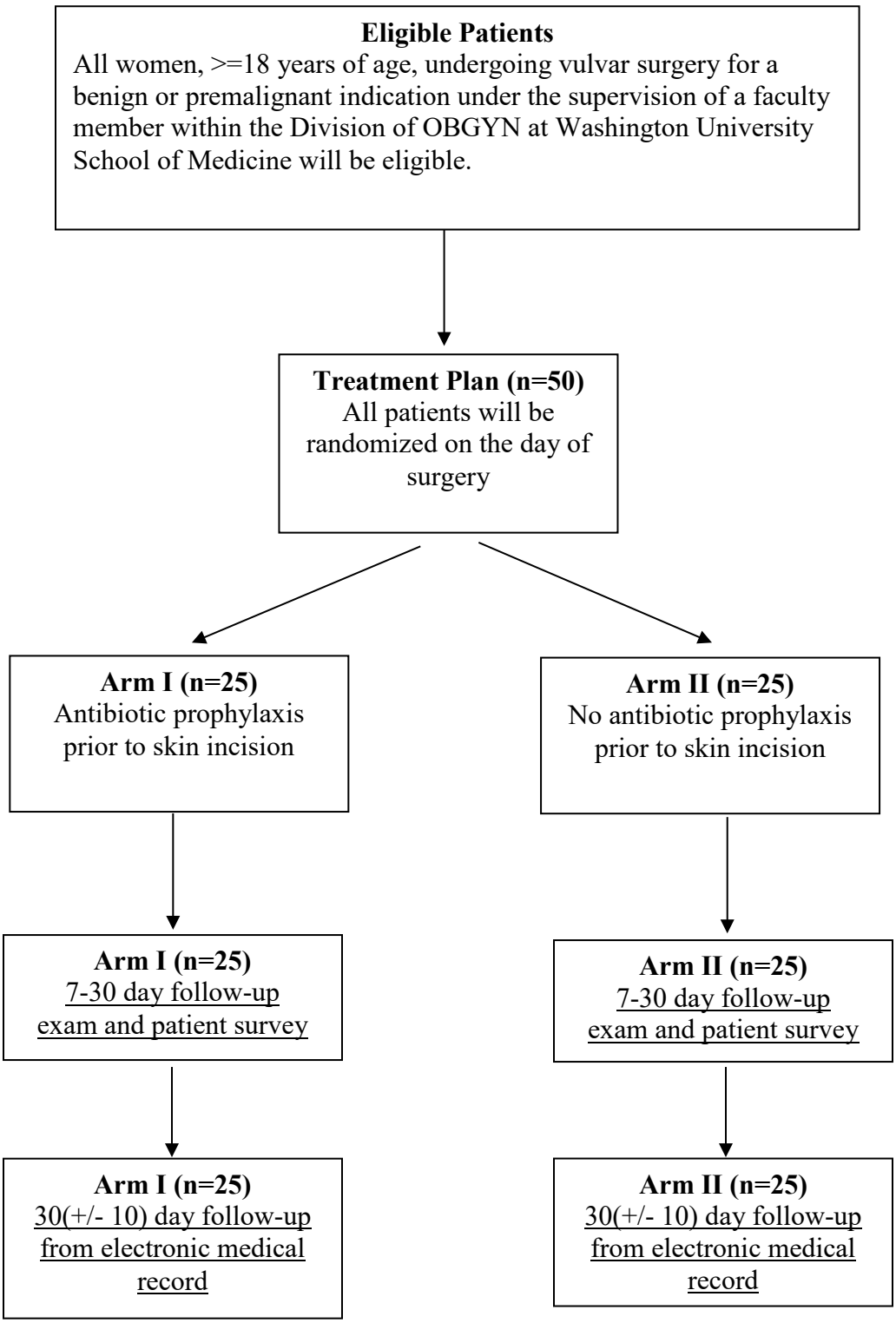
Clinical Trials.gov# **NCT03578965**

Protocol Revision History

Initial Approval Version Date	**04/25/2018**
Amendment #1 Version Date	**06/11/2018**
Amendment #2 Version Date	**08/08/2018**
Amendment #3 Version Date	**12/19/2018**
Amendment #4 Version Date	**04/02/2020**
Amendment #5 Version Date	**09/10/2020**

