Study Protocol

Official Title of Study: A Randomized Controlled Trial of Ultrasonic Aspiration versus CO2 Laser Ablation for the Treatment of Vulvar Intraepithelial Neoplasia

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COMIRB Protocol: 16-0701

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1. Introduction

Vulvar intraepithelial neoplasia (VIN) is a chronic precancerous medical condition causing vulvar dysplasia affecting nearly 50,000 women in the United States each year. [1]The causes of pre-cancer of the vulva are multi-factorial but common risk factors including multiple sexual partners, early age at first coitus, smoking, and a history of vulvar irritation. Common to all of these causes is the association with the infection by the HPV virus. While the HPV vaccine has been used extensively to control the development of pre-cancer of the cervix, the effectiveness of this treatment has not been shown in pre-cancer of the vulva. Additionally, pre-cancers of the vulvar generally affect women in the 4^{th} and 5^{th} decade of life and therefore, many women have not received the HPV vaccine. If untreated, pre-cancers of the vulva can further develop into invasive cancers. The treatment of an actual vulvar cancer can include radical surgery for removal of the vulva, extensive dissection of the groins to obtain lymph nodes, as well as chemotherapy and radiation. These treatments can be incredible disfiguring, painful, and can have significant side effects for women.

Incidence of VIN is increasing among women and there still lacks a standard of care for optimal treatment. Current treatment options aim to treat the symptoms associated with VIN and result in a high recurrence rate. Repeated treatment leads to psychosocial and sexual distress and decreased quality of life for the affected women.[1] Treatment for vulvar dysplasia usually occurs in 3 categories: surgical excision, laser ablation and topical treatment with immune modulators. While the efficacy of all three modalities has been shown, each one has the potential for side effects. Surgical excision is difficult in multimodal disease states as this can leave the vulvar significantly disfigured. CO2 laser ablation, while effective, has been documented to scar and cause significant pain in the 1-2 weeks following surgery. [2] Topical treatments with imiquimod (an immune modulator) take up to 16 weeks to work, are difficult to apply and can cause local site irritation. Due to the high reoccurrence rate and the nature of the current treatments, a more effective treatment option is warranted. An effective treatment that targets only the diseased areas could potentially decrease recurrence rates. Additionally, a more conservative treatment modality could contribute to reduced risks of scarring, discomfort, and psychosocial and sexual distraught.

Currently there are no recent studies that have compared ultrasonic laser aspiration with conventional treatment methods. Von Greunigen et al compared CO2 laser ablation in women with VIN with ultrasonic aspiration in a randomized trial from 2000-2005. This study found no difference in recurrence rates between the two techniques (HR=.96, 95% CI .64-1.50) and suggested that women who underwent ultrasonic aspiration had less pain and less disfigurement as compared to women who underwent CO2 laser ablation. While this study is compelling, due

to its age and statistical flaws, ultrasonic aspiration has yet to be accepted as a major modality by which to treat VIN. [3]

1.1 Significance

Vulva preserving treatments are necessary women with dysplasia in order to maintain function and decrease discomfort typical with a vulvectomy. [4] However, these less invasive techniques have a high recurrence rate. Recurrence is particularly greater for those with HPV and multifocal disease. [5, 6] Women must follow these treatments with long-term surveillance, which often leads to repeat treatment and eventually dysfunction and psychological morbidity. [5] Studies have found that recurrence rates with CO2 laser ablation can range from 25-50% recurrence, while rates for ultrasonic aspiration have been found to range from 22-35% recurrence. [5, 7-13] [2, 14]

Von Greugenigen's study failed to limit the study to women with high-grade dysplasia only. As a result, the final analysis failed to meet statistical power. No RCT has been conducted since looking at reoccurrence difference and QOL outcomes associated with ultrasonic aspiration vs. CO2 laser.[3]

We propose a similar study by which to randomize women to either CO2 laser ablation or ultrasonic aspiration for the treatment of vulvar dysplasia. We estimate that we need 150 patients to achieve statistical power. We will similarly evaluate patients at 3, 6 and 12 months to assess for recurrence and pain. We will also have patients complete quality of life (QOL) surveys to assess which differences in wellness and function following treatment at baseline, 6, and 12 months.

2. Study Objectives

The primary objective of this study is to evaluate the incidence of vulva dysplasia recurrence within 12 months of treatment with CO2 laser ablation or ultrasonic aspiration. Women referred for treatment following diagnosis of VIN II/III will be randomized to receive CO2 laser ablation (typical treatment for these cases) or ultrasonic aspiration (approved treatment providing a more targeted technique).

Secondary objectives will examine incidences of pain, scarring, and sexual and psychosocial distraught following treatment for high-grade dysplasia.

2.1 Hypothesis

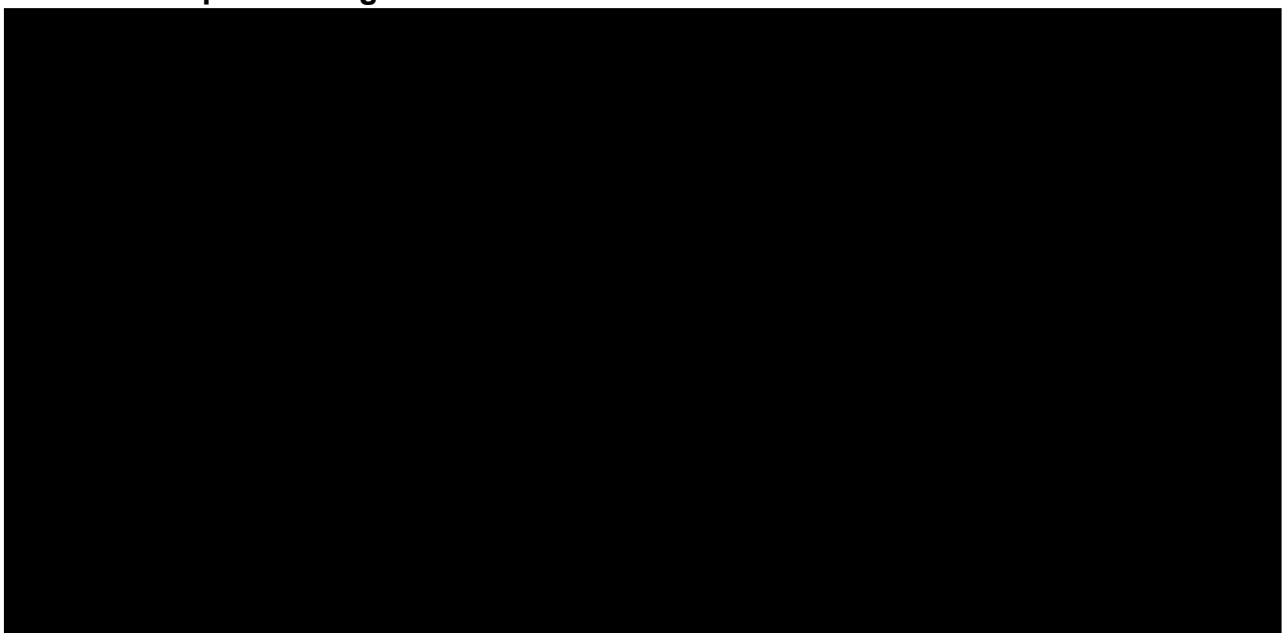
Hypothesis 1: Treatment for VIN II/III with ultrasonic aspiration will have a 60% reduction in recurrence rates over 12 months as compared to CO2 laser aspiration.

