Alterations in the vaginal microenvironment using a non-pharmacological intervention for breast cancer patients treated with aromatase inhibitors

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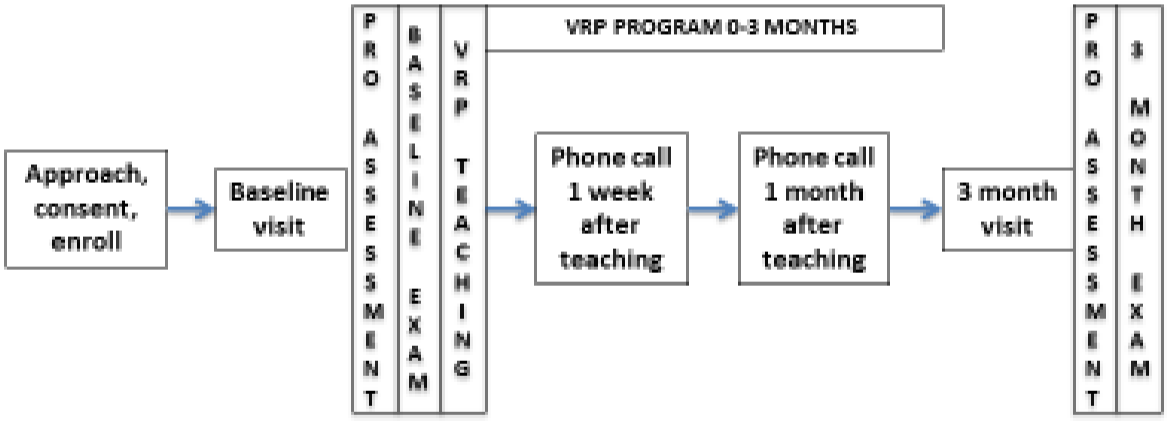
Schema



1.0 INTRODUCTION

Breast cancer is the most common cancer experienced by women, and an estimated 4 million American women are breast cancer survivors.[1] Many of these women must take ongoing medications after adjuvant treatment to further reduce the risk that the cancer returns. Aromatase inhibitors (AIs) are commonly indicated for this purpose. AIs reduce hormone receptor-positive (HR+) breast cancer recurrence by decreasing the level of serum estrogens in postmenopausal women.[2] However, AIs can cause significant side effects that reduce patient adherence. Although estimates vary based on the population surveyed, between 20-55% of women report occasional to frequent non-adherence. [3-5] Early discontinuation of AI therapy results in an increased risk of cancer recurrence and increased risk of breast cancer-related death.[5] Common side effects include vaginal dryness and vulvovaginal atrophy leading to worsening sexual function.[6] This is because normal vaginal lubrication depends on the bioavailability of nitric oxide (NO) in the vaginal epithelium, and this is greatly enhanced by steroid hormones (i.e. estrogen).[7,8] Additionally, the estrogen deprived state of menopause leads to decreased acidification of the vagina (increased pH) which is strongly correlated with

vaginal health.[9] Unfortunately, the increased circulating estrogens from systemic and vaginal hormone replacement therapies may be detrimental for women with HR+ breast cancer due to proven or suspected increase in breast cancer risk.[10,11]. Non-hormonal treatments to decrease vulvo-vaginal side effects and improve adherence to life-saving therapies are lacking and severely needed.

An alternative mechanism for stimulating NO production occurs when vaginal capillary endothelia are exposed to sheer stress or vibration.[12] This mechanism is proposed to explain the symptomatic benefits accrued by the Vaginal Renewal Program (VRP) participants. The physical therapy program known as the VRP was created in 1998 by Ellen Barnard, MSW and Myrtle Wilhite, MD.[9] The VRP employs a therapeutic vibrating wand used in the vagina. This was developed specifically to address concerns common among cancer survivors experiencing vulvovaginal atrophy and dryness. The vibrating wand is approved as class I durable medical device by the US Food and Drug Administration (FDA). The VRP was created to improve symptoms of vulvovaginal atrophy and vaginal dryness - two of the most commonly experienced side effects that lead to AI discontinuation. The VRP is outlined below under *Intervention*. Despite being developed in 1998 and in routine clinical use, little published data exists to support changes in vaginal physiology or symptomatic benefit from the VRP. As a result, the VRP is not covered by insurance and cannot be made widely available to women.