Does antibiotic prophylaxis reduce wound complications after vulvar excision of premalignant lesions:
A Double-Blinded Randomized Controlled Trial

SCHEMA



Glossary of Abbreviations

AE	Adverse event
ACOG	American Congress of Obstetrics and Gynecology
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DSM	Data and Safety Monitoring
DSMC	Data Safety Monitoring Committee
EC	Ethics Committee
EMR	Electronic Medical Record
HCG	Human chorionic gonadotropin
HRPO	Human Research Protection Office (IRB)
IRB	Institutional Review Board
ITT	Intent-to-treat
OHRP	Office of Human Research Protections
PI	Principal investigator
QASMC	Quality Assurance and Safety Monitoring Committee

Does antibiotic prophylaxis reduce wound complications after vulvar excision of premalignant lesions:
A Double-Blinded Randomized Controlled Trial

Table of Contents

1.0 BACKGROUND AND RATIONALE

1.1 Study Disease

Premalignant vulvar lesions are extremely common with the incidence increasing over 400% in the past 30 years, totaling up to 7,500 cases in the United States annually.[1] Surgical excision is recommended when invasive carcinoma cannot be excluded. Depending on lesion(s) size and location, in order to achieve a 1 cm disease-free margin, some excisions can be extensive and at high-risk for wound separation and/or surgical site infection (SSI).[2] Vulvar wound complications are recognized as a major cause of postoperative morbidity but have predominantly been studied in the context of radical vulvectomies performed for cancer staging. Despite the finding that the majority of invasive and in situ vulvar carcinoma lesions are premalignant (57%), there is a lack of data regarding the risk of infection following conservative vulvar excisions.[1] As such, there are no evidence-based guidelines regarding antibiotic prophylaxis for this patient population.

To address this gap in the literature, we performed a retrospective cohort study at our institution which included all vulvar surgeries performed for premalignant lesions from January 2007 to 2017. Of 534 patients included, the overall wound complication rate was 30%. The American Congress of Obstetricians and Gynecologists (ACOG) recommends prophylactic antibiotics for procedures such as anterior colporrhaphy which likely confer a similar infection risk to simple vulvectomies, but makes no recommendations about vulvar excision. If baseline wound complication rates approach 30% as demonstrated in our preliminary data, clinical practice of antibiotic administration should be addressed. Before clinical practice recommendations change we propose to test the central hypothesis that antibiotic prophylaxis will reduce the incidence of a composite wound complication (wound breakdown, SSI, seroma, and/or hematoma) within 30 days postoperatively. We propose a pilot study designed as a double-blinded randomized controlled clinical trial of women who undergo a vulvar excision for a premalignant lesions.

1.2 Study Rationale

The use of antibiotics in common gynecologic procedures such as hysterectomy, laparoscopy, and surgical abortion is well established and has been described in many randomized control trials and meta-analyses.[3-5] The rate of wound infection after vulvar excision for premalignant lesions (7.5%) is equal to or greater than that of vaginal hysterectomy (7-14%), abdominal hysterectomy (1-6%) for which antibiotic prophylaxis is routinely used. With the use of antibiotic prophylaxis, postoperative infection rates decrease greater than 20% for vaginal hysterectomy and 15% for abdominal hysterectomy.[5] The relative risk for developing infection after an elective abortion in women who received antibiotic prophylaxis versus those who did not is 0.58.[6] As a result, antibiotic use is strongly encouraged in these situations. Conversely, to our knowledge, there is no research evaluating the rate of vulvar wound complications after excision of premalignant or benign vulvar lesions and no formal recommendations exist regarding antibiotic prophylaxis.