Hypothesis 2: Treatment for VIN II/III with ultrasonic aspiration will demonstrate decreased incidence of pain and scarring up to 6 weeks following treatment as compared to CO2 laser aspiration.

Hypothesis 3: Treatment for VIN II/III with ultrasonic aspiration will demonstrate a decrease in change of sexual and psychosocial function (as demonstrated with validated instruments) in the 12 months following treatment as compared to CO2 laser aspiration.

3. Preliminary Studies and Research Centers

3.1 Principal Investigator and Research Center



4. Outcome Measures

Primary Outcome: The primary outcome of this study is recurrence rates of dysplasia within 12 months of treatment. Rates of recurrence will be compared for CO2 laser ablation and ultrasonic aspiration, stratifying groups based on HPV and multifocal disease status. Recurrence will be assessed at 3, 6, and 12 months following treatment. Recurrence will be determined by repeat visual exam and colposcopy (followed by biopsy as warranted) at each of the follow-up visits. Those with recurrence will be discontinued from the study and receive appropriate treatment for their recurring dysplasia, per standard of care (SOC).

Secondary outcomes:

Secondary outcomes will compare:

1) Incidence of pain in the initial 7-10 days following treatment. Pain will be assessed using a patient pain scale. Participants will be asked to assess their own pain and report to the research team.

2) Incidence of scarring due to treatment regimen. Participants will be examined during regular post-procedure visit approximately 4-6 weeks following treatment. A visual exam of the vulva will be conducted to assess scaring.

3) Sexual function will be measured at baseline and at the 6 and 12 month follow-up visits. Changes in sexual function will be compared to baseline within each treatment arm. Overall sexual dysfunction rates will be compared between treatment arms for each study time interval. The Female Sexual Function (FSFI) and the Female Sexual Distraught Survey will be used to examine sexual function at each time point.

4) Wellness and Function will be measured using a validated instrument FACT-V health survey, designed specifically for women with vulva disease. The FACT-V provides metrics for functional, emotional, physical, and social well-being. Wellness and function scores will be compared between treatment arms for each study time interval and compared to baseline within each treatment arm.

Demographic and clinical data will also be collected in order to describe the study population and determine differences among the randomized groups. Demographic and clinical data will be verified against the participant medical records to assure data completion and minimize missing data in our analysis.

Demographic data will include: name, medical record number, contact information, date of birth, age, race/ethnicity, relationship status, and smoking status. Identifying information (name, medical record number, and contact information) will not be entered into the database by ancillary sites, and will only be used by research site to verify data, access medical records, and contact the patient for study visits. At these sites, a log will be kept with their identifiable data and participants will be linked to their study chart by study ID.

Clinical Data will include: menopause status, colposcopy results, treatment history, history of STDs, pre-existing medical conditions, concomitant medications, allergies, and vitals (blood pressure, pulse, temperature, respiratory rate, height, weight, BMI).

4.1. Study Endpoints

Patients will be enrolled at participating centers prior to receiving treatment for their VIN II/III. Baseline assessments will include all study surveys and collection of demographic and clinical data.

Pain and scarring will be assessed within the first 6 weeks following treatment. Participants will be followed at 3, 6, and 12 months for recurrence. Participants will be discontinued from the study at time of recurrence, or at the completion of 12 months follow-up. Total participation is 12 months duration.

5. Ethical Considerations

5.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board (IRB) approval before initiation of the study.

All potential serious breaches must be reported to The University of Colorado IRB immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment).

5.2 Institutional Review Board

Before study initiation, the investigator will have written and dated approval from COMIRB for the protocol, consent form, subject recruitment process, and any other written information to be provided to subjects.

The investigator will provide COMIRB with continuing review reports annually. In addition, any revised study materials or amendments will be submitted for approval prior to use/implementation.

Each additional site will obtain local IRB approval prior to any procedures being conducted. The University of Colorado Denver study team will provide study monitoring and will audit study sites, requiring direct access to source data and documents. The study will remain open with each site's local IRB until receipt of notification from coordinating site to close the study. All correspondence with the local IRB will be maintained in the study regulatory files. The sponsor may request additional audit of study sites.

5.3 Informed Consent

Potential Participants will be approached for participation at their initial visit in our gynecologic clinics. Investigators will ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Investigators will:

1) Provide a copy of the consent form and written information about the study prior to clinical study participation. The language will be non-technical and easily understood.

2) Allow time necessary for subject to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the participant and by the person who conducted the informed consent discussion.
4) Obtain IRB approval of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, will fully inform the subject of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication will be documented.

The rights, safety, and well-being of the study participants are the most important considerations and will prevail over interests of science and society.

6. Investigational Plan

6.1 Description of Population to be Enrolled

Women diagnosed with high-grade vulvar intraepithelial neoplasia (VIN II/III) will be eligible to participate. Women with prior treatment for dysplasia will be considered eligible for the study. Prior treatment for dysplasia includes all treatments such as surgery, laser ablation, and/or aldara (a topical agent).

6.1.1. Inclusion Criteria:

- Women 18-89 years old
- Diagnosed with VIN II/III (diagnosed by pathology)
- Referred for vulva sparing treatment for dysplasia
- Available for follow-up of treatment for 12 months

6.1.2 Exclusion Criteria:

- Women who are pregnant
- Women with VIN I dysplasia (diagnosed by pathology)
- Women with vaginal intraepithelial neoplasia (VAIN)
- Women requiring vulvectomy for treatment
- Women unable to provide informed consent

Women with suspected dysplasia will undergo routine biopsy for diagnosis of vulva dysplasia. Pathology will categorize disease as either "low-grade" or "high-grade" or using the grading I, II, and III. Women with high-grade dysplasia, VIN II/III, will be referred for further treatment. Women meeting the inclusion criteria will be eligible for inclusion. Women with low-grade dysplasia, VIN I, will not be included in the study.