2.0 STUDY HYPOTHESIS & OBJECTIVES

2.1 Hypothesis

We hypothesize that the percentage of superficial vaginal cells on cytology evaluation as well as vaginal pH will improve after 3 months of using the VRP in menopausal subjects receiving maintenance AIs for Stage 0-3 hormone receptor-positive breast cancer.

2.2 Primary Objective

To assess for an increase in the percentage of superficial vaginal cells on a cytology evaluation after 12 weeks of VRP use. The reason vaginal cytology is being measured is because it is the method of choice for objective evaluation of vaginal atrophy.[13] Vaginal cytology has been used to prove the efficacy of other therapies that improve symptoms of vaginal dryness and atrophy.[14] The 3-month time point is being used because multiple prospective studies using hormonal therapies to improve vulvovaginal atrophy used this as the primary time point to assess efficacy.[15-20] Assessment parameters for superficial vaginal cells is taken from this literature.[15,16,20]

2.3 Secondary Objectives

2.3.1 To evaluate changes in vaginal pH from the baseline time point to 12 weeks after initiating the VRP in the same patient population.

2.3.2 To evaluate changes in patient-reported outcomes (PROs) **(*see SECTION 9.1.3*)** in the same population between the baseline time point to 12 weeks after initiating the VRP.

2.4 Exploratory Objectives

2.4.1 To assess percentage of subjects who adhere at least 90% to AI therapy throughout the course of the study.

3.0 STUDY DESIGN OVERVIEW & RATIONALE

We will utilize a prospective Simon two-stage Phase II study design. Breast cancer patients who have completed primary active therapy for breast cancer (e.g. surgery, chemotherapy and/or radiation) and are currently taking maintenance aromatase inhibitors (AIs) such as anastrozole, letrozole or exemestane will be approached. We will assess response to the VRP with a blinded standardized interpretation of superficial vaginal epithelial cells. Entrance criteria will stipulate baseline measurements must be < 2%. If the subject has ≥ 4% superficial vaginal cells on cytologic evaluation after the intervention period, then the response will be considered positive.

After documentation of eligibility according to the inclusion and exclusion criteria (***see Section 5.0)*** and after enrollment, the subject will receive instruction in the VRP (***see Section 6.0*** for details and ***Study Schema***). Baseline demographic data, baseline vaginal cell cytology, vaginal pH, and PROs will be collected prior to initiating the VRP instruction. During the time on study, subjects will log their adherence to the prescribed therapy schedule of the VRP and AI therapy. Subjects will receive reminder contacts from study staff/team member 1 week and 1 month after initial instruction. These calls will function to ensure that subjects have had adequate instruction, and problem-shoot any issues with adherence to the program and logging adherence. The subject will return the journal at the 12-week study completion visit when vaginal cell cytology, vaginal pH, and PROs will be assessed.

The primary endpoint of percent superficial vaginal cells will be determined via blinded review by a board-certified pathologist experienced with interpretation of cytology. Secondary endpoints of pH will be logged at the time of the exams and PROs will be determined by standardized, validated scoring metrics for the respective PRO measures used. The exploratory analysis of AI adherence will be determined using patient-reported logs.

4.0 RECRUITMENT AND ENROLLMENT

4.1 Design

A non-randomized, single-arm Simon phase II design will be used with participants who are eligible and give informed, written consent.

4.2 Recruitment

Subjects will be recruited with the assistance of the UWCCC research staff..