Previous studies evaluating vulvar surgery are largely focus on wound complications after the treatment of vulvar cancer specifically with radical vulvectomy and inguinal lymphadenectomy.[7-9] In cancer populations wound complications including infection and breakdown are one of the most common causes of postoperative morbidity resulting in increased healthcare costs and decreased quality of life.[7-9] Extrapolation of this data to premalignant lesions is not valid given the differences in aggressiveness of surgical technique including both depth and width of the excision. More importantly, the majority of vulvar carcinomas are in fact in situ and not invasive and therefore it is important to study premalignant disease.[1] Antibiotic prophylaxis has been suggested to improve the rate of wound complications, but no formalized randomized control trials have verified this practice.[8]

Given the clean-contaminated nature and endogenous flora of the vulva, patients undergoing vulvar excision are at high risk for wound complications. This increased risk would suggest the benefit of antibiotic prophylaxis, however, indiscriminate antibiotic without demonstrated benefit on clinical outcomes is inefficient and potentially detrimental. Haphazard antibiotic administration is associated with antibiotic-resistant bacteria, and over 15% of patients will have adverse reactions to antibiotics ranging from skin rashes and diarrhea to anaphylaxis.[10] Given the growing prevalence of premalignant vulvar lesions, having evidence-based guidelines for or against the use of antibiotic prophylaxis for these excisions would improve evidence-based practice standards for women's health.

We conducted a single-center, retrospective cohort study evaluating all vulvar excisions performed for a benign indication at our institution from 1/2007-1/2017. 534 patients were included, 227 patients who received preoperative antibiotics and 310 who did not. The overall wound complication rate was 28.8% with an infection rate of 6.9%. There was no difference in wound complication rates between patients who received preoperative antibiotics and those who did not (30.4% vs 27.4%, p=0.45). However, because this was a retrospective study it is possible that confounders such as inherent differences in the patient populations, clinical practice of the surgeons, or confounding by indication in who was given antibiotics and who was note may have influenced these findings. Current tobacco use (aOR 1.90, 95% CI 1.26-2.87), and concomitant reconstructive flap or graft (OR 1.67, 95% CI 1.02-2.73) were associated with increased wound complications. In short, the wound complication rate following vulvar surgery for nonmalignant lesions is substantial. It is well established that patients with wound complications require increased hospital stay, increased hospital cost, and decreased quality of life.[3] Given the many confounding variables of this retrospective study, a randomized control trial will provide the most reliable data to determine the role of prophylactic antibiotics to decrease the wound complication rate. We plan to perform a pilot study to evaluate actual rates of wound complications and how long it takes to recruit 50 patients. Relying on retrospective data is difficult given documentation of wound complications and we only had <50% of patients who received antibiotics.

2.0 OBJECTIVES

2.1 Primary Objective

Evaluate for the difference in wound complications between women who receive antibiotic prophylaxis and those who do not:

a) Wound complication will be defined as a composite outcome that includes wound breakdown, sterile site infection, hematoma, seroma diagnosed within 30 days after excision.
    - Sterile Site Infection (SSI) – defined as purulent drainage, cellulitis, abscess, or a wound that requires drainage, debridement or antibiotics associated with a clinical diagnosis of infection.

2.2 Secondary Objectives

Determine the clinical risk factors that correlate with vulvar wound complications.

b) Demographic variables that predispose patients to infection including medical history of diabetes, liver disease, human immunodeficiency virus, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, peripheral vasculature disease, dementia, connective tissues disease, leukemia, lymphoma, peptic ulcer disease, or hypertension. We will also record steroid use or the use of other immunosuppressive medications.
c) Evaluation of vulvar hygiene through physician and patient survey
d) Incidence of adverse events to antibiotic use

2.3 Tertiary Objectives

Evaluate for differences in the following outcomes between women who receive antibiotic prophylaxis and those who do not:

a) Inpatient re-admission for postoperative wound care within 30 days of surgery
b) Antibiotic safety measures including allergic reaction type and severity

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 All women, >=18 undergoing vulvar surgery.

3.1.2 Biopsy proven benign or premalignant lesion requiring surgical management.

3.1.3 Women of childbearing age will be required to have a negative human chorionic gonadotropin (HCG) test within seven days of surgery.

