SELF-CERV Pivotal Study: SELF-Collection for CERVical Cancer Screening

PROTOCOL #: CLN-TP-020

IDE #: N/A - Non-significant risk (NSR), IDE-exempt per 21 CFR §812.2(c)

Sponsor: Teal Health
1012 Torney Ave
San Francisco, CA 94129

Protocol Version History

Protocol Version	Version Date	Summary of Revisions Made	Rationale
1.0	9/29/2023	Initial release	
1.1	10/12/2023	Deleted reference to reporting any clinical results to PI	Clarification and correction as a part of IRB review
1.2	10/17/2023	Deleted reference to PI ability to request clinical results for study participants	Clarification and correction as a part of IRB review
1.3	02/01/2024	Modified sections 9.0 and 14.0, administrative clarifications	To add testing on Alinity m HPV assay and modify sample size, PPA point estimate, statistical analysis and interim analysis sections based upon FDA feedback. Administrative clarifications. No changes to Inclusion/Exclusion, study procedures or modification impacting subject facing materials.

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1.0 STATEMENT OF COMPLIANCE

Protocol Version: 1.3
Protocol Version Date: February 1, 2024

I confirm that I have read this protocol. I will comply with the IRB-approved protocol, and applicable regulations, guidelines, laws, and institutional policies.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitment.

_____ _____

Investigator's Signature Date

_____

Investigator's Name (Print)

2.0 LIST OF ABBREVIATIONS

ACS	American Cancer Society
ASC-H	Atypical squamous cells, cannot rule out high-grade squamous intra-epithelial lesion
ASCUS+	Atypical squamous cells of undetermined significance with positive HPV
CA	Cervical carcinoma
CI	Confidence interval
CIN2+	Cervical intraepithelial neoplasia 2 or higher
CIN3+	Cervical intraepithelial neoplasia 3 or higher
ct	Cycle threshold
DRR	Detection rate ratio
DSMP	Data and Safety Monitoring Plan
EDC	Electronic Data Capture
HPV	Human papillomavirus
hrHPV	High-risk human papillomaviruses
hrHPV+	High-risk human papillomavirus positive
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	Healthcare Provider
HIPAA	Health Insurance Portability and Accountability Act
HSIL	High-grade squamous intraepithelial lesions
IATA	International Air Transport Association (IATA)
ICC	Invasive cervical squamous cell carcinoma
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISF	Investigator Site File
IVD	In vitro Diagnostic
LEEP	Loop Electrosurgical Excision Procedure
LSIL	Low-grade squamous intraepithelial lesions
MAUDE	Manufacturer and User Facility Device Experience - FDA database
NIH	National Institutes of Health
NPA	Negative Percent Agreement
NSR	Non-significant risk
OBF	O'Brien Fleming
OHRP	Office for Human Research Protections
PAP	Papanicolaou test
PHI	Protected Health Information
PI	Principal Investigator
PPA	Positive Percent Agreement
SAP	Statistical Analysis Plan

Se/Sp	Se=sensitivity, Sp=specificity
SoC	Standard of Care
SSRE	Sample Size Re-Estimation
STI	Sexually Transmitted Infection
TA	Target amplification
TPLC	Total Product Life Cycle – FDA database
TMF	Trial Master File

3.0 STUDY SUMMARY

3.1 Synopsis

Full Title	SELF-CERV Pivotal Study: Method comparison of self-collection using the Teal Wand Self-Collection device and HCP (health care provider) cervical collection for detection of high-risk HPV (hrHPV) for cervical cancer screening
Short Title	**SELF-CERV**: SELF-Collection for CERVical Cancer Screening
Protocol Number	CLN-TP-020
IDE Designation	Non-significant risk (NSR), IDE-exempt per 21 CFR 812.2(c)

Study Objectives	**Primary Safety Objectives**
	• To confirm that SAEs from self-collection are equivalent to the rate of SAEs from HCP-collection.
	Primary Effectiveness Objective
	• To evaluate the performance of a self-collect device for hrHPV detection as compared to standard of care (SoC) by:
	  ○ Agreement of hrHPV self-collected sample(s) as compared to HCP-collected sample results.
	  ○ Calculating the invalid rate of tested samples.
	Exploratory Effectiveness Objectives
	• To investigate the potential utility of samples obtained using the novel self-collection device for triage tests compared to HCP-collected including liquid-based cytology and/or other triage tests (e.g., dual stain (p16/Ki-67) cytology).
	• To investigate the potential utility of residual samples obtained using the self-collection device for other diagnostic tests that use vaginal swab samples, such as STI (sexually transmitted infections).

Purpose	To demonstrate that participants who are representative of the intended use population can understand the Instructions for Use (IFU) and appropriately use the Teal self-collection device to collect adequate vaginal cells/material for use in primary hrHPV screening (primary outcome). To produce sufficient primary hrHPV test results following self-collection, as compared to the current SoC method of HCP specimen collection, when paired samples are tested using FDA approved primary hrHPV assays. Residual samples may be used to determine adequacy for additional assays that require vaginal and/or cervical specimens (such as STI, liquid-based cytology, dual stain cytology).

Study Population	Participants presenting from the general population and/or known hrHPV positive and/or abnormal cervical cytology participants referred for colposcopy or LEEP/intervention who meet all other study inclusion criteria and none of the study exclusion criteria, with efforts made to recruit participants with varied age, race/ethnicity, education level, geographic location, and socioeconomic status.
Study Design	Prospective, multi-center, method comparison study recruiting from a general population and enriched population
Inclusion Criteria	**Group 1: Inclusion Criteria - General Population Group** 1. Participant is 25 to 65 years of age and willing to provide informed consent. 2. Participant has an intact cervix. **Group 2: Inclusion Criteria – Enriched Population Group** 1. Participant is 25 to 65 years of age and willing to provide informed consent. 2. Participant has an intact cervix. 3. One or more of the below: • Prior diagnosis of hrHPV within previous 6 months and/or • Positive cervical Pap cytology result (ASCUS, ASC-H, LSIL, HSIL, SCC, AIS) within previous 6 months and/or • Presenting for colposcopy/LEEP/excisional intervention
Exclusion Criteria	**Exclusion Criteria – All Groups** 1. Participant has impaired decision-making capacity or is unable to provide informed consent. 2. Participant has undergone partial or complete hysterectomy including removal of the cervix. 3. Participant on whom any form of cervical tissue alteration or surgery has been performed within the prior < 5 months, including: conization, loop electrosurgical excision procedure (LEEP), laser ablative surgery, or cryotherapy. 4. Participant is pregnant (based on self-reporting). 5. Participant who reports or is experiencing menstrual bleeding. 6. Participant is participating in another clinical study for an investigational device, drug, or biologic that, in the investigator's opinion, would interfere with the results of this study. 7. Any medical reason that, in the investigator's judgment, would disqualify the participant for a routine pelvic exam with cervical sample collection.
Safety Measures	Rate of SAEs from self-collection using study device as compared to rate of SAEs from HCP-collection.

Effectiveness Measures	Primary: • Self-collected samples will be compared to HCP-collected sample using the indicated diagnostic tests for primary hrHPV. NPA (negative percent agreement) and PPA (positive percent agreement) will be calculated. • Invalid tests defined as percent of hrHPV DNA concentrations below the detection clinical threshold as determined by the assay manufacturer. • Device design adequacy for the primary safety and efficacy measures. Exploratory: • Participants' general willingness to use a self-collect device and concerns about self-collection. • Sample adequacy and diagnosis for liquid-based cytology analysis and other testing including STI tests and CINTec Plus cytology.
Study Intervention	Participants will participate in the study as part of a research visit. Following informed consent and enrollment, the participant will be given instructions on how to use the self-collection device and given a usability and a preferences survey. Participants will perform self-collection(s) using the Teal Wand and fill out the surveys. Participants will undergo a pelvic exam with cervical sample collection followed by any other indicated procedures performed by an HCP after self-collection. All self-collected and HCP-collected research samples will undergo primary hrHPV testing. Cytological analysis and any other tests evaluated as exploratory study measures may be evaluated, but on a subset of samples to satisfy research objectives. HCP will report adverse events or relevant clinical observations following self-collection and prior to HCP collection. Following self-collection, participants will undergo a pelvic exam with cervical sample collection performed by an HCP as part of research participation or prior to colposcopy/LEEP/intervention depending on the participant's clinical status. The HCP will also report any adverse events or clinical observations following HCP collection.
Follow-up Schedule	Acute participant participation will last approximately 1 hour or less, with any AEs or SAEs captured acutely and within the following 2 weeks (6 days to 14 days) by electronic survey or research phone call. Any unresolved or unanticipated adverse events reported at the follow up will be followed by the research site and reported.
Total Number of Participants	Up to 870 participants could be recruited in an adaptive design (see statistical plan).

Number of Site(s)	Up to 30 US sites, which may be comprised of academic hospitals/clinics, private clinics, government clinics, community clinics, or large health systems.
Statistical Methodology	PPA and NPA will be reported as derived from the standard 2x2 contingency table, along with corresponding 95% CIs on the agreement measures as detailed in the Statistical Analysis Plan. Descriptive statistics will be used to describe the participants' characteristics. Agreement will be reported for each diagnostic platform.
Interim Analysis	An interim analysis is planned to assess for: • Self-collect primary endpoints of PPA and NPA for detection of HR-HPV for sample size re-estimation and futility.
Estimated Participant Duration	The duration of active study participation for each participant is limited to one study visit and follow up email, or phone contact within two weeks of the study visit.
Estimated Enrollment Period & Study Duration	Study enrollment will occur over approximately 18 months.