To increase accrual, the research staff will employ the following strategies:

1) Study staff will identify current patients with Stage 0-3 breast cancer who are receiving aromatase inhibitors (anastrozole, letrozole or exemestane). Study staff will focus on patients who have upcoming follow-up visits at the UW.
2) Identified patients may be sent a letter or a MyChart message briefly describing the study (see script in Appendix 2)
3) Patients who receive the letter or message will be asked in the letter or message to contact the research staff via phone or email within a 7-day time-frame if they ***do not wish*** to be approached with information about the study ("opt-out").
4) Research staff will contact patients who do not opt-out. Research staff will attempt to contact patients, via phone, up to 3 times over the course of 2-3 weeks to discuss

their interest in learning about the study. At the time of the phone call, patients may decline this conversation if they are not interested in the study. See script in Appendix 3.

5) For patients that staff are not able to contact or who wish to delay the conversation, the research staff will notify the treating physicians to discuss the study further at the time of the clinic visit.
6) For interested patients, research staff will review the trial by phone or in person. With the patient's permission, research staff may ask questions related to medications, recent surgery or anti-cancer therapies and menopausal status to determine gross eligibility.
7) To obtain final consent, enroll subjects into the study and complete baseline evaluations, research staff will employ a standard opt-in approach. This would be scheduled at a time convenient to the patient, and would likely coincide with a scheduled clinical follow-up visit. This would reduce the participation burden for interested patients.
8) Patients may also be approached by a member of their clinical team when present for a routine clinic visit. The clinic team member will introduce the study to potentially eligible patients. If the patient is interested in learning more about the study, a member of the research team will review the study details and continue with the informed consent process.

4.3 Consented subjects will be registered to the study using the OnCore database by study staff.

4.4 Intervention
All subjects on this study will receive the VRP intervention. Enrolled subjects will receive in-person instruction on how to perform the VRP.

The instructor is a certified sexuality counselor who has been trained in the instruction of the VRP.

The VRP consists of instructing subjects regarding digital physical therapy techniques for the vulva and vaginal introitus as well as internal physical therapy techniques using a therapeutic vibrating vaginal wand designed for the VRP and FDA-approved as a class I durable medical device (FeMani Vibrating Massage Wand). Details of the program are outlined in a brochure that will be provided to participants.

4.5 Study Completion Visit After 12 weeks (+/- 4 weeks) subjects will return to see the provider, return log books documenting adherence to prescribed therapy, have repeat vaginal cell cytology samples and pH testing, and complete post-intervention PRO surveys.

5.0 SUBJECT ELIGIBILITY

5.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

_____**5.1.1** Females ≥ age 18 diagnosed with Stage 0-3 breast cancer

_____**5.1.2** Have completed active primary treatment

- Defined as surgery, chemotherapy and/or radiation for the treatment of breast cancer
- Does not include immunotherapy or other targeted therapies such as trastuzumab, CDK 4/6 or mTOR inhibitors

_____**5.1.3** Have been receiving AIs for at least 6 months prior to enrollment

_____**5.1.4** Plan to continue AIs for an additional 3 months

_____**5.1.5** Amenorrhea for at least 12 months at enrollment regardless of cause

_____**5.1.6** Participants must be able to read and write in English

_____**5.1.7** Participants must have < 2% superficial vaginal cells on cytologic evaluation

5.2 Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

_____**5.2.1** Pre-existing hypertonic pelvic floor dysfunction identified in the medical record

_____**5.2.2** Unresolved or recurrent vaginismus identified in the medical record

_____**5.2.3** Aversion to touching one's own body, including genitals, or using vibration therapy on the genitals

_____**5.2.4** Currently receiving estrogen therapy, including topical and/or systemic estrogens

_____**5.2.5** Have received estrogen therapy within 6 months of study enrollment, including topical and/or systemic estrogens

_____**5.2.6** Any surgical procedure to the vagina or vulva, excluding office biopsies, within the previous 12 months

_____**5.2.7** Receipt of pelvic or vaginal or vulvar radiation therapy within the 12 months prior to enrollment or if the subject is anticipated to receive radiation targeted to any of these 3

locations within 6 months following enrollment

5.2.8 Any use of the VRP off study within the last 6 months

6.0 DOSAGE AND ADMINISTRATION OF INTERVENTION

The VRP is a standardized program. The description has been put into pamphlet form and will be given to the subjects as part of the study materials.