6.2 Sample Size

Based on previous studies, approximately 37.5% of patients will reoccur within 12 months with traditional treatment (CO2 laser). [5, 7-13] We can detect a 60% reduction of recurrence to a rate of 15% at 80% power and an alpha of 0.05 with 62 patients per arm. [3] We will enroll an additional 13 patients per arm (n=75 per arm, 150 total) to account for noncompliance, lost to follow-up or misclassification diagnosis.

Approximately 75% of participants will be recruited at the coordinating site, University of Colorado Denver. The other 25% of participants will be recruited at the secondary sites Regional West Medical Center, and The University of Oklahoma are the secondary sites recruiting participants.

6.3 Research Design and Duration

This study will employ a randomized controlled trial (RCT) design. This is a phase III study to determine the effectiveness of a more targeted treatment therapy for VIN II/III (comparing ultrasonic aspiration versus CO2 laser ablation). Potential participants will be identified through the gynecological clinical practices following diagnosis of VIN II/III and will be randomized (1:1) to one of the treatment therapies. Randomization will be stratified for multi-focal disease and HPV status.

Participants will be followed for 1 year following initial treatment for recurrence of vulva dysplasia. Study events will be documented on the study clinical research forms for each visit. The study will continue until 150 participants have completed procedures, which is expected to take approximately 3 years.

7. Treatments

Both the Sonopet Ultrasonic Aspirator and the CO2 laser ablation devices are FDA approved devices for the treatment of vulvar dysplasia.

7.1 Treatment Assignment

Participants will be randomized 1:1 to either treatment with Ultrasonic Aspiration or CO2 laser ablation after consent of study. Prior to treatment, participants will receive a local anesthesia (lidocaine) to numb the affected area.

- Ultrasonic Aspiration: The Sonopet Ultrasonic Aspirator (manufactured by the Sponsor of this study) provides precise control of soft tissue while simultaneously allowing fine bone dissection in close proximity to delicate structures. The Sonopet Ultrasonic Aspirator is precise in its technique and allows users to independently control power, suction, and irrigation with one hand piece to maximize user control and efficiency. [1] The standard use of the Sonopet aspirator is to obtain a power density of 1,000 watts/cm2 in order to desiccate the tissue. The tissue will change color to a yellow color indicating the epidermal layer had been ablated.

- CO2 Laser Ablation: Lasers provide an efficient method of achieving rapid

excision, coagulation, or vaporization of pelvic abnormalities. The carbon dioxide laser has been considered an effective modality for multiple tasks related to the treatment of intraepithelial neoplasia of the lower genital tract, most commonly for large lesions and for multifocal manifestations of human papilloma virus (HPV). The use of this technology is limited in some areas because of healthcare provider training and experience and because of a lack of availability of equipment. CO2 laser also leaves destruction of the skin at treatment site, and therefore no tissue remains for further histology. However it still remains a preferred treatment modality for VIN among women. [1] The treatment area will be identified by a 3-4 mm region beyond the affected area of the cervix. The entire circumference of the anticipated ablation area is outlined as if outlining a circle with dots. These dots are then connected, and the entire area is ablated with a consistent continuous movement of the laser beam at a pulse of 10 W. The area is measured periodically with a graduated probe used through the colposcope, and the ablation continues to a depth of 7-10 mm

Following treatment participants will be prescribed NSAIDs for pain relief and a topical salve will be placed on the affected area to reduce the risk of scarring. Participants will be asked to refrain from exercise and sexual intercourse for two weeks following treatment.

All study treatment will be conducted by study-trained investigators only. The investigators chosen to participate in the study will all be board-certified gynecologists and will not include providers in-training. Gynecologists are trained to perform vulva sparing treatment in the clinical setting. All investigators elected for this study have a minimum of 3 years of clinical practice following fellowship. The coordinating site will host an in-service for all participating investigators prior to initiation of the study. The in-service will review the standard operating protocols of both devices. Ongoing monitoring and site visits by the PI will also be conducted to insure investigator compliance. In addition, secondary analysis will examine treatment differences per investigator.

Block randomization will be conducted using randomization statistical software. Research personnel will login into the study database and enter information for block randomization on the day of surgery. The randomization software associated with the REDCap data tool will provide the research team with the treatment assignment. Stratification variables will include multifocal disease and HPV status. The statistician responsible for statistical analysis will be blinded to the treatment received.

8. Study Procedures

Participants will conduct the following study visits over 12 months. All costs associated with routine standard of care procedures for diagnosing and treating vulva dysplasia will be the responsibility of the patient and/or their insurance provider.

V0: Screening: All screening will be conducted during routine standard of care (SOC) visits to our gynecologic oncology clinic or colposcopy clinic after review of colposcopy results. Baseline assessment and quality of life assessments will be conducted at this visit, and informed consent will be obtained prior to any study procedures being conducted.

V1: Enrollment Visit: All enrollments will be conducted at the time of treatment visit. Prescribed treatment will be covered by insurance, per SOC.

V2. Pain will be assed at 7-10 days following treatment. Participants will self-evaluate pain by responding to a <5-minute survey (administered electronically or via phone) asking them to rate their pain using a standard patient pain scale.

V3.
Visit 3: Approximately 4-6 weeks following treatment you will be asked to come in for a follow-up visit. A study doctor will assess your scarring at this visit. This is part of routine care. This visit is expected to take approximately 20 minutes.

V4: A SOC 6 month (± 30 days) follow-up will be conducted following treatment. Assessments include physical exam with colposcopy (biopsies performed at the provider's discretion). Assessments at 6 months are to be conducted per standard of care. This visit will take approximately 30 minutes. Quality of life assessments will be conducted at this time. This visit can take place at Colorado, Oklahoma, or Nebraska site, depending on where subject was screened.

V5: End of Treatment: A SOC 12 month (± 30 days) follow-up will be conducted following treatment. Assessments include physical exam with colposcopy (biopsies performed at the provider's discretion). Assessments at 12 months are per standard of care. This visit will take approximately 30 minutes. Quality of life assessments will be conducted at this time. This visit can take place at Colorado, Oklahoma, or Nebraska site, depending on where subject was screened.