4.0 INTRODUCTION

4.1 Background

Population-based cervical cancer screening using regular cytological examinations of a cervical Pap smear can substantially decrease the incidence and mortality from cervical cancer [1-3]. Early detection and removal of precancerous cervical lesions results in nearly a 100 percent survival rate but drops to 57% with regional spread of cancer, and 17% if the cancer spreads distantly [4]. Despite a 50% reduction in cervical cancer-related deaths since the implementation of cervical cancer screening ("Pap smears") in the previous 60 years, more than 12,000 women are diagnosed each year in the United States, and more than 4,000 women die of the disease [5]. According to the American Cancer Society (ACS), "over 50 percent of cervical cancers are detected at a regional or distant stage – most occurring among women who did not have a recent Pap test" [3, 4]. Racial and ethnic minorities and socioeconomically disadvantaged groups have higher rates of incidence and cancer-related deaths, and lower rates of participation in guideline-based screening and treatment [5, 6]. After incorporation of updated screening recommendations including hrHPV testing in 2012, an expected decrease in screening frequency among women ages 30-65 was observed with only 64% of women up to date with cancer screening and an even more concerning drop in screening among women 21-29 years old was noted [7].

Since the beginning of the COVID-19 pandemic, screenings for cervical cancer have plummeted. Research from Epic Health Research Network reported that in March 2020 cervical cancer screenings were down 94% [8]. A survey of providers between October 2021 and June 2022 showed an 86% reduction in cervical cancer screening early in the

pandemic with 28% continued reduction at the time of survey completion. Almost half (45%) were attributed to staff shortages. Self-collection, which does not require healthcare provider services, was cited to be a useful tool to address screening backlogs and that if the backlog is not addressed, the underserved populations would face a future of worsened cervical cancer disparities [9].

Improving access to screening is an essential step to address the disparate outcomes of cervical cancer in the United States. Worldwide, self-collection has been proposed as a strategy to reach individuals non-compliant to traditional cervical cancer screening [10-13]. Screening for high-risk human papillomaviruses (hrHPV) is more sensitive than cytology and is a more effective method for preventing cervical cancer [14-16]. Recent systematic reviews and meta-analyses have shown that offering hrHPV self-collection at home to non-attendees can significantly increase attendance and the detection of high-grade cervical lesions, compared to currently widely used reminder letters for HCP-based screening [10, 11]. Most studies have found at least a double response rate to submitting a self-sample vs scheduling an on-site HCP-collected cervical cytology, even among under-screened populations [16-18]. Furthermore, with improved hrHPV PCR-based testing technology, the sensitivity for detection of human papillomavirus (HPV) infections is comparable in most self-collected samples when compared to HCP-collected samples. Kaiser Permanente ran a similar study across 20,000 women who were behind on their screening and found that 50% more women chose to return a self-collected sample than schedule an in-office screen. A large population-based cervical cancer self-collected study in Argentina found that hrHPV-based screening doubles the detection rate ratio (DRR) for hrHPV screening [17]. These studies have led some countries, such as Australia, to institute a self-collection option nationally [16, 18].

As part of a comprehensive cervical cancer screening program, the utilization of self-collected samples has advantages from both a public health and individual participant perspective. Some of the barriers to screening can be mitigated by self-collection, and resources can be better allocated to participants at the highest risk of developing cervical cancer. In this study, we will evaluate the performance of a novel self-collection device that has the potential to support both cervical cytology analysis and hrHPV testing, with the long-term goal of increasing participation, and with the potential to include at-home screening options for women during and after the pandemic. There are currently no FDA-approved devices in the United States for self-collected cervical samples for HPV.

4.2 Rationale

Limited access to and insufficient uptake of screening remain persistent barriers to cervical cancer elimination. Women who are not screened regularly have higher cervical cancer incidence [1, 7, 19, 20]. Early detection of cervical neoplasia is critical. when precancerous lesions are caught early and removed, there is nearly 100 percent 5-year survival; if caught at an advanced stage, the 5-year survival rate drops to 17 percent [21, 22].

The percentage of women overdue for cervical cancer screening in the United States has increased in the last decade, from 14% in 2005 to 23% in 2019. Furthermore, the COVID-19 pandemic has had an enormous impact on cervical cancer screening, particularly among underserved populations [8], who are already more likely to experience barriers to cervical cancer screening [21, 22]. There is a critical need to expand options for women to continue screening for early detection of cervical cancer.

Since human papillomavirus (HPV) infection is known to be a major cause of cervical cancer, high-risk HPV (hrHPV) testing is recommended as part of cervical cancer screening both as primary screening and in combination with cytology [23]. In fact, in 2020 the American Cancer Society updated their guidelines to include primary HPV testing every 5 years as their preferred method of screening for women ages 25-65.

Testing for hrHPV offers several advantages over cervical cytology alone, including high sensitivity and the option of detection from self-collected samples [10, 23]. Self-collection is a feasible method to reach under-screened women [24, 25]. Self-collected samples are both highly concordant with clinical collected samples for detection of HPV, and highly acceptable by women participants [11, 24, 25]. While hrHPV self-collection has shown comparable diagnostic agreement to HCP collected samples, self-collected “Pap smears” are insufficiently sensitive using currently available collection devices [26]. Combining hrHPV self-collection with a “self-Pap” could improve access to screening while increasing the positive predictive value of a hrHPV test result.

In this study, we will evaluate the performance of a novel self-collect device, the Teal Wand, for self-collected hrHPV when compared to HCP collected samples. The device is designed for cell collection from the cervix and/or vaginal canal (see Device Description). The device is self-directed by the individual, like a vaginal swab, vaginal applicator, or a tampon. The cell collection substrate (“sponge”) is soft, made of a medical-grade sponge, and does not enter past the external cervical os. Our long-term goal is to demonstrate the performance of the Teal Wand for self-collected HPV to incorporate self-collection into cervical cancer screening algorithms.

In our Pilot study, we evaluated the performance of the device among more than 215 participants. We found a high positive and negative percentage agreement for detection of hrHPV using on the Roche cobas (4800 and 8800) and BD OnClarity whether using PreservCyt or SurePath preservatives. Safety was excellent with no serious adverse events reported and an adverse event rate lower than or comparable to standard of care. Minor bleeding or spotting was counted as an adverse event for the purposes of the study to understand outcomes of the investigational device, even though this can be an expected outcome of a routine cervical collection. To confirm these results, we propose a pivotal trial to evaluate the diagnostic accuracy of this device for the detection of hrHPV.

5.0 STUDY OBJECTIVES AND MEASURES

Primary Safety	
Objectives	**Measures**
To evaluate SAEs to confirm that: ● SAEs from self-collection are equivalent to the rate of SAEs from HCP-collection.	Rate of SAEs from self-collection using study device as compared to rate of SAEs from HCP-collection.
Primary Effectiveness	
Objectives	**Measures**
• To compare the agreement of the Teal Wand self-collect device for detection of hrHPV as compared to standard of care by: o Detection of hrHPV from self-collected samples as compared to HCP-collected sample results. • Device design adequacy for the primary safety and efficacy measures o Recording the invalid rate of tested samples.	• PPA and NPA for each collection group. • Sample invalid test rate defined as percent of beta-globin DNA concentrations below the detection threshold as determined by the manufacturer.
Exploratory Effectiveness	
Objectives	**Measures**
• To investigate the potential utility of samples obtained using the Teal Wand self-collection device for cytological analysis by examining cytological preparations collected from the device compared to HCP collected liquid-based Cytology to assess sample adequacy and diagnosis using liquid-based cytology and/or other diagnostic triage tests (such as Roche CinTec+ Cytology). • To investigate the potential utility of a single sample collection for other diagnostic tests that use vaginal swab samples, such as STI (sexually transmitted infections).	• Sample adequacy and diagnosis concordance for liquid-based cytology/CinTec+ cytology analysis. • Confirmation of Pap diagnosis by histopathology, when collected and available. • Agreement between self- and HCP-collected samples for STIs using FDA approved assays.

6.0 STUDY DESIGN

6.1 General Design

Eligible participants will be recruited from up to 30 US investigational sites according to the sample size estimates described in the analysis section. The majority of participants will be "enriched", i.e., undergoing colposcopy/intervention and/or who have an established hrHPV infection and/or abnormal Pap cytology diagnosis with a portion recruited from a general screening population. Participants will use the Teal self-collect device to collect their own vaginal samples using the instructions provided, and either place the sponge in an empty vial at the time of collection or give the entire Teal Wand to research staff for sample processing. There will be at least 3 geographically diverse recruiting/collection locations

performing routine screening for primary hrHPV, and at least 3 sites also collecting from hrHPV positive participants and those referred for colposcopy/LEEP/intervention.

It is expected that each recruitment group (e.g., enriched, and general population) will have hrHPV positive participants, as some participants from the general population group will present with newly diagnosed hrHPV and some of the enriched population may have cleared their hrHPV infection. The analysis will not be for an "intent-to-treat", but cases will be evaluated "as treated" for analysis purposes and enrollment will continue until a known number of hrHPV positive and negative participants are affirmatively diagnosed using the HCP collected sample results as indicated in the statistical analysis plan.