3.1.4 Scheduled to undergo surgical management for their vulvar disease supervised by a faculty member within the Division of OBGYN at Washington University School of Medicine

3.1.5 Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

3.2.1 Women who are pregnant

3.2.2 Women scheduled to undergo a radical vulvectomy

3.2.3 Women scheduled to undergo a concomitant graft, flap or plastic surgery

3.2.4 Women <18 years of age

3.2.5 History of prior vulvar radiation

3.2.6 Inability to sign an informed consent form prior to registration on study

3.2.7 Inability to understand spoken or written English

3.2.8 Prisoner

3.3 Inclusion of Minorities

3.3.1 Members of all races and ethnic groups are eligible for this trial. As our patient population is solely female, only women will be eligible for this study.

4.0 REGISTRATION AND RANDOMIZATION PROCEDURES

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility as indicated in section 4.1.
2. Assignment of unique patient number (UPN) as indicated in section 4.2.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below

1. The registering MD's name
2. Patient's race and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by the PI or designated sub-investigator
6. Completed source document verifying negative pregnancy test (within 7 days of surgery).
7. Copy of appropriate source documentation confirming patient eligibility

4.2 **Assignment of UPN**

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used.

4.3 **Patient Registration and Randomization**

Prior to recruitment all Gynecology attending physicians of Washington University will receive an email from the principal investigator asking for permission to screen their patients for recruitment and to consent them for involvement in the study. Physicians will have the opportunity to opt out of the study over the next two weeks in which case their patients will not be screened for eligibility. If they agree to participation their patients will be included in the recruitment process noted below.

All potential women who are scheduled with OBGYN faculty or fellows for vulvar surgery will be identified and screened for eligibility prior to their preoperative appointment. The principal investigator and members of the research team will identify patients who meet the inclusion criteria and who do not meet one of the exclusion criteria (eligibility checklist). PHI is obtained from the electronic medical record and if not available from the electronic medical record than physician operating room schedules will be used to determine eligibility. The attending physician will be emailed by a research assistant regarding the patient's eligibility for the study. Attending physician emails will be obtained from a Washington University ListServs. During their preoperative or anesthesia appointment, the patient will receive a pre-surgical packet which is given to all patients undergoing gynecologic surgery at Washington University. This packet will include a brief description (Appendix A) of the study and contact information to reach a member of the research team who will be available if the patient should have any questions about the study. At either of these appointments, or otherwise on the day of surgery, a member of the research and surgical team will discuss the study with the patient and assess their willingness to be enrolled in the study. It will be emphasized to the patients that other than receiving antibiotics or not there will be no differences in their medical care regardless of whether they choose to participate in this study. All potential participants will be given the opportunity to have all of their questions regarding the research study answered prior to making a decision to participate.

If the patient consents to the study an informed consent form will be signed with the patient at any of these encounters and she will be given a copy of the signed, dated consent. The PI and designated members of the research team will complete informed consent with participants.

We are not offering any incentives or financial remuneration for participation in the study. Patients who decline participation will receive prophylactic antibiotics as deemed appropriate by their attending surgeons.

A 1:1 randomization will be done by computerized random number generation by Department of Biostatistics at Washington University in St. Louis using REDCap.

Randomization will occur on the day of surgery following confirmation of eligibility as outlined in Section 4.1. The Principal Investigator or designated sub-investigators will review, sign, and date the eligibility checklist. On the day of surgery the research assistant or designated team member will verify the remaining eligibility, negative urine HCG test within 7 days of surgery.

The research team members working on this study have experience reviewing laboratory results in the electronic medical record and will confirm the negative urine HCG test when required. The research assistant will then document the results in a source document that will remain in the patient's research record. Once a participant consents to be enrolled in the study and is deemed eligible, the research assistant will randomize the patient using REDCap.

The principal investigator along with all members of the study team involved in data analysis as well as the patients will be blinded to the randomization group. The patients will not be aware if they receive antibiotics given the antibiotics are flushed through the patient's IV line which they will have regardless of their assigned study arm. The research assistant will disclose the randomization group to the anesthesiologist who will screen the patient for allergies and then obtain the appropriate antibiotics from the pharmacy and administer the antibiotics as appropriate. These will be administered prior to the procedure and so the surgeon will remain blinded to the administration. Standard practice regarding antibiotic prophylaxis is not clear, and therefore some surgeons use antibiotics preoperative and some do not. Thus, this study will not result in increased cost to the patient.