Study Calendar

	V0: Screening	V1: Enrollment	V2: Pain Assessment	V3: Scarring Assessment	V4: 6 month follow up (±30 days)	V5: 12 month follow up (±30 days)	Unanticipated Visit
	Baseline visit	0-30 days following V0	7-10 days after treatment (survey only)	4-6 weeks after treatment	6 months following treatment	12 months following treatment	
Procedures							
Informed Consent	X						
Confirm eligibility (Inclusion/Exclusion criteria)	X						
Randomization		X					
Medical History	X						
Concomitant Medications and Procedures	X	X		X	X	X	X
Adverse Events	X	X		X	X	X	X
Lesion assessment/colposcopy (biopsy if needed)	X	X		X	X	X	X
Physical Exam	X				X	X	X
Vitals (inc. height/weight)	X	X		X	X	X	X
Scar Assessment				X			
Pain Assessment			X	X	X	X	X
Surveys	X				X	X	

9. Study Assessments

Investigators will be expected to use the treatment assignment provided and will not have the option to elect a preferred treatment. Data will be analyzed per protocol so only participants receiving the correct treatment assignment will be included in the final analysis. Training of all study investigators will be conducted prior to initiation and regular monitoring and site visits will be conducted throughout the study to ensure continued compliance. Secondary analysis will look at differences in treatment performance and scarring assessment among the investigators. Any differences will be noted in any publication of the data.

Women with gynecologic disease are afflicted with a number of psychological and social issues disrupting quality of life. Patients report changes to their social and functional well-being as well as changes to their sexual health. Quality of life assessments will be conducted at baseline, 6, and 12-month follow-ups. Patients struggling with psychosocial aspects will be referred for clinical consult as needed. The University of Colorado Hospital staffs a group of social workers who are available to meet with patients in a private clinical office if the patient expresses a psychosocial issue that requires attention.

9.1 Social and Functional Well Being

Perceived health status can be an important factor in the functional assessment for women with gynecologic disease. We plan to study overall wellness and social support as it relates to treatment in women diagnosed with VIN II/III using the following validated survey instruments:

- FACT-V: In order to assess functional health status we will use the Health Status the Functional Assessment of Cancer Therapy (FACIT) instrument specific for vulva disease called FACT-V (appendix 1.2). [16]

9.2 Sexual Function

Sexual function is often affected following treatment for dysplasia due to the high occurrence of scarring and discomfort associated with these procedures. We will evaluate sexual function as it relates to treatment women diagnosed with VIN II/III using the following validated survey instruments:

- Female Sexual Function Index (FSFI) validated survey instrument, (appendix 1.3) for overall sexual function. [17]

- Female Sexual Distress Survey (FSDS), a validated instrument for measuring sexual distraught (appendix 1.4) [18].

10. Protection Against Risks

Study staff will obtain all necessary Good Clinical Practice (GCP) and human protection HIPAA training to oblige to such standards for maintaining participant's privacy. REDCap, a secure data collection system, will be used to capture data.[19] REDCap tools provide the highest possible degree of assurance that data

will be secure. The University IT department also provides encrypted email services to internal and external recipients. Any study information communicated among the research staff will be done using the encrypted University email service.

There is a risk that subjects may feel uncomfortable answering the survey questions, particularly those regarding their sexual function. Participants will be informed that they may skip any question they feel uncomfortable answering.

11. Event reporting

11.1 Adverse Events

An Adverse Event [AE] is defined as any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable or definite). An unanticipated event is defined as any adverse experience where the nature, severity or frequency is not described in the application form or detailed in the consent form. This can also include non-compliance issues such as over enrollment of subjects without prior COMIRB approval.

The causal relationship to study treatment will be determined by the PI and used to assess all AEs and unanticipated problems. The causal relationship can be one of the following:

Possibly related: In the opinion of the PI, the adverse event is unlikely to be related to the study intervention, drug or device.

Probably related: In the opinion of the PI, it is more likely than not that the adverse event is related to the study intervention, drug or device.

Related to the research: An event is "related to the research procedures" if in the opinion of the principal investigator, it was more likely than not [probably] to be caused by the research procedures or if it is more likely that not [probably] that the event affects the rights and welfare of current participants.

The PI will report any unexpected event that is deemed to be probably related or related to the research within 5 days, per COMIRB's policy.

The risks associated with the ultrasonic aspirator and the CO2 laser ablation devices are similar with the exception that early studies suggest scarring may be significantly decreased with the use of the ultrasonic aspirator. [1] Previous studies have also suggested that the ultrasonic aspirator will have less recurrence of dysplasia following treatment. [3]Since these early studies have failed to provide significant power, this is only hypothesized at this time and is the primary outcome for this phase III study.

Adverse events that are deemed not related will be documented in the study AE log, subject study charts, and reported to COMIRB at the time of annual review,

per their policy. The coordinating site will review AEs at interim analysis. Anticipated clinical adverse events may include:

- Pain and/or discomfort (~25% of women)
- Presence of scarring (~30% of women receiving CO2 laser, less than 5% in women receiving ultrasonic aspirator)
- Dysureia or burning (~25% of women)
- Adhesions (less than 5%)
- Infection: yeast, UTI, or other (~10% of women)
- Abnormal discharge (less than 10% of women)
- Eschar (~10% of women). [1]

11.2 Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see *NOTE**: below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above

Suspected transmission of an infectious agent (e.g., pathogenic or non-pathogenic) via the study treatment is an SAE.

**NOTE: The following hospitalizations are not considered SAEs:*

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

Participants experiencing a SAE should be discontinued from the study and followed per clinical standard of care. SAEs should be documented on the AE CRF and reported to local IRB and the coordinating site within 48 hours of notification of event.

There are no known reports of serious adverse events following CO2 laser and ultrasonic aspiration for vulva dysplasia.

11.2.1 SAE Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study procedures, must be collected, including those thought to be associated with protocol-specified procedures. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study treatment, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or unrelated to the study intervention must be reported to the sponsor agent within 24 hours. SAEs must be recorded on the SAE Report Form;

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study intervention or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the sponsor (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

11.3 Non-Serious Events

A non-serious adverse event is an AE not classified as serious.

11.3.1 Non-Serious Adverse Events (NSAEs) Collecting and Reporting

The collection of non-serious adverse event (NSAE) information will begin at initiation of study treatment.

Non-serious AEs will be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study treatment, or those that are present at the end of study treatment as appropriate.

Non-serious Adverse Events are provided to local IRB and the sponsoring agent via annual safety reports (if applicable), and interim or final study reports.