Following informed consent and enrollment, the participants will be provided with the instructions for use (IFU) which will describe how to use the self-collection device. After the participant self-samples, a subsequent sample is collected by an HCP following standard of care methods. The study will proceed as follows:

1. The participant will perform self-collection with the Teal Wand using the IFU only. Two self-collection schemes are possible:

    a. Collection Scheme 1. Self-collected samples collected with the Teal Wand and stored dry before resuspension by the testing laboratory ("dry sample") into preservative (20mL PreservCyt) and processed according to the manufacturer's IFU.

    b. Collection Scheme 2. Self-collected samples collected with the Teal Wand and transferred to preservative (20 mL PreservCyt) following collection. Processed according to manufacturer's IFU ("wet sample").

Scheme a or b will be determined by the Sponsor and will not vary or randomize during the study.

2. The last sample is collected by a trained HCP using an FDA approved comparator collection device Rovers Cervex-Brush (Rovers Medical Devices B.V.) for method comparison.

This sample collection order allows for the HCP to visually evaluate the cervix and vagina to assess for any injury caused by the investigational device. Because the HCP will have direct visualization to the cervix and sample using a device that is designed to contact the cervical os, it is not anticipated that the self-collection(s) will inhibit HCP collection, based on results from the pilot study.

Each sample set collected will be tested on one or more FDA approved primary HPV assays. At least 3 clinical laboratory locations will test sample sets using the indicated tests/systems per FDA approved labeling.

Upon arrival at the respective laboratory, the self-collected samples will be resuspended per provided protocol in preservative (Scheme 1) and processed per manufacturer's instructions thereafter or processed (Scheme 2) per manufacturer's instructions.

Then, aliquots will be collected from comparative samples (up to 4 mL) for HPV testing on each HPV platform prior to cytology/other testing, if performed. Testing results (hrHPV results, including genotypes and Ct values where applicable) will be collected for all samples. Residual samples may be directed to Pap cytology or another cytology/triage assay or STI testing (exploratory measure). If a biopsy is collected during the participant visit (not required as part of the study, but if it is done per SoC), the de-identified biopsy and/or Pap cytology pathology report will be collected, and diagnostic results tabulated.

Usability and labeling/user comprehension for the Teal self-collection device and self-collection process will be tested and recorded for each participant at each recruitment/collection site. At least 80 participants will undergo usability testing to represent the final proposed end-to-end user experience (e.g., simulated "at home" unboxing and specimen return).

Participant enrollment and sample collection will occur over approximately 18 months.

6.2 End of Study Definition

A participant is considered to have completed the study when the following activities have been completed: designated self-collection, HCP sample collection, the Usability Survey, the Preferences Survey, and a 6-to-14-Day Follow-up Survey. Loss to follow up is expected to be low and will be reported.

7.0 PARTICIPANT SELECTION

7.1 Inclusion Criteria

Participants are eligible to be included in one of the following study groups only if all the given group's inclusion criteria are met:

Group 1: Inclusion Criteria - General Population Group
1. Participant is 25 to 65 years of age and willing to provide informed consent.
2. Participant has an intact cervix.

Group 2: Inclusion Criteria – Enriched Population Group
1. Participant is 25 to 65 years of age and willing to provide informed consent.
2. Participant has an intact cervix.
3. Participant has a prior diagnosis within the last 6 months of hrHPV and/or positive cervical cytology result (ASCUS, ASC-H, LSIL, HSIL, SCC, AIS) and/or is presenting for colposcopy/LEEP/excisional intervention.

7.2 Exclusion Criteria

Participants will be excluded from this study if any of the following criteria apply:

Exclusion Criteria – All Groups
1. Participant has impaired decision-making capacity or is unable to provide informed consent.
2. Participant has undergone partial or complete hysterectomy including removal of the cervix.

3. Participant on whom any form of cervical tissue alteration or surgery has been performed within the prior < 5 months, including: conization, loop electrosurgical excision procedure (LEEP), laser ablative surgery, or cryotherapy.
4. Participant is pregnant (based on self-reporting).
5. Participant who reports or is experiencing menstrual bleeding.
6. Participant is participating in another clinical study for an investigational device, drug, or biologic that, in the investigator's opinion, would interfere with the results of this study.
7. Any medical reason that, in the investigator's judgment, would disqualify the participant for a routine cervical cancer screening.

7.3 Vulnerable Populations

Pregnant women, those who lack consent capacity, and cognitively impaired persons will not be included in this research study.

7.4 Participant Identification and Recruitment

Any person with an intact cervix may be recruited for participation in this study. If they meet the eligibility criteria and consent to using the Teal Health self-collection device, they may participate.

Candidate participants for enrollment in the general population group may be identified based on review of clinic schedules or other appropriate means including direct approach for eligibility screening.

Candidate participants for enrollment in the HPV enriched group may be identified based on participants with recent (within last 6 months) hrHPV+ results and/or abnormal Pap cytology and/or presenting for a colposcopy/LEEP/conization, ablative or cryotherapy.

7.5 Informed Consent and Enrollment

The informed consent process will make clear that participation in all aspects of the study is voluntary, and that participants may end their participation at any time. The informed consent process will include contact information for the Investigator, who can be contacted if participants or potential participants have questions or concerns. The informed consent form may be paper or electronic.

A research participant will be defined as "enrolled" in the study when they meet the following criteria:

- The participant has signed the informed consent form.
- The participant and study staff have completed all screening documentation.
- The Investigator has verified that the participant meets all the inclusion criteria.
- The Investigator has verified that participant meets none of the exclusion criteria.

7.6 Participant Stipend or Payment

Reasonable compensation for participant participation is offered if allowed by central and/or local institutional review boards (IRB) and guidelines. Compensation is proposed by the Sponsor in consideration of the fact that study participation will require additional time on the

part of the participant to read the device instructions for use (IFU), use the self-collection device, and complete the study surveys.

7.7 Early Termination and Withdrawal

Participants are free to withdraw from participation in the study at any time and for any reason without prejudice to their future medical care by the study team or study site.

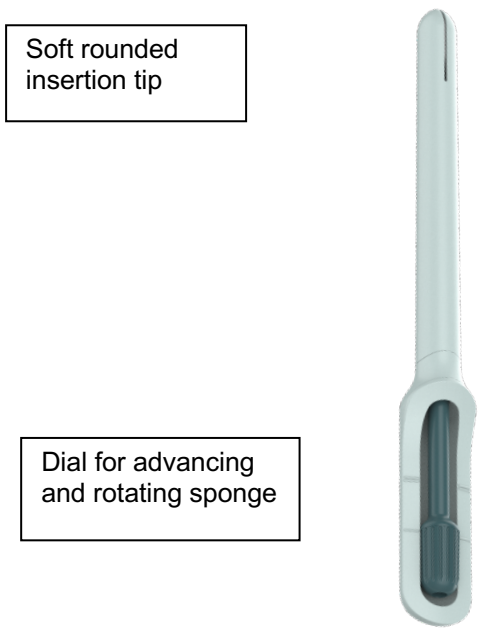
8.0 STUDY DEVICE

8.1 Device Description

The Teal Health Self-Collection Device is a single use, disposable device intended for the collection of vaginal cells/material for evaluation of primary high-risk HPV (hrHPV) testing which is currently recommended for cervical cancer screening. The device consists of medical grade injection molded polymer components that are designed to be like a tampon in terms of product diameter and the distal-most components are fabricated from biocompatible and soft/atraumatic materials. The device is designed to facilitate easy and robust assembly with secure snap-fit assembly and easily controlled sliding and rotating components.

The device is designed for a woman to insert into her vaginal canal with the device dial knob facing forward and in sight.

Figure 1: Teal Health Self-Collection Device undeployed and with collection sponge deployed.

Teal Wand Undeployed	Teal Wand Deployed for Collection
	

8.2 Device Use

IFU · COLLECTION INSTRUCTIONS

The participant follows the approved Instructions for Use for collection by assuming a comfortable position for device insertion, gently guiding the soft rounded tip into the vagina until the cervix is met or resistance is felt. The user then slides the Dial up to the double lines to extend the collection sponge and rotates the dial to exfoliate cells and complete a collection. The user slides the dial down to retract the sponge and removes the device from the vagina.

The participant will either remove the sponge according to the IFU and place the detached sponge into a collection vial (Scheme 1) or leave the device for the research staff to detach the sponge and place in the collection vial. For “wet” collection (Scheme 2), the participant will leave the device for research staff to transfer to preservative.

8.3 Procedure Visit: Self-collection Procedure and Surveys

Following informed consent and enrollment at the participating clinical site, the participant will be provided with the self-collection device and instructions for use (IFU), with the addition of possible video instructions for use.

Using only the IFU (printed and/or video), the participant will perform self-collection sample(s) collection with Teal Wand device(s).

The participant will then do one or both of the following:

- Scheme 1: Detach the sponge and transfer it to an empty vial (“dry sample”). The vial will be collected by research staff and transferred to the designated laboratory and/or
- Scheme 2: The Teal Wand will be left by the participant in the room for the research staff to process.

The research staff will then do the following:

- Package samples for shipment to the designated laboratory for analysis.

Following self-collection(s), an HCP-collection will be done.