5.0 RESEARCH/TREATMENT PLAN

5.1 **Intervention**

The administration of preoperative prophylactic antibiotics will be as per the randomization protocol. Women randomized to prophylactic antibiotics will receive a cefazolin as per ACOG guidelines. If she has a penicillin allergy then clindamycin will be used. Prophylactic antibiotics should be administered prior to skin incision. A traditional surgical timeout will be performed. During the timeout it will be announced that the patient is on study. The surgeon will then turn to anesthesia and ask "whichever arm we are randomized to are we okay to proceed?". Once the anesthesia team answers yes indicating the antibiotics have been infused if appropriate, the surgical procedure will then be performed in the normal fashion. The skin and subcutaneous tissues will be opened either with a scalpel or with Bovie electrocautery on cutting current. Closure of subcutaneous tissue and skin will be performed at the discretion of the attending surgeon. Suturing will be performed under the supervision of the attending, fellow, or a member of the surgical team considered to have received appropriate training. At the time of surgery an operative data collection sheet (Appendix B) will be filled out by the surgeon collecting information on number of incision(s), method of incision and skin closure, suture used, if the subcutaneous tissue is closed,if local anesthesia was used, and if so, the type and when injection was placed (before incision or after closure).

5.2 **Patient Follow-up**

The patient will be discharged the day of surgery per standard practice.

A standardized physical examination of the wound will be performed by a healthcare provider at the postoperative visit 7-30 days postoperatively. Data from the patient's physical exam assessment (Appendix C) and administered patient survey (Appendix D) will be collected at this postoperative visit. If a patient is admitted to the hospital at the time of her scheduled clinic follow-up, the physical exam, assessment and surveys will be administered as an inpatient as per the protocol. The required follow-up data will be collected in telephone calls and/or at clinic visits until 30(+/- 10) days postoperatively. If patients present greater than 40 days postoperatively they will be considered lost to follow-up. All data from admissions to outpatient facilities prior to 30(+/- 10) days postoperatively will be included in our analysis.

5.3 **Women of Childbearing Potential**

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding and women who have had a tubal ligation) are required to have a negative serum/urine pregnancy test within seven days of surgery.

5.4 **Duration of Therapy**

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue the study, involvement in the study should be discontinued and the reason(s) for discontinuation documented appropriately.

Follow-up assessment may continue for 30 days (+/- 10) after surgery or until one of the following criteria applies:

- Death
- Loss to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as per standard of care for a postoperative patient.

6.0 REGULATORY AND REPORTING REQUIREMENTS

6.1 **Definitions**

6.1.1 **Adverse Events (AEs)**

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

6.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

6.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

6.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

6.1.5 **Unanticipated Problems**

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.1.6 **Noncompliance**

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

6.1.7 **Serious Noncompliance**

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

6.1.8 **Protocol Exceptions**

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

IRB Pre-approval of all protocol exceptions must be obtained prior to the event.

6.2 **Reporting to the Human Research Protection Office (HRPO) at Washington University**

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

6.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

6.4 Reporting to [DRUG MANUFACTURER]

Not applicable.

6.5 Reporting to the Institutional Biosafety Committee

Not applicable.

6.6 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the principal investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 7.1.4) associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after initial receipt of the information.

- Report any serious, unexpected adverse experiences (Section 7.1.2), as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

6.7 Timeframe for Reporting Required Events

Adverse events will be tracked for 30 days following the last day of study treatment. For the purposes of this protocol, reportable adverse events are allergic reaction to either cefazolin or clindamycin.