For the external component, the program begins by instructing the subject to use a quarter-sized amount of moisturizing lubricant on the fingers. Using this moisturizer, a press-release motion is taught to be used over the entire vulva. This is repeated for the vaginal introitus. These activities are encouraged to be performed 3 to 4 days per week.

For the internal component, the instructor will select the appropriate size of the FDA-approved vibrating vaginal wand to be used in this study. The subject will be instructed in the proper lubrication of the vibrating wand and how to insert it to the deepest comfortable depth. When the vibration function is activated, the subject is instructed to find a comfortable position and allow a 5-minute vibration cycle. These activities are encouraged to be performed 3 to 4 days per week.

7.0 PATIENT MATERIALS

7.1 Instructional materials
Subjects will receive a pamphlet outlining the steps of the program for quick, accurate and discrete reference after they receive in-person instruction.

7.2 Program materials
Subjects will receive personal lubricant in sufficient quantity to perform the program per protocol for 12 weeks. They will also receive the FeMani Vibrating Massage Wand free of charge. This a class 1 durable medical device approved by the FDA.

7.3 Log materials
Subjects will receive a logbook and will be asked to record the amount of times they perform both the internal and external portions of the VRP on a weekly basis as well as number of times they did not take their Aromatase Inhibitor.

8.0 TREATMENT COMPLIANCE

8.1 Assessment of Treatment Compliance
A member of the study team will contact subjects at 1-2 weeks and 1 month (+/- 1 week) after baseline VRP instruction to assess adherence to the program, to remind the subject to log adherence to the VRP, to remind the subjects to document when they take their AI, to answer any questions regarding the program, and to offer any additional instructions regarding the program. The preferred contact will be phone-based.

8.2 Subject replacement
For this study, lack of adherence will be defined as < 3 days/week participation for 2 weeks or

more as assessed on the 1-month phone call. If a subject is found to be not adhering to the study protocol, a new subject will be enrolled in a 1:1 ratio. Subjects lost to follow-up for any reason will be replaced in a 1:1 ratio. All subjects enrolled and not lost to follow-up, regardless of adherence status, will have their data collected and analyzed accordingly.

9.0 STUDY EVALUATIONS

9.1. Study Procedures

The Schedule of Events summarizes the timing of evaluations and data collection (***Appendix 1).*** Baseline PRO assessments should be conducted after eligibility is verified and before any tests, procedures, or trainings to prevent influencing subject perceptions.

9.1.1 Pre-intervention cytology collections

A clinician trained in the collection of lower female genital tract cytology specimens will collect the vaginal cell cytology. The collection is done in a process similar to a routine PAP test. A swab is placed into the vagina and is wiped against the vaginal wall to collect cells and fluids. The amount collected will be equivalent to a routine PAP test. The cytology specimen will be transported to the pathology department inside a Biohazard bag inside an opaque sealed envelope. The specimen will be prepared by standard cytology techniques. Slides will be housed in a UWCCC research office.

At the end of the study, slides will be randomly labeled and organized such that it is impossible t o identify timing of collection, or even if the slides are associated with the same participant. Following this blinding, all slides will be interpreted by a trained cytopathologist and destroyed after final study analysis

9.1.2 Pre-intervention vaginal pH collections

At the time of cytology collection, standard clinical-grade pH paper will be used to swab the vagina to assess vaginal pH. This will be interpreted by a clinician blinded to the study and recorded by the clinician.

9.1.3 Pre-intervention PRO assessments

If the subject has been found eligible, gives written consent and is enrolled, baseline demographic data will be gathered from the patient and the medical record and baseline PROs will be collected**.** PROs being assessed in this study will be: Vaginal Symptoms Questionnaire, NIH PROMIS Global Health scale, NIH PROMIS Female Sexual Function Profile, NIH PROMIS Global Satisfaction with Sex Life scale, NIH PROMIS Anxiety 8a scale, NIH PROMIS Depression 8a scale. PROs will be completed at the instructional visit, prior to receiving the instructions.