For the HCP-collected samples, the HCP will obtain a sample as per the standard of care method using a standard of care cervical cytobrush/broom (Rovers Cervex-Brush, designated by study for consistency) and transfer it into 20mL PreservCyt as per SoC.

Self-collected and HCP-collected samples will be tested using an FDA approved primary HPV IVD and may be further tested for cytological analysis or other tests as exploratory measures.

Following the study procedures, participants will fill out two surveys: 1) a Usability Survey, and 2) a Preferences Survey. This may be done either on a paper form or by electronic email survey. The survey categories evaluate the device (understanding of the instructions, ease of use, etc.) and assess barriers to care and preventative services, and expectations

and attitudes toward self-collection. The main objectives of the surveys are to examine the participant's ability to use a cervical cancer screening sample self-collection device with the instructions provided and to obtain information regarding overall interest and satisfaction with sample self-collection for cervical cancer screening.

8.4 6-14 Day Follow-up Communication

According to the participant's preference, there will either be a follow-up study email from the secure study database and/or phone call sent/made to each study participant between 6 and 14 days after sample self-collection. At least 3 attempts should be made to contact each participant before a participant is considered lost to follow up, including at least 1 phone call.

Participants will be asked if they have experienced any anticipated or unanticipated adverse events since sample collection at the study visit. Study personnel will record any collection-related AEs post-procedure reported by the participant.

This follow-up communication will be performed by site clinical research staff.

9.0 SAMPLE HANDLING AND ANALYSIS

All study self-collected and HCP-collected samples will be de-identified and bear a unique identification code linked to the participant. Samples will not bear any participant names or protected health information (PHI). Self-collected and HCP-collected samples will be packaged as per IATA and UN 3373 - Category B human biological substance shipping requirements and shipped to one or more designated and accredited central laboratories for processing, evaluation, and testing.

Collected samples should not be refrigerated or frozen prior to the shipping process but may be put in insulated containers during shipping to mitigate extreme temperatures. The self-collected and HCP-collected samples transferred to preservative will be processed in an identical manner prior to testing with the selected primary HPV detection assays and other tests as detailed below. The dry sponge self-collected sample (Scheme 1) will be resuspended at a designated time after collection date following the provided protocol (detailed below) prior to processing by the laboratory.

Three (3) distinct laboratory locations will process samples for the primary endpoint (primary hrHPV). Exploratory endpoint tests and analyses may be conducted at a single lab or multiple labs.

Scheme 1 Dry Sponge Processing: Upon receipt at the laboratory, a qualified technician will remove the sponge from the empty vial and transfer the sponge to a 20 mL PreservCyt solution according to laboratory instructions for resuspending a dry sponge. The sample will then be processed as described below.

All self-collected and HCP collected samples in preservative will then be processed per the assay manufacturer's instructions as follows: 3- 4 mL will be aliquoted for HPV testing on indicated platforms and other exploratory tests (e.g., STI, additional tests). The remaining sample volume may be processed for either liquid based cytology (LBC) or p16/Ki-67 dual stain from LBC in selected samples and/or retained or discarded.

Any discordant and/or invalid test results will be investigated, and further testing may be performed by the laboratory (including testing with a different HPV test).

Invalid test results will be re-run up to one additional time per standard operating procedure. Discordant samples, positive concordant, and a subset of negative concordant samples will be run on two additional HPV DNA assays and the result that is present in 2 of 3 results will serve as the "true" result for analysis. This procedure is designed according to the molecular composite comparator method described in Section 14.7 with the adjudicated result serving as the results toward the study efficacy endpoint.

Participation in this research study is not intended to replace the participant's standard screening and the participant should undergo routine screening on schedule. The participant informed consent (ICF) includes this information.

Test results from this study are for research purposes only and will not be reported directly to the participant.

9.1 HPV Testing

All study samples will be processed and tested for the presence of 14 oncogenic/high-risk HPV genotypes including:

1. HPV 16
2. HPV 18
3. HPV 31
4. HPV 33
5. HPV 35
6. HPV 39
7. HPV 45
8. HPV 51
9. HPV 52
10. HPV 56
11. HPV 58
12. HPV 59
13. HPV 62
14. HPV 68

Study samples will be tested using at least one of the following FDA approved:

- Roche cobas® 4800/6800/8800 HPV Test (Roche Molecular Systems Inc., Rotkreuz, Switzerland)
- BD Onclarity™ HPV Assay on the BD Viper™ LT or BD COR™ Systems (Becton, Dickinson and Company, Franklin Lakes, NJ. USA)
- Abbott Alinity m HR HPV Assay on the Alinity m System (Abbott, Abbott Park, IL, USA)

Samples will be tested on each system according to the manufacturer's instructions for use. Negative samples with the process control (β-globin) DNA concentration that does not fall within the HPV Test pre-determined range will be considered invalid. The results of HPV testing on self-collected and HCP-collected samples will be considered concordant if they are both positive at the cut-off value as determined by the FDA approved assay. Cycle threshold values will be obtained for positive hrHPV on all assays tested.

9.2 Cytology (Exploratory Measure)

Cytological studies may be performed on the remaining self-collected and HCP-collected sample material in PreservCyt media, using an approved cytology system by certified cytotechnologist, following laboratory standard operating procedures, and reported using the Bethesda system classification. Cytological studies are summarized as follows.

- All cytology samples will be assessed for:
    - Adequacy (>5,000 cells per slide, estimated based on ten fields counted at 400x magnification) and,
    - Diagnoses according to Bethesda System.
- Cytological diagnoses from self-collected samples will be compared to HCP-collected samples.
- Cytological results will be grouped as the diagnosis of atypical squamous cells of undetermined significance or higher (ASC-US or higher: ASCUS, ASC-H, LSIL, HSIL, SCC) and as high-grade dysplasia (HSIL or higher: HSIL, SCC), or atypical glandular cells (AGC, AIS, EC).

CINTec PLUS Cytology Evaluation

A subset of the residual samples may undergo evaluation using Roche CINTec PLUS dual stain (p16/Ki-67) immunohistochemistry evaluation. The results will be interpreted according to the manufacturer's instructions by a trained cytotechnologist and/or pathologist. This is an exploratory endpoint to determine if the sample collection could be adequate to run in conjunction with primary HPV testing.

9.3 Biopsy and/or Surgical Pathology Results (collected when available)

Histopathology results and Pap cytology will be recorded in the research record when a biopsy (LEEP or other surgical excision) or Pap cytology is collected as part of the participant's non-research course of care (following colposcopy, for example), to evaluate these data in combination with other results.

9.4 Longer term participant follow up

Additional HPV testing, Pap cytology and biopsy results may be obtained from the participant records following study participation for up to 3 years. These data are not considered part of primary endpoint analysis and may be collected in the interest of public health research.

9.5 STI Tests & Future Research

Residual sample may be used for testing with other HPV assays, triage testing, and/or STI testing to explore sample adequacy of the self-collection for additional tests.

Remnant study samples (including collected cellular tissue in stabilization media, collected vaginal sponge samples, and testing derivatives) may be retained in a study biorepository for future research by the Sponsor, or by current or future research and development partners, for further development of a self-collection device for cervical cancer screening, HPV testing, or STI testing.

All samples will be de-identified per Protection of Human Subjects, 45 CFR 46, and the HIPAA Privacy Rule.

10.0 COMPARISON OF USUAL CARE AND STUDY PROCEDURES

A study participant's routine medical care will not be affected by participation in this research study.

11.0 ADVERSE EVENT REPORTING

The Investigator is responsible for recording and reporting adverse events observed during the study. Adverse Event information will be recorded on the Adverse Event Case Report Form (AE CRF) and will be reported to the Institutional Review Board (IRB), as per the IRB reporting requirements, and to the Study Sponsor.

11.1 Definition of an Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical symptoms in participants, users, or other persons, during their participation in the study whether or not related to the investigational medical device.

Information recorded CRFs capturing acute AE's or those captured during the follow up period will include the nature of the event, date of onset, seriousness, severity, relationship to device and/or procedure, action taken, and outcome.

11.2 Anticipated Adverse Events and Assessment

In this study, safety will be evaluated to confirm that:

- SAEs are equivalent to the rate of SAEs from HCP-collection.

All SAEs will be reported to the sponsor and IRB, if applicable.

Adverse events (AEs) following self-collection will be recorded acutely and within 2 weeks of the specimen collections. HCP observation of adverse events related to self-collection and HCP collection will be recorded on the HCP Observations after Sample Collection CRF. Any acute adverse events determined to be related to the investigational device will be reported as adverse events and any unanticipated events related to HCP collection will be reported as adverse events. All unanticipated adverse events will be reported. Any unresolved or unanticipated adverse events during the follow up interval will be reported as adverse events.

Anticipated adverse events[1] include:

- Moderate to heavy vaginal/cervical bleeding
- Allergic reaction/hypersensitivity
- Self-collection device sponge detachment in the vagina
- Pain/discomfort/pinching sensation

[1] These AEs have been derived from a search of the FDA MAUDE and TLPC databases for HPV tests, cervical collection devices, and STI IVDs indicated for vaginal self-collection. The Teal Pilot study identified no new, novel or additional risks.

AEs will be reviewed and adjudicated by an HCP for study device relatedness on the appropriate CRF.