11.3.1.1 Anticipated Risks

While the study anticipates minimal risks, the following outlines any potential minimum risk to subjects:

i. Breach of Confidentiality: Data obtained using information from medical records, poses minimum risk. All procedures in which information is being obtained will be conducted per standard of care. There is a risk that a patient's privacy may not be protected. This risk is uncommon.

ii. Discomforts: Persons receiving treatment for Vulvar Intraepithelial Neoplasia can anticipate the following risks: infection, dysuria, burning, adhesions, light bleeding, and discharge. Participants could expect to experience pain and discomfort following surgery for approximately 1 week. Participants should refrain from exercise and sexual intercourse in the two weeks following surgery in order to avoid addition discomfort.

iii. Recurrence: Current treatment for vulva-sparing has a recurrence rate of 25-50% of return disease. Recurrence, left unmanaged, could lead to cancer of the vulva, vagina, or the cervix.

Participation in this study will not have any influence on the patient's current treatment. The study may include risks that are unknown at this time.

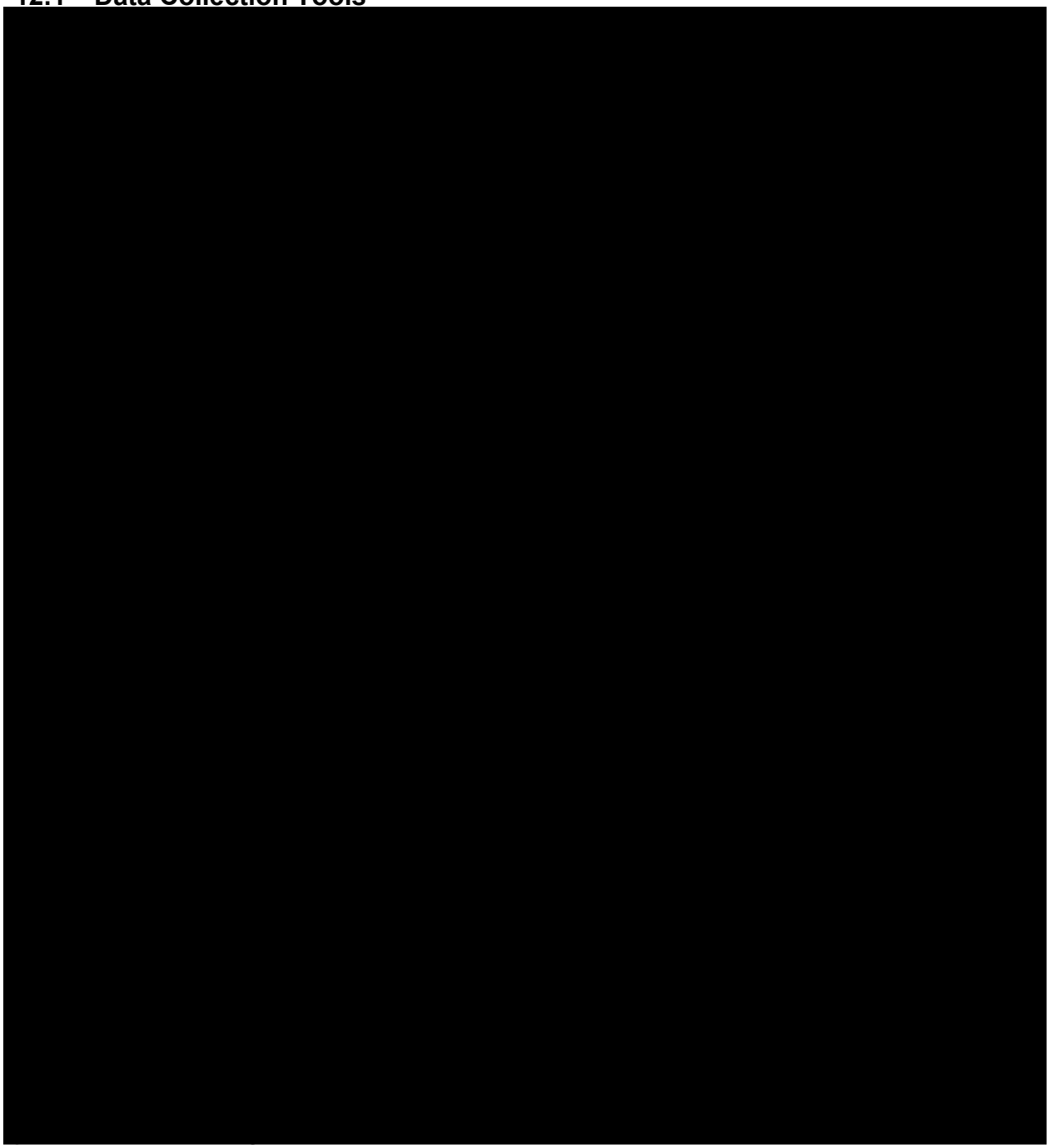
12. Data Collection and Confidentiality

This study will obtain approval for conduct through the Colorado Multiple Institutional Review Board (COMIRB) for research involving human subjects. All patients within the Gynecologic Oncology clinic at the University of Colorado Cancer Center who meet the study criteria will be considered eligible for the study. We will not enroll any vulnerable populations as defined by ethical guidelines, but will follow participants that may become pregnant during the 12 month participation duration. Potential participants will be screened by the PI/Co-I and the research team and approached for consent. Consent will occur prior to the initiation of any study procedures at a scheduled clinic visit in the Gynecologic Oncology clinics of participating sites. Potential participants will be provided a private setting for in-person consent and will be adequately informed of the study intent, requirements, and potential risks and benefits. Patients will also be informed that any participation is voluntary and will not affect any clinical care they are to receive. Research staff providing consent will be certified in Collaborative Institutional Training Initiative (CITI) and Human Insurance Portability and Accountability Act

(HIPAA) trainings for ethics and human protection. Patients will have time to review the consent and ask any questions prior to signing consent.

For secondary sites, additional approval will be obtained by the institution's local IRB.

12.1 Data Collection Tools



12.2 Data Integrity and Protection of Confidentiality

13. Study Monitoring

There are no investigational treatments associated with consent into the study, as both treatments are currently approved for the treatment of VIN in women 18-89 years old. Each study site will obtain local IRB approval. The Primary Investigator will be responsible for monitoring the study for unanticipated problems and SAEs and report them to lead and local IRBs as appropriate. No interim analysis will be conducted.