All PRO assessments will be done electronically via REDCap, UW Qualtrics, or on paper at the UWCCC/UWHC..
They will require approximately 20 minutes to complete. If the surveys are completed on paper, a member of the study staff will collect the PRO assessments in an opaque-sealed envelope and transport them to the secure locked study office that is administering this study. Surveys will be identified by study ID and date of completion to protect confidentiality of subject.

9.2.1 Post-intervention cytology collections

A clinician trained in the collection of lower female genital tract cytology specimens will collect the cytology. The amount collected will be equivalent to a routine PAP test. The cytology specimen will be transported to the pathology department and stored as documented in ***Section 9.1.1***. At the completion of each stage of the study, all pre-intervention cytology collections and post-intervention cytology collections will be pooled and interpreted with the specimens blinded as to the timing of the collections.

9.2.2 Post-intervention vaginal pH collections

At the time of cytology collection, standard clinical-grade pH paper will be used to swab the vagina to assess vaginal pH. This will be interpreted by a clinician blinded to the study and recorded by the clinician.

9.2.3 Post-intervention PRO assessments

All PRO assessments will be done electronically via REDCap or UW Qualtrics, or on paper at the UWCCC/UWHC. They will require approximately 20 minutes to complete. If the surveys are completed on paper, a member of the study staff will collect the PRO assessments in an opaque-sealed envelope and transport them immediately to the secure locked study office that is administering this study. Surveys will be identified by study ID and date to protect confidentiality of subject. PROs will be completed by the subject prior to vaginal swab/collection.

9.3 Logbooks

The logbooks will be provided to subjects at the baseline visit. We will ask the subject to enter the d a y s they have performed the VRP program during the study. They will also be asked to record the number of days of each week that they did not take their Aromatase Inhibitor. Subjects will be reminded to enter data into this log with phone calls approximately 1 week and approximately 1 month after VRP instruction. Logbooks will be collected from subjects at the study completion visit.

9.4 Study Completion Visit

All subjects will be asked to return 12 weeks (+/- 4 weeks) after in-person instruction of the VRP program. Subjects will complete post-intervention PROs prior to undergoing vaginal swab/collection. Subjects will be asked to bring and turn in the logbooks for analysis.

9.5 Adverse Device Effects

Adverse Device Effects will be reported by the subject or investigator for the duration of the study. Unanticipated adverse device effects will be reported to the appropriate regulatory agencies per section 15.

10.0 MEASUREMENT OF INTERVENTION EFFECT

10.1 Response

A positive response to the VRP intervention will be confirmed if the percentage of superficial vaginal cells changes from $< 2\%$ to $\geq 4\%$ from pre-intervention to post-intervention.

11.0 STATISTICAL METHODS

All statistical analyses will be done by the study biostatistician. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below.

11.1. Subject Information

For all subjects who are enrolled in this study, descriptive statistics will be provided.

11. 2 Sample Size Determination

The Simon Two Stage design will be utilized for this study. The null hypothesis that the true positive response rate is 10% will be tested against a one-sided alternative using the exact binomial test. The study will be powered to detect a positive response rate of 30% or greater with approximately 80% power and a type I error rate of 5%.

The first stage sample size will be 15 patients. If there are 1 or fewer responses in these 15 patients, the study will be terminated. If the trial goes on to the second stage, a total of 25 patients will be studied (i.e. additional 10 patients will be recruited). The null hypothesis will be rejected if 6 or more responses are observed in 25 patients. We will assess response with a blinded standardized interpretation of superficial vaginal epithelial cells by a board-certified pathologist.

11.3 Primary Endpoint

We expect the percentage of superficial vaginal cells to be greater at the post-intervention time point when compared to the pre-intervention time point. If the percentage of superficial vaginal cells is $\geq 4\%$ following the intervention, then the response will be considered positive.

11.4 Secondary Endpoint

Changes in the vaginal pH will be analyzed to determine the extent to which the changes correlate with changes in the primary outcome and with patient reported outcomes. Given the longitudinal nature of the study, linear and generalized linear mixed effects models will be fit to the data gathered. The restricted maximum likelihood (REML) criterion will be used and 95% semi-parametrically bootstrapped confidence intervals will be obtained for all parameters. All statistical analyses will be conducted using R (R Core Team 2014).