11.3 Definition of Serious Adverse Event (SAE)

An adverse event is classified as serious if the AE results in any of the following outcomes:

- Death
- Life-threatening - The participant was at substantial risk of dying at the time of the serious adverse event or use or continued use of the device or procedure might have resulted in the death of the participant.
- Hospitalization or prolongation of hospitalization – Accident & Emergency Department (including Observation Unit) visits that do not result in admission to hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Disability or permanent damage - The serious adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the participant's body function/structure, physical activities and/or quality of life.
- Congenital anomaly/birth defect - Exposure to a medical device prior to conception or during pregnancy may have resulted in a serious adverse outcome in the child.
- Required intervention to prevent permanent impairment/damage – A medical or surgical intervention was necessary to preclude permanent impairment of a body function, or to prevent permanent damage to a body structure, either situation suspected to be due to the use of an investigational device or procedure.
- Other Serious (Important Medical Events) - When the event does not fit the other outcomes, but the event may jeopardize the participant and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

11.4 Definition of Unanticipated Adverse Device Effect (UADE)

Unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, or 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 participants.

11.5 Severity Assessment

Severity assessment refers to the severity of the AE, not the seriousness of the event. The following definitions should be used to guide selection of severity.

Mild: An event that does not interfere with activities of daily living. No medical intervention is required.

Moderate: An event that interferes with activities of daily living, limits usual activities. No or minimal medical intervention is required.

Severe: An event that prevents normal everyday activities. Medical intervention or therapy is required.

Note the distinction between the gravity and the intensity of an adverse event. Severity is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity but would not be classified as serious unless it met one of the criteria for serious events listed in section 12.3.

11.6 Causality

The relationship between the use of the collection device and/or procedure of each adverse event shall be assessed and categorized. The presence of confounding factors, such as concomitant medication/treatment, the natural history of an underlying disease, other concurrent illness or risk factors shall also be considered.

Relationship	Description
Not Related	No relationship exists with the use of the device/procedure, or the event is clearly related to other factors.
Unlikely	The relationship with the use of the device/procedure seems not relevant and/or the event can be reasonably explained by another cause.
Possibly Related	The relationship with the use of the device/procedure is weak but cannot be ruled out completely.
Probably Related	The relationship with the use of the device/procedure seems relevant and/or the event cannot reasonably be explained by another cause.
Causal	The event is associated with the device/procedure beyond a reasonable doubt.
Unknown	The investigator is unable to determine whether the event is associated with the use of the device/procedure.

11.7 Unresolved Adverse Event

An adverse event that is unresolved at the time of 6-14 Day Follow-up should be followed to resolution. A phone call is recommended at least once a week until the AE is resolved. Three (3) attempts to contact the participant should be documented in the participant's medical record.

12.0 DEVICE MALFUNCTION AND/OR DEVICE FAILURE REPORTING

Device malfunctions or device failures should be documented on a Device Malfunction CRF. Teal may request that the device be returned for analysis. If this request is made, Teal will provide instructions for return.

NOTE: Device failures or malfunctions are not to be reported as adverse events, unless they result in, or contribute to adverse events.

13.0 STUDY MANAGEMENT

13.1 Quality Assurance and Quality Control

The study will be carried out in compliance with the ethical principles that have their origin in the current version of the Declaration of Helsinki, International Conference on Harmonization (ICH), Good Clinical Practices (GCP) guidelines, applicable US Code of Federal Regulations (CFR), and any additional requirements imposed by the investigational site's local IRB, central IRB, and/or local authorities.

13.2 Product Administration

Study devices will be manufactured in accordance with FDA Quality System Regulation (QSR) and ISO 13485:2016 Quality Management Systems and provided to each participating site by the Sponsor after IRB approval. The Investigator will maintain adequate records of the receipt and disposition of all study devices. The Investigator is responsible for ensuring that the devices are used according to this protocol and any approved amendments. The Investigator is responsible for keeping complete and accurate records of all devices used or unused in a log provided by the Sponsor.

13.3 Data Handling and Record Keeping

Source documents may include a participant's medical record, clinic charts, the Investigator's study files, questionnaires, and the results of diagnostic tests such as laboratory tests. These documents will be used to enter data on the Case Report Forms (CRFs/eCRFs). In some cases, data may be entered directly onto the CRF, in which case the CRF is the source document (i.e., Baseline Demographics and Medical History (if completed by participant, CRF surveys). Data to be collected includes, but is not limited to:

- Demographics
- Medical history
- Surveys – user feedback
- Adverse events
- Device malfunctions
- Test results/analysis

The Investigator is responsible for ensuring that data are properly recorded in each participant's source documents, CRFs, or directly into the EDC.

All written study documents must be completed in a legible manner; any missing data will be explained. Data entry errors will be corrected with a single line through the incorrect entry and the correct data is entered above/near the correction. All changes will be initialed and dated.

CRFs, Informed Consent Forms (ICFs) and all other study documentation containing participant information will be stored by the site under secure conditions when not in use. Computers and all storage devices containing study data will be compliant with institutional

and regulatory requirements including applicable HIPAA rules and be password protected. Access to data is restricted to study personnel and when required the IRB or other regulatory bodies as required by law.

Essential trial documents and data will be retained by the investigator in an Investigator Site File (ISF) and by the Sponsor in a Trial Master File (TMF) for at least two years following the last approval of a marketing application or formal discontinuation of clinical development or longer if required by local regulations. No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

Data Management Software System

Study data including demographic data and laboratory data will be entered into a validated study data management software system(s) to ensure consistent data entry and data quality. Clinical laboratory test result data will be entered directly from the source documents generated by the testing instruments. The database will have limited access only to authorized individuals and provides an audit trail for the generation, modification, and/or deletion of records.

Capturing of participant survey responses and specimen data (e.g., test results) will be done electronically in the Sponsor's electronic data capture (EDC) system, hosted on secure servers. The EDC database is password protected, encrypted, and accessible only by designated site study personnel, the designated CROs, and key Teal representatives. Automatic daily back-ups are stored in a secure manner to ensure maximum security and continuity.

Email survey response data will be captured automatically in the EDC system on an on-going basis. Sample test result data will be delivered electronically in the form of de-identified PDF-format instrument reports and manually entered in the database.

13.4 Confidentiality and Privacy

Participant confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

To ensure privacy, all personal identifiers (e.g., name, email, etc.) and electronic surveys, as well as any other personal health information will be stored in a secure database.

All research activities will be conducted in as private a setting as possible.

All study staff engaged in the conduct of this project will have completed training on the protection of human participants and the Health Insurance Portability and Accountability (HIPAA) Privacy Rule. In addition, all key personnel (i.e., Principal Investigator, individuals involved in identifying/recruiting participants, obtaining informed consent, or interacting and intervening with participants) will have undergone Good Clinical Practice (GCP) training.

Information about study participants will be kept confidential and managed according to HIPAA requirements. All participants will sign an informed consent and HIPAA authorization form (may be combined or separate) that includes specific privacy and confidentiality rights. Study data will be maintained per federal, state, and institutional data policies.

The Investigator(s) will ensure that the identities of participants are protected by using de-identified participant identification codes. The log of participant identifying information that links participants to their study-specific identification code will be maintained by the investigator. The log and all study records will be maintained in locked rooms and access will be limited to essential study personnel. Electronic study records/files will be stored on a department server and accessed via networked computers that are password-protected with access provided only to authorized study personnel.

Authorized representatives of the following groups may need to review this research as part of their responsibilities to protect research participants: representatives of the IRB and federal oversight agencies, such as the Office for Human Research Protections (OHRP). The Sponsor's clinical monitors may review study-related documents and underlying source documentation to ensure quality and integrity of study data. The clinical study site will permit access to such records.

13.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or investigational plan requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

A major deviation is one that impacts participant safety. All other deviations will be considered minor and will be reported according to IRB requirements.

It is the responsibility of the Principal Investigator and study staff to use continuous vigilance to identify and report deviations. The Principal Investigator is responsible for assessing whether the deviation constitutes noncompliance as defined by the reviewing IRB and if so, reporting it within the required time frame(s).

13.6 Protocol Amendments

Any significant amendments to the protocol that impact participant safety or study results will require review and approval by the IRB and Sponsor before the changes are implemented to the study. All changes to the consent form will be IRB approved.

13.7 Study Registration

The study will be registered on the US National Institutes of Health (NIH) website at *www.clinicaltrials.gov* during the study.

13.8 Publication Policy

It is expected that the knowledge gained, including pre-specified positive or negative outcomes, from the study will be disseminated through presentations at academic meetings and/or by publishing in a peer-reviewed journal. If the study is terminated early, release of

outcomes will be expedited if appropriate. Requirements of the current version of Uniform Requirements for Manuscripts submitted to biomedical journals published by International Committee of Medical Journal Editors will be followed. Participants will not be identified in any presentations or publications.

13.9 Sharing of Results

A participant's test results from any testing performed in the study (self-collect and HCP collect) will not routinely be included in their health record.

14.0 STATISTICAL ANALYSIS

14.1 Descriptive Statistics

Descriptive statistics will be used to summarize the characteristics of the participants in the study. Basic summaries of diagnostic test results will be tabulated including the dichotomized test result, the adequacy of the sample collected, and any other measures made during the collection and testing of the samples.

Summary statistics for continuous variables will include the number of participants, mean, standard deviation or standard error, median, minimum, and maximum.

Nominal categorical variables will be summarized using counts and percentages. Ordinal variables may be analyzed as if they were continuously scaled. Participant disposition, the number and percentage of participants who complete and discontinue as well as reasons for early discontinuation will be presented. Demographic and baseline characteristics will be summarized descriptively.