13.1 Medical Monitoring

Medical monitoring and monitoring of SAEs across all sites will be monitored by Dr. [redacted] on a continuous basis. All SAEs must be reported to [redacted] at the University of Colorado within 48 hours of event. The sponsoring site will be responsible for reporting such events to the overseeing IRB within 5 days of event. Interim analysis will be done with data from all sites after 4 months of enrollment to examine any increased risk of SAEs as expected from standard of care.

13.2 Safety Monitoring Plan

The Principal Investigator (PI) will be responsible for executing the safety monitoring plan, and complying with all reporting requirements to local and federal authorities. This safety monitoring plan will be conducted via the use of a safety officer. The safety officer will be a 3rd party reviewer, affiliated with the University of Colorado Denver but with no direct affiliation to the research study or the sponsor. The safety officer will be identified by the PI prior to initiation of the study. This study does not require a full data safety monitoring board since there are no investigational devices or treatment interventions in this study.

The safety officer is responsible for providing an independent safety review and trial guidance during the course of the study. A summary of the safety officer's activities is as follows:

- Review the initial protocol and make recommendations towards safety concerns
- Review study recruitments and enrollments over course of the study
- Review procedures for data quality control over the course of the study
- Set the parameters for monitoring review, and interim safety analysis
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety conduct issues
- May submit recommendations for corrective actions to the PI to address safety concerns

Per the Safety Monitoring Plan, SAEs, UAPs and reportable AEs are reported to the safety monitor, IRB and the sponsor per study protocol. All SAEs, UAPs and reportable AEs are to be reported to the safety monitor within 5 business days of receiving notification of the occurrence. Non-reportable AEs will be reported in the safety monitoring report provided to the safety officer every 12 months.

Each subject's treatment outcomes will be discussed by the Investigators and Clinical Research Coordinators (CRCs) at regularly scheduled disease-oriented working group meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The PI will provide a safety report to the safety monitor on a 12-month basis. The report will include a protocol summary, current enrollment numbers, summary of data to include specific SAEs, UAPs and AEs, all protocol deviations, and protocol amendments. The safety report will also include, if applicable, the results of any efficacy data analysis conducted, as well as any sponsor-related safety reports. Results and recommendations from the review of this annual report by the safety monitor will then be submitted by the site to the IRB of record at the time of continuing review.

The coordinating site (UCD) is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial's annual safety report to the safety officer to include minutes from monthly PI teleconferences. Research staff at the University of Colorado Denver Department of Obstetrics and Gynecology will conduct monitoring internally of the coordinating site internally and for all secondary sites outside the institution. Each participating site will be responsible for submitting the results and recommendations from the annual safety review to their IRB of record at the time of continuing review.

14. Statistical Analysis

A per protocol analysis will be conducted. Participants receiving treatment per protocol will be included in the final analysis. Investigators will not have the option to change treatment assignment.

Descriptive statistics using means, frequencies, and percentages will be computed to describe the study population. Participant data will be analyzed employing the per protocol approach. Student's *t*-test (for continuous variables) and chi-square tests (for categorical variables) will be used to compare the two groups for demographic, and secondary outcome variables: pain, scarring, QOL scores. For the primary outcome measure rate of recurrence for each of the study endpoints, 3 months, 6 months and 12 months will be calculated per treatment arm and compared with initial bivariate analysis using chi—square analysis. Additional predictors for recurrence (pain, scarring, sexual function, and general wellness) will be compared similarly with chi-square for categorical variables and t-tests for continuous variables. Potential covariates (age, race, previous disease, etc.) will also be analyzed using bi-variate analysis. Variables found to be significant in the bivariate analysis will be included in multivariable analysis using logistic regression. Logistic regression models will be used to identify significant independent predictors associated with recurrence for each treatment arm. The logistic model will allow for control of study covariates. A p-value of <0.05 will be used to demonstrate statistical significance. IBM SPSS version 22 will be used for all statistical analyses.

Incidence of AEs and SAEs will be compared between treatment arms using chi-square analysis. A p-value of <0.05 will be used to demonstrate statistical significance.

14.1 Primary Endpoint

The primary endpoint for the study is recurrence of vulvar dysplasia. Recurrence will be assessed by physical exam and colposcopy. Further exam by biopsy will used to assess recurrence when appropriate, per provider's discretion. All clinical guidelines for referring to colposcopy should be followed, per standard of care.

14.2 Secondary Endpoints

The secondary endpoints for this study are as follows:

Pain: Pain in the initial 7-10 days following treatment will be self-assessed using a pain scale. Average pain scores and incidence of high-level of pain will be determined for each treatment arm.

Scarring: Scarring in the 6 weeks following treatment will be assessed via visual exam by a study investigator. Incidence rates of scarring will be determined for each treatment arm.

Sexual function and sexual distraught: Sexual function and distraught will be assessed at baseline, 6, and 12 months following treatment. Mean scores for

function and distraught will be determined for each treatment arm per study time-point. Sexual function and distraught will be measured with validated instruments, The Female Sexual Function Index, and the Female Sexual Distress survey (Appendix 1.3 and 1.4).

Wellness and Function: General wellness and function will be assessed at baseline, 6, and 12 months following treatment. Mean scores for general function will be determined for each treatment arm per study time-point. Wellness will be measured using the validated instrument FACTS survey for vulvar malignancies (Appendix 1.2).

15. Study Management

15.1 Compliance with the Protocol

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be reviewed by the study investigators and appropriate collaborators. The investigator will not implement any deviation or change to the protocol without prior review and documented approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

15.1.1 Protocol Amendments

Any amendments to the protocol will be first reviewed by the study team and then submitted to the IRB of the lead site for approval. Sub-sites will then be required to submit the protocol amendment to their local IRB and maintain all submission and approvals in their regulatory files. Sites will not initiate any changes to study procedures until after approval of the protocol amendment by their local IRB. Insignificant changes (i.e. personnel changes) may not have to be submitted to the sponsor and/or lead site first.

15.1.2 Subject Withdrawals

All participant documentation up until study withdrawal will be maintained and used for data analysis. In the event a participant is lost to follow-up, 3 documented attempts will be made to contact the participant to conduct an end of treatment visit. If after 3 attempts, the participant still does not return, a certified letter noting withdraw from study should be sent to the participant. The study coordinator will maintain a return receipt for such. Additionally, the study coordinator should send a self-addressed package to the participant for return of any study medications and/or study documents.

15.1.3 Participant Confidentiality

Data obtained during conduct of this study is to remain confidential and private. Participant confidentiality must be obtained in accordance to regulations set forth by Good Clinical Practice and HIPAA. Release of study data should only be done through the publication/presentation of results, lead by the Principal Investigator (PI). Study sites should not release any confidential data or

findings of this study without the consent of the PI and the study sponsor.