11.5 Patient Reported Outcomes

PRO assessments will be analyzed to determine if therapeutic response and/or side effects of therapy are accompanied by measurable changes in the PROs. These responses will be summarized with descriptive statistics.

11.6 Adherence to AI Therapy

Adherence to AI therapy will be recorded using a patient-reported log.

12.0 SUBJECT COMPLETION/WITHDRAWAL

12.1 Completion

A subject will be considered to have completed the study if she returns for the 12-week study completion visit.

12.2. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up

- Withdrawal of consent (no further treatment AND no further follow-up)
- Lack of adherence to the study procedures

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal and survival status. When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the study records.

13.0 RECORDS TO BE KEPT

13.1 Data Management

The PI and UWCCC research study personnel will maintain study data at UW.

13.2 Study Records

13.2.1 Data will be collected directly from subjects, from study interventions and from medical record review. Baseline data to be collected will include: Age, race, marital status, insurance, ECOG performance status, cancer histology and stage, treatments received, history of anxiety or depression, current or previous treatment for anxiety or depression, and whether or not the patient is receiving care from a mental health provider.

13.2.2 All paper research data, including the original signed consent forms and completed questionnaires, will be stored and protected in the UWCCC research offices.

13.2.3 All subjects will be entered into OnCore. The following fields will be completed in OnCore: demographics (name, MR number, birthdate, race, ethnicity, contact information, zip code at registration), insurance type, consent information, study ID #, disease information, enrolling staff, subject statuses and dates.

14.0 ADVERSE EVENT REPORTING

14.1 Definitions

14.1.1 Adverse Device Effect Definitions

Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse Device Effect

Any adverse effect on health or safety (serious or non-serious) caused by, or associated with the use of a device. For the UWCCC, “caused by” is equal to “definitely related” and “associated with” is equal to “probably” or “possibly” related.

Serious Adverse Event (SAE)

Section 15.0, while addressing the required reporting of UADEs, refers to “SAE” forms. These forms are the standard reporting tools within the UWCCC for reporting serious events for drug studies. This study will use SAE reporting tools for reporting UADEs.

14.1.2 Attribution Definitions

Not Related
An adverse device effect that is not related to the use of the VRP.

Unlikely
An adverse event for which an alternative explanation is more likely or the relationship in time suggests that a causal relationship is unlikely.

Possibly
An adverse device effect that might be due to the use of the VRP device. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probably
An adverse device effect that might be due to the use of the VRP device. The relationship in time is suggestive. An alternative explanation is less likely.

Definitely
An adverse device effect that cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive.

14.2 Procedures

14.2.1 Adverse Device Effects

All adverse device effects and special reporting situations possibly, probably, or definitely related to the VRP, its exercises, its assessments and its instruments, whether serious or non- serious, will be reported from the time a signed and dated informed consent is obtained until the study completion visit.

14.2.2 Unanticipated Adverse Device Effects

Unanticipated adverse device effects, including those spontaneously reported to the investigator within 30 days after the 12-week study completion visit, must be reported per section 15.4. The PI or site co-I assume responsibility for appropriate reporting of unanticipated adverse device effects to the regulatory authorities.

15.0 DATA AND SAFETY MONITORING & REGULATORY COMPLIANCE

15.1 Oversight and Monitoring Plan

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all Unanticipated Adverse Device Effects (UADE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports) described in Section II of this document.

- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.
- Ensures that notification of UADEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

15.2 Monitoring and Reporting Requirements

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCC monitoring requirements for trials without an acceptable external DSMB are as follows:

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT or study meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOT or study meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a semi-annual basis by the study team for review by the DSMC.

15.3 Review and Oversight Requirements

a) Unanticipated Adverse Device Effects – Reported Within 24 Hours

Unanticipated adverse device effects (UADEs) requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 10 working days, all available subsequent UADE documentation must be submitted electronically along with a 24 hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to saenotify@uwcarbone.wisc.edu. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

See Section *15.4* for detailed instructions on SAE reporting.

b) Unanticipated Adverse Device Effects – Reported within 10 Days

Unanticipated adverse device effects requiring reporting within 10 business days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the UADE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the UADE requires reporting to the FDA and other participating investigators.