14.2 Primary Safety Outcome Measures and Analysis

Measures. Rate of SAEs from self-collection using study device as compared to rate of SAEs from standard of care collection performed by a healthcare professional. Literature will be consulted to ensure that rates of SAEs do not present unexpected SAEs or inconsistent rates of SAEs. SAE's for this type of procedure are expected to be rare.

Data Analysis. Each collection will count as a data point (unpaired). For each adverse event observed in the study, a summary of the associated collection method and information on relatedness and severity will be tabulated. Overall adverse event rates will be derived for each collection method, and comparisons between methods will be made. The rate and the corresponding 95% confidence interval (CI) will be presented for each collection method. In addition, the rate of SAEs between methods will be compared using Fisher's exact test. If the assumptions of the Fisher's exact test are not satisfied, i.e., counts of SAEs less than five, then the test will still be performed, and the resulting p-value provided for context only.

14.3 Primary Effectiveness Outcome Measures and Analysis

Measures. The primary outcomes are NPA (negative percent agreement) and PPA (positive percent agreement) for detection of hrHPV, and the invalid rate of the tested samples. Concordance of paired samples (self-collect compared to the HCP-collect) will be analyzed.

Data Analysis. PPA and NPA for hrHPV detection will be calculated between the participant Teal Wand self-collection device and the standard of care collection method, consistent with FDA's 2007 guidance, *Statistical Guidance on Reporting Results from Studies Evaluating Diagnostics Tests*.

		Standard of Care Collection Method ("Non-Reference Standard")	
		+	-
Teal Health Collection Device ("New Test")	+	a	b
	-	c	d
	Total	a+c	b+d

Positive Percent Agreement (PPA) = 100 x a/(a+c)

Negative Percent Agreement (NPA) = 100 d/(b+d)

This pivotal study will evaluate the positive and negative percent agreement *(PPA and NPA)* for hrHPV detection between the Teal Wand (Scheme 1 or 2) independently when compared to the HCP collected samples. 95% Wilson method will be reported for each agreement metric for each Teal Wand collection method.

As primary effectiveness endpoints for the study, PPA and NPA will be evaluated based on acceptance criteria on the lower bound of the corresponding 95% confidence interval. These acceptance criteria are dependent on which Teal Wand collection method is used and either scheme is analyzed independently. Schemes will not be combined:

- Collection Scheme 1. Self-collected samples collected with the Teal Wand and stored dry before resuspension by the laboratory ("dry sample") into preservative (20mL PreservCyt) and processed according to the manufacturer's IFU.

- Collection Scheme 2. Self-collected samples collected with the Teal Wand and transferred to preservative (20 mL PreservCyt) following collection. Processed according to manufacturer's IFU ("wet sample").

To arrive at the primary performance goal/point estimate, the Sponsor evaluated the available self-collect data published in a recent updated meta-analysis by top researchers in the field, notably Dr. Marc Arbyn, who has conducted several well-regarded meta-analyses of the international self-collect research landscape. The update of his group's 2018 [23] meta-analysis was published in 2022 [27], and provided valuable insights and rationale for proposing a performance goal of 87% PPA and 88% NPA. The meta-analysis presents pooled data which demonstrates that target amplification (TA) HPV DNA assays (those represented by the FDA approved primary HPV assays which will be utilized with the Teal Wand) offer the highest agreement

(statistically significantly better for relative sensitivity and PPA compared to other HPV detection modes). Further, the calculated relative sensitivity (Se) and specificity (Sp) for TA assays are very high, both approach 1.00 (pooled relative Se of 0.98, Sp of 1.00) for detection of CIN2+. These data demonstrate a high probability that those with cervical dysplasia (CIN2+) will have HPV detected by self-collect using the TA DNA assays (relative sensitivity >95%), while maintaining a high probability that those without cervical dysplasia will have a negative test result (relative specificity ~1.00). The percent agreement at which all studies showed >95% Se and Sp was 0.87 and 0.88, respectively in our analysis, which provides strong support for the endpoints in this study. The sample size of 225 hrHPV+ and 198 hrHPV- cases was based on meeting the point estimate for PPA (0.87) and NPA (0.88), as described above. An interim analysis will be run after 60% of the collections in each group have been tested for HPV. The interim will be performed for re-estimation of the sample size required to meet the end of study success. (Details on the planned interim analysis can be found in Section 14.5).

The coprimary endpoints for this study are PPA and NPA, and the acceptance criteria are set as:

- PPA of Teal Wand test compared to the clinician collection result will be at least 0.80 as measured by the lower bound of the corresponding 95% CI
- NPA of Teal Wand test compared to the clinician collection results will be at least 0.80 as measured by the lower bound of the corresponding 95% CI.

The study sample size has been derived based on the assumed performance of PPA of 0.87 and NPA of 0.88. Based on expected NPA of 0.88, a sample size of 198 HPV- cases was determined to reach at least 80% power to obtain a CI of at least 0.80. Based on expected PPA of 0.87, a sample size of 225 HPV+ cases was determined to yield a 0.80 lower bound of the CI when at least 80% power.

Data Analysis. Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) for detection of high-risk HPV for self-collected samples compared to the HCP-collected SoC method for each hrHPV assay/test system used and PPA and NPA of hrHPV will be calculated.

Overall percent agreement (OPA) for hrHPV detection will be calculated between the participant Teal Wand self-collection device and the standard of care collection method as another means to report agreement. This is an alternative way to represent PPA and NPA.

Measures: The invalid rate of the tested samples (expected not to exceed 10%) / Device design adequacy for the primary safety and efficacy measures.

To evaluate the invalid rate of the tested samples, the number, and percent of samples with failed test results or inadequate quality control will be reported. Invalid tests are defined as percent of hrHPV DNA concentrations below the detection threshold on the initial run as determined by the assay manufacturer. As such, the implication is that the sample is invalid, and the user did not perform critical tasks adequately.

Self-collection usability and labeling comprehension adequacy rate (≥ 90% proper execution on critical tasks (sponge deployment and rotation) and > 75% on all tasks) as evidenced by

binary or Likert scale responses on the Usability survey administered to a minimum of 80 users.

The Usability Survey data will be linked to sample adequacy information (e.g., invalid rate) to assess the usability of the self-collection methods. Summaries of participant responses will be reported as number of Participants and percentage by individual response. Responses to specific questions could be correlated with the adequacy of the collected sample.

14.4 Exploratory Effectiveness Outcome Measures and Analysis

The following measures are exploratory and may be evaluated on a subset or none of the residual samples.

Measure 1. Sample concordance diagnosis for liquid-based cytology and/or CINTec PLUS cytology analysis.

> Data Analysis. Evaluation of concordance of cytological preparations and/or CINTec PLUS cytology from self-collected samples compared to HCP-collected liquid-based cervical cytology and/or CINTec PLUS cytology. Sample adequacy and diagnosis will be recorded and compared.

Measure 2. Sample concordance diagnosis for detection of gonorrhea, chlamydia, mycoplasma, and/or trichomonas (STIs) using PCR based assays.

> Data analysis. Evaluation of concordance of diagnosis of STIs will be recorded and compared.

14.5 Planned Interim Analysis

The proposed sample size for the study of 225 positive HPV and 198 negative HPV for self-collected samples was based on the expected agreement and the 95% confidence interval (CI) lower bound acceptance criterion for futility, early stop for favorable results, or sample size re-estimation possible following interim analysis.

The interim analysis is designed with two purposes:

1. The unblinded analysis of the data after 60% of the targeted HPV positive cases and the targeted HPV negative cases for futility will be addressed first. The study has been designed with performance targets for PPA and NPA. Therefore, the futility evaluation will be targeted to stop the study if the performance at the interim is well below the proposed targets of 0.80 PPA/NPA for CI lower bounds.
2. In addition, the interim analysis can be used to re-estimate the sample size to meet the end of study acceptance criteria, provided sufficiently promising results are observed at the interim. A maximum sample size of 870 total cases (HPV+ and HPV- combined) may be considered in the re-estimation. Early stopping could be possible for favorable results.

14.5.1 Futility

For futility, an observed PPA at the interim of less than 0.80 or an observed NPA of less than 0.80 will be defined as a basis to halt the study early. As the outcome data are required

to assess the futility of the study, then the alpha level for the interim analysis and the end of study alpha level must be adjusted to ensure an overall type I error probability of 0.05. Like the O'Brien Fleming approach, a standard adjustment of using α=0.012 at the interim and α=0.04 at the end of study is appropriate. Therefore, an end of study evaluation of the acceptance criteria will be based on a (1-α)100% or 96% CI meeting the targeted lower bound.