15.1.4 Clinical Monitoring

Clinical monitoring of the study will be conducted by research personnel (data manager) from the University of Colorado Denver for all additional sites. The University of Colorado will conduct their own audit and validation of study entry with internal research personnel through the Clinical Research Support Center. In order to conduct monitoring, study sites should make staff and resources available for the following:

- Initial in-service of the study site, including investigator training and site tour
- Regular attendance of progress meetings
- Research staff available for interim monitoring visits
- All study documents (consents, CRFs, et) available for site visits in which the monitor will verify accuracy of data as entered into the electronic database
- Response to data requests via fax/email if site visit is not necessitated
- Maintenance of all regulatory documents and accessible for monitor review (UCD may request these be sent to the lead site for regulatory maintenance)
- Research staff available to response to data queries and resolve inconsistencies in study records
- Close out of the study at the study site

The study monitor will provide each site with a report of the monitoring visit to be submitted to their local IRB. In addition to monitoring visits, a monthly conference call will take place among all sites to discuss treatment outcomes, enrollment, significant toxicities, dose modifications, and responses. These meetings will be documents and the minutes shared with all sites.

Additionally, the University of Colorado DSMC may request a site audit to evaluate conduct and compliance of the investigational protocol as a study site. All study documents and regulatory documents must be available to audit. The audit reviewer will also require direct access to study source (participant medical records relating to study) and time with the site investigator and/or regulatory personnel during their visit.

15.2 Records Retention

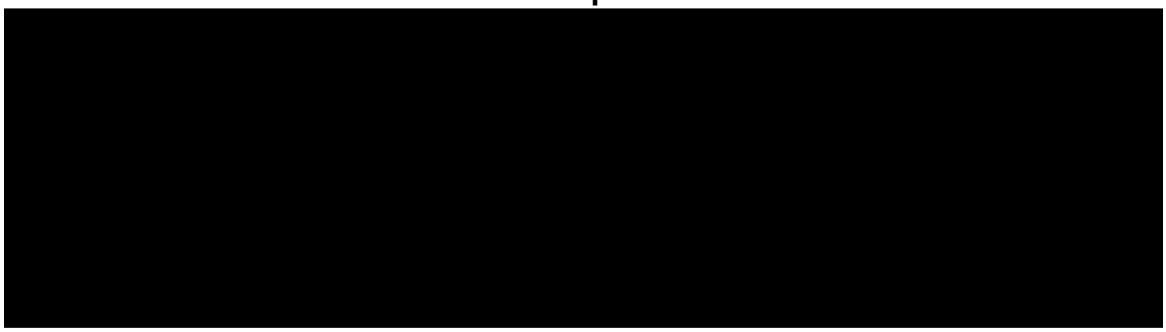
Study documents will be retained for 7 years after the IRB acknowledgement of study closure, per HIPAA regulations.

All study documentation should remain on study site in a secured area with limited access.

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by UCD, whichever is longer.

If the investigator withdraws from the study (e.g. relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another investigator, IRB). Notice of such transfer will be given in writing to the study sponsor.

15.2.1 Research Electronic Data Capture



15.2.2. Data Management

15.2.3 Confidentiality and Reporting of Results

The information on individual subjects arising from this study is to be considered confidential and transmitted to the sponsor only in a form that will not permit identification of the individual. The information obtained from the subjects that can be identified with the subject will remain confidential within the research team. Research teams will maintain all records in a secure area with limited access. Regulatory and sponsoring agencies may request access to the study records and related medical records of each participating subject. If requested, the subject's identity will remain confidential to the extent permitted by the applicable laws and regulations. The results of the research will be released to public agencies including regulatory agencies, clinical investigators, and research organizations without reference to items identifiable to a particular subject. The results will be published such that the identity of the subjects will not be disclosed and cannot be ascertained.

15.3 Publication Policy

Data on the use of the study interventions and results of all clinical study are considered confidential. UCD will lead any publication of the results of the study. Any publications or presentations that result from this study will maintain confidentiality of study participants.

15.4 Conflict of Interest

Investigators will be affiliated with their study sites and have no affiliation with the sponsoring agency. They will receive support for this clinical trial from the study sponsor but will not profit from results, either positive or negative, with regard to the product being evaluated. The sponsoring agent could profit from the successful development of this product.

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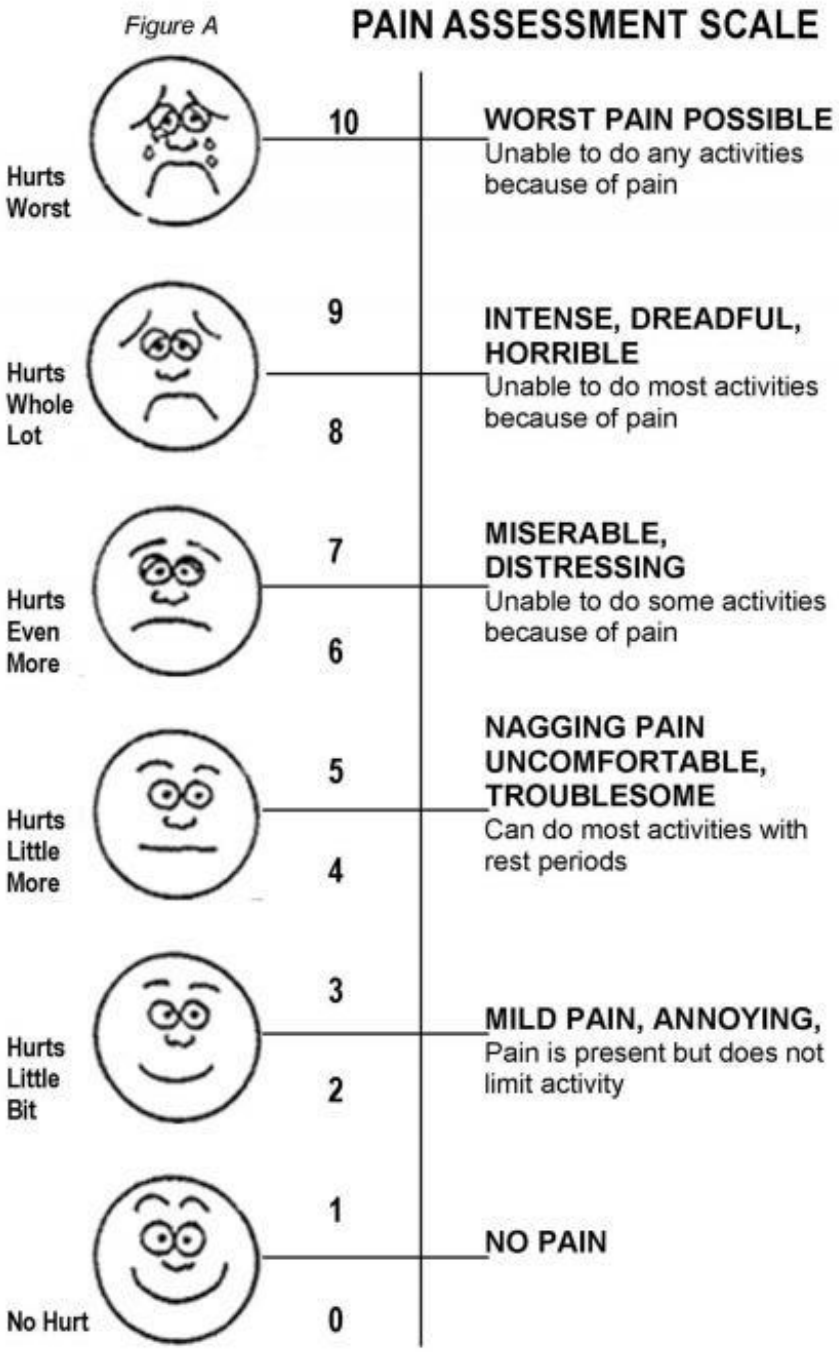
Appendix 1: Survey Instruments