For a multiple-institutional clinical trial the PI is responsible for ensuring UADEs are reported to the FDA as well as to all participating investigators.

See Section *15.4* for detailed instructions on UADE reporting.

c) Sponsor-Investigator Responsibilities for UADE Review

In the event the UWCCC Principal Investigator is acting as the Sponsor-Investigator (i.e., the PI holds the IDE), the PI assumes responsibilities of the study sponsor in accordance with FDA 21 CFR 812.150. In this capacity, the UWCCC PI reviews all reports of serious adverse events occurring on the study at the UWCCC and participating external sites and makes a determination of 1) **suspectedness** (i.e., whether there is a reasonable possibility that the drug caused the AE); and 2) **unexpectedness** (the event is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed) in the context of this study. UADEs with suspected causality to study device and deemed unexpected are reported as IDE Safety Reports by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within 15 calendar days. All fatal or life-threatening UADE that are unexpected and have suspected causality to the study device will be reported by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within 7 calendar days.

Refer to Section 15.4c for UWCCC PI instructions for reporting to the FDA.

d) Study Progress Review

Protocol Summary Reports (PSR) are required to be submitted to the DSMC in the timeframe determined by the risk level of the study (quarterly; semi-annually; or

annually). The PSR provides a cumulative report of UADEs, as well as instances of non-compliance, protocol deviations, and unanticipated problems, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.

Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews, etc.) occurring since the prior review of the protocol by the DSMC. Additionally, the DSMC requires the study team to submit external DSMB or DSMC reports, external monitoring findings for industry-sponsored studies, and any other pertinent study-related information.

In the event that there is significant risk warranting study suspension or closure, the DSMC will notify the PI of the DSMC findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, Cooperative Group Study Chair, etc.) and other appropriate agencies. DSMC findings and requirements for follow-up action are submitted to the CRC.

15.4 Expedited Reporting of Serious Adverse Events

Depending on the nature, severity, and attribution of the unanticipated adverse device effect a UADE report will be phoned in, submitted in writing, or both according to the table below. All UADEs must also be reported to the UWCCC Data and Safety Monitoring Committee Chair. All UADEs must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting time line for the UADE in question by using the following table. Then refer to sections A and B below if the UADE occurred at the UWCCC.

Non-Significant Risk Device Studies: Expedited Reporting Requirements for Unanticipated Adverse Device Effects (UADE) From [the Date/Time of Written Consent Signature Through the Study Completion Visit]

FDA REPORTING REQUIREMENTS FOR UNANTICIPATED ADVERSE DEVICE EFFECTS (21 CFR Part 812.150)

Sponsor-Investigators **MUST** report UADE to the UWCCC DSMC as outlined in this table.

Definition of UADE: Any **serious** adverse effect on health or safety, any life-threatening problem or death **caused by, or associated with a device**, if that effect, problem, or death was **not previously identified in nature, severity, or degree of incidence in the investigational plan or application**; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

An adverse effect is considered **SERIOUS** if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) Results in inpatient hospitalization or prolongation of existing hospitalization
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Note: For the UWCCC, "caused by" is equal to "definitely related" and "associated with" is equal to "probably" or "possibly" related. Additionally, "not previously identified in nature, severity, or degree of incidence in the investigational plan or application" is equal to "unanticipated."

ALL unanticipated adverse device effects that meet the above criteria MUST be reported within the timeframes detailed in the table below.

Grade 1-3 Timeframe	Grade 4-5 Timeframe
10 Business Days	24-Hour; 5 Calendar Days

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The UADE must initially be reported within 24 hours of learning of the UADE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Business Days" - A complete expedited report on the UADE must be submitted within 10 business days of learning of the UADE.

Reporting to the IRB of Record

Sponsor-Investigators **MUST** report the UADE to the IRB of Record according to the IRB's reporting guidelines.