For PPA, 60% of the targeted HPA+ cases yield 135 out of the planned 225 cases. If the number of Teal Wand self-collection test results that agree with a SOC clinician collected sample HPV+ test result is 107 or fewer out of 135, the study will be deemed in jeopardy of failure for futility. Given a range of underlying true PPA values, the following probabilities of observing so few in agreement based on the binomial distribution were derived:

Table 1. Probability of observing PPA less than 80% at the interim (n=135) given various underlying, true PPA values:

True PPA	P(X ≤ 107 | X ~ B(n=135, p=True PPA)
0.84	0.086
0.85	0.045
0.86	0.020
0.87	0.008

Based on the table above for PPA, the interim analysis at 135 HPV+ subjects indicates that if the observed PPA is below 0.80, the probability of observing such a result when the true PPA is 0.86 or above is at 2% or less. If the true PPA is 0.87, the probability of observing agreement with HPV+ clinician test results of less than 0.80 would be less than 1%, or highly unlikely. Further, if the unlikely event did occur even with a true PPA of 0.86 or higher, the probability of successfully meeting the end of study goal is less than 1%, without any re-estimation of sample size. The table below summarizes the likelihood of observing an end of study agreement rate between Teal Wand self-collection HPV testing and clinician collected SOC HPV testing that would meet the study primary endpoint for PPA. Since the interim analysis requires unblinding, an adjustment to the 95% CI to 96% for the end of study results is required to account for the alpha-spend.

Table 2. Probability of observing end of study PPA with a 96% CI with a lower bound of at least 0.80, given various underlying, true PPA values

				For Remainder of the Study		
True PPA	**Interim PPA (n_1=135)**	**P(X ≤ 107 | X ~ B(n_1=135, p=True PPA)**	**Max. SS***	**Number of cases in agreement needed***	**PPA (x/n_2) needed in remainder of study (n_2=MaxSS-135)**	**P(X ≥ x | X ~ B(n_2, p=True PPA)**
0.85	107/135, or 0.793	0.045	225	193-107= 86	86/90, or, 0.956	0.0015
0.86		0.020				0.0031
0.87		0.008				0.0064
0.85		0.045	300	255-107 = 148	148/165, or,	0.052
0.86		0.020				0.101

				For Remainder of the Study		
True PPA	**Interim PPA (n_1=135)**	**P(X ≤ 107 | X ~ B(n_1=135, p=True PPA)**	**Max. SS***	**Number of cases in agreement needed***	**PPA (x/n_2) needed in remainder of study (n_2=MaxSS-135)**	**P(X ≥ x | X ~ B(n_2, p=True PPA)**
0.87		0.008			0.897	0.181
0.85		0.045	400	337-107 = 230	230/265, or, 0.868	0.235
0.86		0.020				0.396
0.87		0.008				0.585

*In the original targeted sample size of 225, the number of cases in agreement that would yield a Wilson's 96% CI with a lower bound of at least 0.80 would be 193 out of 225, or observed PPA of 0.858; In a final sample size of 300, the number of cases in agreement that would yield a Wilson's 96% CI with a lower bound of at least 0.80 would be 255 out of 300, or observed PPA of 0.85; In a sample size of 400, the number of cases in agreement that would yield a Wilson's 96% CI with a lower bound of at least 0.80, would be 337 out of 400, or observed PPA of 0.843.
**Probability of lower bound of 96% CI of 0.80 or above, with no requirement on the point estimate.

Based on the above analyses, a lower bound of 0.80 could be obtained for a 96% CI at the end of a study of 400 HPV+ cases with nearly 60% probability, when the interim yields a PPA of less than 80%, which is highly unlikely (probability<1%).

For NPA, 60% of the targeted HPV- cases is 119 out of the currently planned 198 for HPV-. If the number of Teal Wand self-collection test results that agree with a SOC clinician collected sample HPV- test result is 95 or fewer out of 119 for either HPV-, the study will be deemed in jeopardy of failure for futility. Given a range of underlying true NPA values, the following probabilities of observing so few in agreement based on the binomial distribution were derived:

Table3. Probability of observing NPA less than 80% at the interim (n=119) given various underlying, true NPA values

True NPA	P(X ≤ 95 | X ~ B(n=119, p=True NPA)
0.85	0.077
0.86	0.040
0.87	0.018
0.88	0.007

Based on the table above for NPA, the interim analysis at 119 subjects indicates that if the observed PPA was below 0.80, the probability of observing such a result when the true PPA is 0.86 or above is at 4% or less. If the true NPA is 0.88, the probability of observing agreement with HPV- clinician test results of less than 0.80 would be less than 1%, or highly unlikely.

Further, if the unlikely event did occur even with a true NPA of 0.86 or higher, the probability of successfully meeting the end of study goal is nearly 50%. The table below summarizes the likelihood of observing an end of study agreement rate between Teal Wand self-collection HPV testing and clinician collected SOC HPV testing that would meet the study

primary endpoint. Since the interim analysis requires unblinding, an adjustment to the 95% CI to 96% for the end of study results is required to account for the alpha-spend.

Table 4. Probability of observing end of study PPA with a 96% CI with a lower bound of at least 0.80, given various underlying, true PPA values

				For Remainder of the Study		
True NPA	**Interim NPA (n_1=119)**	**P(X ≤ 95 | X ~ B(n_1=119, p=True NPA)**	**Max. SS***	**Number of cases in agreement needed***	**NPA (x/n_2) needed in remainder of study (n_2=MaxSS-119)**	**P(X ≥ x | X ~ B(n_2, p=True NPA)**
0.86	95/119, or 0.798	0.045	198	170-95= 75	75/79, or, 0.949	0.010
0.87		0.020				0.018
0.88		0.008				0.032
0.86		0.045	250	213-95 = 118	118/131, or, 0.901	0.108
0.87		0.020				0.181
0.88		0.008				0.283
0.86		0.045	300	255-95 = 160	160/181, or, 0.884	0.208
0.87		0.020				0.335
0.88		0.008				0.492

*In the original targeted sample size of 198, the number of cases in agreement that would yield a Wilson's 96% CI with a lower bound of at least 0.80 would be 170 out of 198, or observed PPA of 0.859; In a sample size of 250, the number of cases in agreement that would yield a Wilson's 96% CI with a lower bound of at least 0.80 would be 213 out of 250, or observed PPA of 0.852; In a sample size of 300, the number of cases in agreement that would yield a Wilson's 96% CI with a lower bound of at least 0.80, would be 255 out of 300, or observed PPA of 0.85.
**Probability of lower bound of 96% CI of 0.80 or above, with no requirement on the point estimate.

Based on the above analyses, it is highly unlikely that a lower bound of 0.80 could be obtained for a 96% CI at the end of a fully doubled study of HPV- cases, when the interim yields a PPA of less than 80%. A similar argument would apply for PPA and the HPV- cases.

14.5.2 Sample Size Re-estimation (SSRE)

The other purpose for the interim analysis is to re-estimate the sample size to meet the primary endpoint acceptance criterion based on a set of clinical practice test results. Therefore, the interim is referred to as a SSRE or Sample Size Re-Estimation analysis, The interim analysis will require unblinded review of the study endpoint data by an unblinded statistician and a corresponding alpha penalty for the interim re-estimation. The interim will be performed when at least 135 of the 225 targeted HPV+ and 119 of the targeted 198 HPV- cases (by clinician collection) have been determined.

As there are two co-primary endpoints, the estimates of PPA and NPA, the following discussion of the interim analysis will be performed separately for each endpoint, i.e., each endpoint will have its own sample size readjustment.

The plan for the interim analysis is to only re-estimate the sample size when the interim result is in the "promising zone", as compared to pre-defined favorable and unfavorable zones[28]. The promising zone will be defined as those estimated values of PPA or NPA at

the interim that correspond to conditional probabilities of meeting end of study goal between 0.50 and 0.90 when true PPA/NPA was assumed to be 0.87/0.88. The favorable zone is dependent upon the endpoint and the expected performance.

Table 5. Sample Size Re-Estimation (SSRE) definition of interim results for PPA

Zone	PPA	No. Agree out of n=135
Unfavorable	<0.85	<115
Promising	[0,85 0.90)	115-120
Favorable*	>0.90	≥ 121

**Favorable in this case would mean that the study could stop early for success, given that the alpha spend at 0.60 interim would be for alpha=0.012, or that the corresponding point estimate of at least 0.896 would have a lower bound of the 99% CI of at least 0.80.*

The favorable zone at the interim would correspond to PPA at the interim of at least 0.896, or agreement of 121 or more out of the 135 at the interim. This would yield a 99% Wilson's CI with the lower bound of at least 0.80, and the study could theoretically stop early for success – for the HPV+ arm of the study.

Since there is regulatory target of at least 35 HPV16+ cases to be included in the study, the study may need to continue enrolling HPV+ cases towards meeting the target of 35 HPV16+ cases. Therefore, the overall number of HPV+ cases that are enrolled could exceed the targeted sample size – even if the study does meet its stopping success criterion at the interim.

Table 6. Sample Size Re-Estimation (SSRE) definition of interim results for NPA

Zone	NPA	No. Agree out of n=119
Unfavorable	<0.85	<101
Promising	[0,85 0.90)	101-106
Favorable*	>0.90	≥ 107

**Favorable in this case would mean that the study could stop early for success, given that alpha spend at 0.60 interim would be for alpha=0.012, or that the corresponding point estimate of at least 0.899 would have a lower bound of the 99% CI of at least 0.80*

The favorable zone at the interim for NPA would correspond to a similar agreement of 108 or more out of the 119 at the interim or observed NPA of 0.896. This would yield a 99% Wilson's CI with the lower bound of at least 0.80, and the study could stop early for success on the HPV- arm of the study.

The promising zone for PPA/NPA at the interim analysis corresponds to a range of observed performance metrics that support likely end of study success but may warrant some sample size re-estimation (SSRE). The two tables below demonstrate the likelihood of observing results in each of the interim zones, given the true underlying PPA or NPA, respectively.