Deaths	
Any reportable death while on study or within 30 days of study	Immediately, within 24 hours, to PI and the IRB
Any reportable death while off study	Immediately, within 24 hours, to PI and the IRB
Adverse Events/Unanticipated Problems	
Any reportable adverse events as described in Sections 6.1 and 6.2 (other than death)	Immediately, within 24 hours to PI and within 10 working days to the IRB
All adverse events regardless of grade and attribution should be submitted cumulatively	Include in DSM report
Noncompliance and Serious Noncompliance	
All noncompliance and serious noncompliance as described in Sections 6.3 and 6.4	Immediately, within 24 hours, to PI and within 10 working days to the IRB

7.0 STUDY CALENDAR

Within 7 days prior to enrollment	**Preoperative surgery holding area or preoperative/anesthesia appointment**	**Day of Surgery**	**7-30 days after surgery**	**30(+/- 10) days after surgery**
Negative urine/ blood HCG test (for WOCBP)	Consent form signed	Randomization/Antibiotic Administration	Evaluation in clinic	Follow-up in EMR for wound complications and adverse events
		Data collection sheet	Assessment of wound for infection or separation	
		Collection of adverse events at time of antibiotic administration	Completion of patient survey	
			Evaluation for adverse events	

8.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Forms	**Submission Schedule**
Original Consent Form	Prior to registration
Registration Form Eligibility Form On-Study Form	Prior to starting treatment
Day of Surgery Data Collection Form (Appendix B)	After surgery
2-week follow-up data collection form (Appendix C)	Postoperative appointment (7-30 days postop)
Vulvar Hygiene Survey (Appendix D)	Postoperative appointment (7-30 days postop)
30 day postoperative follow-up form	30(+/- 10) days postoperative follow-up
Adverse Event Forms	Entire Study Period

9.0 MEASUREMENT OF EFFECT

The purpose of this study is to assess for differences in wound outcomes between women receive prophylactic antibiotics and those who do not. The primary outcome will be a composite of wound complications, which will include wound infection or disruption within 30(+/- 10) days following surgery. This rate will be calculated as a composite from the postoperative follow-up forms as well as from chart review of the electronic medical record including up to 30 (+/- 10) days

postoperatively. We will assess to see the wound complication rate is lower in either of these groups and as such should become the standard of care.

Secondary outcomes will include determining clinical risk factors that correlate with vulvar wound complications as well as evaluating patient understanding of vulvar hygiene and its effect on wound complications. Lastly, we attempt to secondarily describe adverse events occurred in response to prophylactic antibiotic use.

10.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

11.0 STATISTICAL CONSIDERATIONS

11.1 **Study design overview:** This study is designed as a randomized phase II clinical trial. This design will provide a direct assessment of the null hypothesis that there is no improvement in vulvar wound complication rates associated with antibiotic prophylaxis. All patients on this study will be randomized by the clinical research staff of the Division of Gynecologic Oncology. The sequence of treatment assignments will be concealed from the patients, the surgeons, the Principal Investigator, and the research staff performing the analysis. Blocked Randomization with equal probabilities to the two treatment regimens will be carried out following study registration.

Randomization will not be stratified by any factors.

12.0 Data collection: The principal parameters to be collected, analyzed and reported to determine the relative efficacy of the two treatment regimens are:

12.1.1 **Outcome measure:** Wound disruption or infection occurring within 30(+/- 10) days of the primary surgery. Incidence of wound infection (defined as purulent drainage, cellulitis, abscess or a wound that requires drainage, debridement or antibiotics associated with a clinical diagnosis of infection). Demographic factors as well as secondary outcomes such as hospital readmission, antibiotic safety measures will be collected. Data regarding vulvar hygiene will be obtained from patient surveys.

12.2 **Accrual rate, sample size and duration**: According to institutional data about 60 patients undergo simple vulvectomy or wide local excision for benign or premalignant indications annually. We anticipate it will take approximately one year to accrue the 50 evaluable patients necessary for this pilot trial. This accounts for the possibly number of refusals and screen failures.

12.3 **Hypotheses, planning parameters, and sample size justification:**

Primary hypothesis: This study will determine the effectiveness of antibiotic prophylaxis in reducing the rate of SSI after a vulvar excision for a premalignant lesion. We *hypothesize* that women who receive antibiotic prophylaxis will have lower rates of composite wound complications than their counterparts who do not receive antibiotics. The design of this study will provide evidence of benefit with regard to wound complication rate.

Planning parameters: The patient population selected for this study is all women undergoing vulvar surgery for benign or premalignant lesions.