Reporting to the FDA

Sponsor-Investigators **MUST** report the evaluation of any UADE to the FDA within 10 business days after first receiving notice of the UADE.

A. UADE Requiring *[24]* Hour Reporting Occurs at UWCCC:

1. Report to the UWCCC:

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website (http://www.uwccc.wisc.edu) for

specific instructions on how and what to report to the UWCCC for *[24]* hour initial and follow-up reports. **A follow-up report is required to be submitted within 10 days of the initial *[24]* hour report.**

For this protocol, the following UWCCC entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Ryan Spencer, MD; Principle Investigator
c) DOT Manager and/or POD Manager.
d) Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

2. Report to the IRB:

Consult the UW-IRB website for reporting guidelines.

B. SAE Requiring *[10]* Day Reporting Occurs at UWCCC:

1. Report to the UWCCC:

Reference the **SAE SOP** and the **SAE Reporting Workflow for DOTs** on the UWCCC website (http://www.uwccc.wisc.edu) for specific instructions on how and what to report to the UWCCC for *[10]* day reports.

For this protocol, the following entities are required to be notified:

a) saenotify@uwcarbone.wisc.edu
b) Any appropriate parties listed on SAE Routing Form
c) Ryan Spencer, MD; Principle Investigator
d) DOT Manager and/or POD Manager

2. Report to the IRB:

Consult the UW-IRB website for reporting guidelines

C. Other Reporting Requirements

Reporting to the FDA
Unanticipated Adverse Device Effects occurring on studies on which a UW PI is acting as sponsor-investigator must be reported to the FDA within the appropriate time frame. Mandatory and voluntary reporting guidelines and instructions are outlined on the FDA website: http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

15.5 Regulatory Considerations

15.5.1 Clinicaltrials.gov

It will be registered at Clinicaltrials.gov within 21 days of enrolling the first participant. Registration will include descriptive and recruitment information, contact information of the study PI, and administrative data. The WHO (ICJME) Trial Registration Dataset (V.1.2.1) will be used as a guide for inputting information into the registry at Clinicaltrials.gov. Additionally, within 12

months of the trial completion date, details about demographics, outcomes and analysis (completed and planned), and adverse events will be reported therein.

15.5.2 Advertisements

No advertisements will be distributed for this study.

15.5.3 Informed Written Consent and HIPAA Authorization

Each subject must provide informed, written consent and HIPAA authorization

15.5.4 Tissue /Specimen Collection

Cytology samples will be obtained at multiple time points in this study specifically for research purposes as outlined in ***Section 9.0.*** This will be specified in the consent form, in addition to the fact that no banking of serum specimens will occur. Results will not be released to the subjects and no genetic analysis will be conducted on the specimens.

15.6 Certificate of Confidentiality

A Certificate of Confidentiality will not be necessary for this study. Although it will collect information on patient-reported outcomes that will include stated anxiety and depression, these tools cannot diagnose Major Depressive Disorder or Anxiety Disorders. None of the serum collections will be used to produce sensitive genetic information.

15.7 Conflict of Interest

Conflict of interests must be disclosed to the PI and institutional review board at the beginning of the study or when the conflict arises if not present at the initiation of the study. Respective institutional guidelines should be followed regarding conflict of interest forms that are required for investigators.

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Appendix 1 – Schedule of Events

	Enrollment[a]	VRP instruction visit	1 Week Post-Instruction	1 Month Post-Instruction	12-week follow-up visit[d]
Informed consent	X				
Eligibility checklist	X				
Baseline demographics		X			
PRO evaluations[b]		X			X
Cytology swab	X				X
pH collection	X				X
VRP Instruction		X			
Collect VRP use logbook					X
Phone Call[c]			X	X	

A. The enrollment and VRP instruction visit may be conducted at the same time.
B. The PROs will be: Vaginal Symptoms Questionnaire, NIH PROMIS Global Health scale, NIH PROMIS Female Sexual Function Profile, NIH PROMIS Global Satisfaction with Sex Life scale, NIH PROMIS Anxiety 8a scale, NIH PROMIS Depression 8a scale
C. Phone calls to assess adherence
D. +/- 4 weeks