Table 7. Zones for re-estimation of sample size and the associated zones for PPA at interim of 135 HPV+ cases

Assumed true PPA	Zone	PPA at interim (p_1)	Probability of entering zone	P(meet acceptance at end of study | interim result)*
0.85	Unfavorable	<0.85	0.465	≤ 0. 285
	Promising	[0.85, 0.90)	0.457	0.396 – 0.879
	Favorable	≥ 0.90	0.078	^
0.86	Unfavorable	<0.85	0.337	≤ 0.382
	Promising	[0.85, 0.95)	0.527	0.503 – 0.927
	Favorable	≥ 0.90	0.136	^
0.87	Unfavorable	<0.85	0.221	≤ 0.491
	Promising	[0.85, 0.90)	0.558	0.613 – 0.960
	Favorable	≥ 0.90	0.221	^

**Conditional probability of meeting end of study (at n=225) acceptance criterion (lower bound of the Wilson's 95% CI is ≥ 0.80); ^ favorable would correspond to early stopping for success.*

Table 8. Zones for re-estimation of sample size and the associated zones for NPA at interim of 119 HPV- cases

Assumed true NPA	Zone	NPA at interim (p_1)	Probability of entering zone	P(meet acceptance at end of study | interim result)*
0.86	Unfavorable	<0.85	0.305	≤ 0.317
	Promising	[0.85, 0.90)	0.561	0.443 – 0.920
	Favorable	≥ 0.90	0.134	^
0.87	Unfavorable	<0.85	0.201	≤ 0.414
	Promising	[0.85, 0.90)	0.586	0.448 – 0.954
	Favorable	≥ 0.90	0.212	^
0.88	Unfavorable	<0.85	0.119	≤ 0.520
	Promising	[0.85 ,0.90)	0.563	0.652 – 0.976
	Favorable	≥ 0.90	0.318	^

**Conditional probability of meeting end of study (at n=198) acceptance criterion (lower bound of the Wilson's 95% CI is ≥ 0.80); ^ favorable would correspond to early stopping for success.*

The sample size will be re-estimated based on the interim analyses with the maximum study wide sample size of 870 (HPV+ and HPV- clinician test results combined). Based on the observed PPA or NPA, the interim results will fall into one of the three zones:

- If the interim estimate does not fall into the futility range, but is in the unfavorable zone, the study may continue to accrue to its originally planned sample size.
- If the interim estimate falls in the favorable zone, then the study could potentially be stopped for success, i.e., the resulting Wilson's 99% CI on the interim data has a lower bound which exceeds 0.80.
    - In general, to meet the required 35 HPV16+ cases, the number of cases overall and HPV+ of other subtypes may exceed the targeted sample size.
    - The sponsor reserves the right to share favorable interim results with the FDA through an unblinded statistician regardless for the purpose of

performance goal negotiation and in the interest of speeding access for public health reasons.
    - If the interim analysis shows promising or favorable results, and the target of 35 HPV16+ subjects is met, the Sponsor may submit a marketing application to the FDA while enrolling the remainder of any required samples.
- If the interim estimate falls within the promising zone, then the conditional probability of meeting the acceptance criterion on the lower bound of the 96% Wilson's CI at the end of the planned study will be derived from the actual interim results data (unblinded). Based on this assessment, the sample size may be increased or decreased to meet the acceptance criterion of the PPA or NPA with a lower bound of the 96% Wilson's CI of at least 0.80. The power to reach this endpoint will be targeted at a minimum of 80% but possibly increased to consider power of up to 90% as well.
    - The SSRE will be performed by an unblinded statistician, and the results of the analysis provided only to a limited, prespecified group of team members, based on need.

14.6 Subgroup Analysis

To examine agreement of the collection method across specific HPV genotypes of interest (e.g., HPV16, HPV18, HPV31, HPV Other) and combinations, including differences in cycle threshold (ct) values, will be evaluated. PPA and NPA will be estimated and presented along with the corresponding 95% Wilson's CI for each subgroup. No formal hypothesis testing will be performed since the study is not powered for these comparisons.

Additional analyses will be performed to evaluate the PPA for different types of HPV, especially for the types that are associated with a higher risk of cancer: HPV 16 and HPV 18 as well as a group of other high-risk types of HPV. For PPA, the analysis will focus on the subset of those hrHPV+ cases that have been indicated to have the specific type or one of a group of types. NPA will be the same across the different types of HPV since it only includes those cases that are hrHPV-. If available, histopathology/cytology results will be evaluated in combination with HPV results and reported as cross tabulations.

Invalid rates will be reported in aggregate, and evaluated based on the comparator results (e.g. the number of invalid self-collect samples with a positive clinician collect vs. negative clinician collect). No formal hypothesis testing will be performed as the study is not powered for these comparisons.

14.7 Composite Comparator Analysis

As Arbyn and colleagues present in the 2022 meta-analysis [27], FDA and other regulators have recommended the use of agreement statistics to verify the performance of collection devices using FDA approved HPV assays, such as those proposed herein, which precludes the need for large and costly diagnostic test accuracy studies due to the previously validated sensitivity and specificity of the assays and clinical cutoffs for detection of HPV based on histological outcomes. Some amount of discordance is expected given the differing assays and established clinical cutoffs. In anticipation of these discordances, a composite molecular comparator utilizing three FDA-approved HPV screening TA assays will be employed to evaluate all HPV+ samples (whether by SC, CC, or both) and a subset of negative results in accordance with FDA interaction. In the absence of histological outcomes

(not all participants will be biopsied in this study as part of their diagnosis and treatment course according to the current guidelines), the composite comparator can serve to gain additional insight into performance of self-collection on the indicated assays and will serve to adjudicate discordant results toward the primary endpoint analysis such that the result returned in 2 of 3 assays will serve as the result.

For all positive samples (whether by SC, CC, or both) and a subset of negative cases, the clinician collected samples will be processed on 3 FDA approved HPV assays (Roche cobas 6800/8800, Roche cobas 4800, BD Onclarity, or Abbott Alinity m). Liquid based cytology (ThinPrep Pap) may be performed on discordant clinician collected samples as information only. This concept was discussed in the March 2019 meeting of the Microbiology Devices Panel titled “New Approaches in the Evaluation for High-Risk Human Papillomavirus Nucleic Acid Detection Devices” [29].

The primary purpose of the molecular composite comparator is to determine a specimen to be a true negative, given the extremely high negative predictive value for the FDA-approved HPV assays included in this study. Because the Teal Wand is a collection device rather than an assay, this approach will provide more information on samples. Discordance analysis according to this approach will be provided as supplemental data.

15.0 RISK/BENEFIT ASSESSMENT

15.1 Benefits

There are no direct benefits to the study participant for participating in this study. The data obtained in this study are designed to provide a sufficient basis for marketing authorization to implement self-collection into cervical cancer screening.

15.2 Risks and Mitigation

Potential risks of the self-collection device are:

- Mild discomfort and minimal or increase in vaginal bleeding. These are the same risks associated with the commercially available Rovers Cervex-Brush® that that is a Class II 510k (K930955) cleared device and other FDA cleared cervical collection devices. Risks will be minimized by explicit instructions on how to use the device. Furthermore, risk is mitigated by design using a soft sponge material and atraumatic design.
- The self-collect device will be used in a simulated environment (private space in clinic). HCP will complete a CRF to document any negative sequelae related to the self-collection process prior to Pap collection.
- Allergic reaction/hypersensitivity to any of the materials used in the collection device. This risk is expected to be rare, with the following medical grade materials used:
    - Collection Device: medical grade polycarbonate and thermoplastic polyurethane rubber material.
    - Sponge: open cell polyurethane foam material (FDA approved material currently used in CytoSponge, K181020 and PapCone, K083012).
- Sponge could detach from the shaft, requiring retrieval. This risk is mitigated by robust design, design verification testing and by participant self-collection being performed at the clinic, so the investigator may intervene, if necessary.

- Bacterial contamination of self-collection device. This risk is mitigated since the Teal device will be exposed to Ethylene Oxide (EtO) sterilant following manufacture.

Other risks include:

- Emotional discomfort when completing the surveys. Participants will be told that if they feel uncomfortable about responding to one or more items on the survey they do not have to respond to the item(s).

15.3 Risk/Benefit Analysis

The risks associated with this study are minimal, and there are potential benefits to society, including the potential for the self-collection device to be available for in clinic or home use.

16.0 STUDY MONITORING

Monitoring will be performed during or at the conclusion of the study by individuals that are appropriately trained and qualified to assess continued compliance with the protocol and applicable regulations. In addition, the monitor will verify that the study records are adequately maintained, that the data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The investigator/institution guarantees direct access to original source documents by the Sponsor personnel, their designees, and appropriate regulatory authorities.

A protocol-specific Sponsor developed Clinical Monitoring Plan will describe the frequency and extent of the monitoring, including source documentation verification required for the study. Data will be reviewed for trends in changes in the site compliance, and appropriate corrective and preventive actions as well as corrective action plans, will be developed. This review may trigger increased monitoring frequency and/or implementation of corrective action plans at the site.

Monitors will be selected and assigned by Sponsor's clinical management or personnel authorized to supervise the monitoring program.

17.0 ECONOMIC BURDEN TO PARTICIPANTS

There are no costs that participants are responsible for because of participation in the research.

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