Sample size justification: The total sample size of the pilot study is 50 evaluable women (prophylactic antibiotics, n=25 vs. no antibiotics, n=25) to provide preliminary data for grant funding for a large adequately powered RCT. This study will be a pilot study to evaluate actual rates of wound complications and

how long it takes to recruit 50 patients. Based on our prior analysis, we see an average of 53-55 patients per year who meet our study criteria. Ultimately we estimate a sample size of 293 women per group will be needed for 80% power to detect a clinically meaningful 33% difference in wound complication rates between study groups. See trial design in section 11.5.

12.4 **Trial design and Statistical analyses:**

The null hypothesis is that there is no improvement in wound complication rate associated with antibiotic prophylaxis (H_0: p_antibiotic-p_noantibiotic=0), where p stands for wound complication rate. The one-sided alternative hypothesis is that there is improvement (H_a: p_antbiotic-p_noantibiotic < 0). Anecdotal evidence suggest up to a 35% decrease in wound complication rate association with prophylactic antibiotics. The power analysis is based on detecting a 33% reduction in wound complication rate from 30% (no antibiotic) to 20% (antibiotic) at a significance level of 0.05.

In order to conduct the larger multicenter trial we propose a pilot study consisting of 50 evaluable women in order to establish the feasibility of our study.

Statistical analysis:
Statistical analysis will be performed by intention to treat analysis. However, if there are a large number of patients who are treated with prophylactic antibiotics off protocol or if patients follow-up greater than 30 days postoperatively we will perform a sensitivity analysis and will analyze per protocol.

Descriptive statistics will characterize and investigate baseline clinical and surgical characteristics between groups as well as evaluate the difference in adverse events. Categorical factors will be compared between groups by using the Chi-squared or Fisher's exact test as appropriate. Independent t-test and Mann-Whitney U-test will be used to compare normally and non-normally distributed continuous variables, respectively. The primary outcome will be compared between groups by using a Chi-squared test. We will calculate common relative risks and 95% confidence intervals associated with the primary outcome. All analyses will be performed using SAS version 9.4 (SAS Institute, Cary, NC).

13.0 REFERENCES

1. Judson PL, Habermann EB, Baxter NN, Durham SB, Virnig BA. Trends in the incidence of invasive and in situ vulvar carcinoma. Obstetrics and gynecology. 2006;107(5):1018-22.
2. ACOG Committee Opinion No. 509: Management of vulvar intraepithelial neoplasia. Obstetrics and gynecology. 2011;118(5):1192-4.
3. ACOG Practice Bulletin No. 74. Antibiotic prophylaxis for gynecologic procedures. Obstetrics and gynecology. 2006;108(1):225-34.

4. Mittendorf R, Aronson MP, Berry RE, Williams MA, Kupelnick B, Klickstein A, et al. Avoiding serious infections associated with abdominal hysterectomy: a meta-analysis of antibiotic prophylaxis. American journal of obstetrics and gynecology. 1993;169(5):1119-24.
5. Ayeleke RO, Mourad S, Marjoribanks J, Calis KA, Jordan V. Antibiotic prophylaxis for elective hysterectomy. The Cochrane database of systematic reviews. 2017;6:Cd004637.
6. Sawaya GF, Grady D, Kerlikowske K, Grimes DA. Antibiotics at the time of induced abortion: the case for universal prophylaxis based on a meta-analysis. Obstetrics and gynecology. 1996;87(5 Pt 2):884-90.
7. Gaarenstroom KN, Kenter GG, Trimbos JB, Agous I, Amant F, Peters AA, et al. Postoperative complications after vulvectomy and inguinofemoral lymphadenectomy using separate groin incisions. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2003;13(4):522-7.
8. Wills A, Obermair A. A review of complications associated with the surgical treatment of vulvar cancer. Gynecologic oncology. 2013;131(2):467-79.
9. Janda M, Obermair A, Cella D, Perrin LC, Nicklin JL, Ward BG, et al. The functional assessment of cancer-vulvar: reliability and validity. Gynecologic oncology. 2005;97(2):568-75.
10. Idsoe O, Guthe T, Willcox RR, de Weck AL. Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. Bulletin of the World Health Organization. 1968;38(2):159-88.