Appendix 1.1 Pain Assessment Scale

Figure A



Appendix 1.2 FACT-V (Version 4)

For Vulva Cancer diagnosis only

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4

GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	<u>FUNCTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**

GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>ADDITIONAL CONCERNS</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
V1	I am bothered by discharge or bleeding from my vulva	0	1	2	3	4
V2	I am bothered by odor coming from my vulva	0	1	2	3	4
Cx3	I am afraid to have sex	0	1	2	3	4
V3	I am bothered by swelling/fluid in my legs	0	1	2	3	4
Cx4	My vagina feels too narrow or short	0	1	2	3	4
V4	I am bothered by discomfort in my groin or legs	0	1	2	3	4
Cx5	I am afraid the treatment may harm my body	0	1	2	3	4
BI4	I am interested in sex	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
BI1	I have trouble controlling my urine	0	1	2	3	4

V5	I am bothered by itching/burning in my vulva area	0	1	2	3	4
Cx7	I have discomfort when I urinate	0	1	2	3	4
V6	I am bothered by pain or numbness in my vulva area	0	1	2	3	4
V7	I have trouble bending	0	1	2	3	4
V8	I have discomfort when I am sitting	0	1	2	3	4
V9	I am bothered by wearing compression stockings	0	1	2	3	4
H&N1	I am able to eat the foods that I like	0	1	2	3	4

Appendix 1.3 Female Sexual Function Index (FSFI)

These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible.

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.
Sexual intercourse is defined as penile penetration (entry) of the vagina.
Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.
Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.
Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

1. Over the past 4 weeks, how often did you feel sexual desire or interest?
   - o Almost always or always
   - o Most times (more than half the time)
   - o Sometimes (about half the time)
   - o A few times (less than half the time)
   - o Almost never or never

2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire

or interest?

- Very high
- High
- Moderate
- Low
- Very low or none at all

3. Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

4. Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?

- No sexual activity
- Very high
- High
- Moderate
- Low
- Very low or none at all

5. Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?

- No sexual activity
- Very high confidence
- High confidence
- Moderate confidence
- Low confidence
- Very low or no confidence

6. Over the past 4 weeks, how often have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

7. Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse?

- No sexual activity

- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

8. Over the past 4 weeks, how difficult was it to become lubricated ("wet") during sexual activity or intercourse?

- No sexual activity
- Extremely difficult or impossible
- Very difficult
- Difficult
- Slightly difficult
- Not difficult

9. Over the past 4 weeks, how often did you maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

10. Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- No sexual activity
- Extremely difficult or impossible
- Very difficult
- Difficult
- Slightly difficult
- Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?

- No sexual activity
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?

- No sexual activity
- Extremely difficult or impossible

- Very difficult
- Difficult
- Slightly difficult
- Not difficult

13. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?
- No sexual activity
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

14. Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?
- No sexual activity
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

15. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

16. Over the past 4 weeks, how satisfied have you been with your overall sexual life?
- Very satisfied
- Moderately satisfied
- About equally satisfied and dissatisfied
- Moderately dissatisfied
- Very dissatisfied

17. Over the past 4 weeks, how often did you experience discomfort or pain during vaginal penetration?
- Did not attempt intercourse
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

18. Over the past 4 weeks, how often did you experience discomfort or pain following vaginal penetration?

- Did not attempt intercourse
- Almost always or always
- Most times (more than half the time)
- Sometimes (about half the time)
- A few times (less than half the time)
- Almost never or never

19. Over the past 4 weeks, how would you rate your level (degree) of discomfort or pain during or following vaginal penetration?

- Did not attempt intercourse
- Very high
- High
- Moderate
- Low
- Very low or none at all

1.4 Female Sexual Distress Scale (FSDS-R)

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes how often that problem has bothered you or causes you distress during the past 30 days including today. Circle only one number for each item, and take care not to skip any items.

How often do you feel...	**Never**	**Rarely**	**Occasionally**	**Frequently**	**Always**
1. Distressed about your sex life	**0**	**1**	**2**	**3**	**4**
2. Unhappy about your sexual relationship	**0**	**1**	**2**	**3**	**4**
3. Guilty about sexual difficulties	**0**	**1**	**2**	**3**	**4**
4. Frustrated by your sexual problems	**0**	**1**	**2**	**3**	**4**
5. Stressed about sex	**0**	**1**	**2**	**3**	**4**
6. Inferior because of sexual problems	**0**	**1**	**2**	**3**	**4**
7. Worried about sex	**0**	**1**	**2**	**3**	**4**
8. Sexually inadequate	**0**	**1**	**2**	**3**	**4**
9. Regrets about your sexuality	**0**	**1**	**2**	**3**	**4**
10. Embarrassed about sexual problems	**0**	**1**	**2**	**3**	**4**

11. Dissatisfied with your sex life	**0**	**1**	**2**	**3**	**4**
12. Angry about your sex life	**0**	**1**	**2**	**3**	**4**
13. Bothered by low sexual desire	**0**	**1**	**2**	**3**	**4**