14.0 Acknowledgements

We would like to thank the Alvin J. Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital in St. Louis, Missouri, for the use of the Clinical Trials Core which provided statistical services. The Siteman Cancer Center is supported in part by an NCI Cancer Center Support Grant #P30 CA91842.

Appendix A

Washington University School of Medicine
Division of Gynecologic Oncology

Does antibiotic prophylaxis reduce wound complications after vulvar excision of premalignant lesions:
A Double-Blinded Randomized Controlled Trial

We are currently studying the use of antibiotics to decrease wound complication rates in women undergoing vulvar surgery for noncancerous indications. Given the location of this surgery we know women who undergo vulvar surgery are at a high risk for wound complications after surgery including wound infections and skin separations which can require special care for closure, including special dressings, nursing care and sometimes antibiotics. This represents a burden for patients, and family members who assist with wound care. Receiving antibiotics prior to your surgery may lead to a decreased complication rates. As such, we are performing a study to determine if our patients would benefit from the use of preoperative, preventative antibiotics.

All women, age 18 and older, undergoing vulvar surgery for a noncancerous indication are eligible for this study. If you choose to participate in this study you will be randomly assigned to receive antibiotics or not. Prior to skin closure we will measure the length and depth of your incision. Other than these two interventions there will be no other changes from the routine management.

If you choose not to participate in this study you will receive antibiotics at the discretion of your surgeon and you will receive routine operative and postoperative care.

There is no financial charge to participate in this study nor is there financial compensation for participation.

If you have any questions please contact one of the members of our research staff: Zuhra Korkutovic at (314) 273-1580.

Thank you very much,

Mary Mullen, M.D.

Appendix B – Day of Surgery Data Collection Sheet

Date of surgery: ____/_____/____

Patient ID _____

Did the attending surgeon know whether the patient received antibiotics? Yes No

Number of Incision(s): _____

What did you use to make the skin incision (circle one only)?

A) Scapel

B) Bovie electrocautery

C) Other _____

Subcutaneous Tissue Closed Yes No

Was the skin closed with single interrupted stitches? Yes No

If no, how did you close the incision(s)?_____

Skin incision closed with what kind of suture _____

Local anesthesia used? Yes No

If yes, type of local anesthesia used _____

If yes, injection placed (circle appropriate) Before incision After Closure

Appendix C – 2-week Follow-up Data Collection Sheet

Patient ID _____

Date of Follow-up visit _____

Wound Separation Yes No

Length of Separation _____

Width of Separation _____

Depth of Separation _____

WTD Dressing Yes No

Wound Vac Yes No

Infection Yes No

Erythema Yes No

Seroma Yes No

Hematoma Yes No

Purulent Drainage Yes No

Postoperative Antibiotics Yes No

If antibiotics, which one _____ PO IV

Hospital Admission for Wound Yes No

Wound Culture Sent Yes No

Need for Debridement Yes No

Postoperative Fever Yes No

Appendix D. Vulvar Hygiene Survey (Patient)

Subject ID: _____

Date: _____

Vulvar Hygiene Survey

Have you heard of vulvar hygiene or vulvar wound care prior to today? YES NO

PRIOR TO SURGERY… Date of surgery: ____/____/_____

Did your doctor instruct you about vulvar wound care? YES NO

Did your doctor talk about sitz baths? YES NO

How many times a day should you do sitz baths or cleanse with a showerhead after surgery?

1 2 3 4

Did your doctor talk about keeping your vulva dry? YES NO

Did your doctor talk about cleaning your vulva after urination or bowel movement?

YES NO

Did you make it a point not to regularly sit and to lie/stand when possible?

YES NO

AFTER SURGERY… Date of post-op survey ____/____/_____

Did you regularly perform vulvar wound care? YES NO

Did you perform sitz baths or cleanse with a showerhead two-three times a day?

YES NO

If yes, how many days did you do this? _____

Did you actively keep your vulva dry? YES NO

If yes, how many days did you do this? _____

Did you clean your vulva after urinating or having a bowel movement? YES NO

If yes, how many days did you do this? _____

If yes, how many days did you do this? _____