Rwanda WISH Study
(Women's Improvement of Sexual and reproductive Health)

Statistical Analysis Plan of Primary and Secondary Endpoints

Author: Marinus Verwijs, Project Manager
Supervisor: Janneke van de Wijgert, Professor and Chief Investigator
Version date: 2 October 2017

Sponsor	University of Liverpool
Study site	Rinda Ubuzima P.O. Box 4560, Kigali, Rwanda Tel: +250-788439009
Chief investigator (CI)	Professor Janneke van de Wijgert, PhD MPH MD Institute of Infection and Global Health, University of Liverpool Ronald Ross Building, 8 West Derby Street, Liverpool L69 7BE Tel office: +44-151-795-9613; Tel mobile: +44-755-719-5108 Email: j.vandewijgert@liverpool.ac.uk
Principal Investigator (PI)	Stephen Agaba, MD Tel mobile: +250-788 357 866 Email: agabask@gmail.com
Funder	European and Developing Countries Clinical Trials Partnership (EDCTP)
Funding period	1 Jan 2016 – 31 Dec 2017
Data collection period	5 Jul 2016 – 14 March 2017
Protocol version, date	Version: 0.5; Date: 8 November 2016
Previous approved versions, dates	Version: 0.4; Date: 6 June 2016

Table of Contents

1. Background

1.1 WISH objectives and endpoints

The current standard of care for urogenital infections in Rwanda is syndromic management. Many urogenital infections are asymptomatic and therefore completely missed, and the management of vaginal discharge syndrome (VDS) is known to be suboptimal. We conducted the WISH (Women's Improvement of Sexual and reproductive Health) study to address this problem. Data collection took place at the Rinda Ubuzima (RU) research clinic in Kigali, Rwanda, from July 2016 to March 2017. The study was sponsored by the University of Liverpool (UoL).

The primary objective of the WISH study is to evaluate whether it is feasible to improve urogenital infection care in high risk women in Kigali, Rwanda (see 'study population' below), using point of care (POC) diagnostic testing for HIV, *Trichomonas vaginalis* (TV), and bacterial vaginosis (BV) in all women; POC testing for *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), and syphilis in pregnant women and women assessed to be at high risk for these infections using a risk scoring questionnaire; and management of vaginal candidiasis, urinary tract infection (UTI), genital ulcers/inguinal buboes, and lower abdominal pain (LAP) in women reporting relevant symptoms. The secondary objectives of the study are 1) to evaluate the performance and 2) cost effectiveness of the POC tests for CT/NG, TV and BV; and 3) to obtain the opinions of stakeholders (clinicians, programme implementers and policymakers) about the potential improvement of urogenital infection care in Rwanda as well as 3b) the potential roll-out of novel vaginal microbicides and multipurpose prevention technologies for HIV and pregnancy prevention as soon as efficacious products become available. This statistical analysis plan (SAP) describes the statistical analyses to be undertaken to achieve the primary objective and the first secondary objective (POCT performance), as well as some related exploratory analyses. The other secondary objectives will be analysed separately.

Primary objectives	Primary endpoints
1. Implement improved urogenital infection care services and monitor and evaluate these services	• Monitoring and evaluation indicators, such as: – Inputs: Procurement experiences/costs, infrastructure and training requirements; – Activities/outputs: Numbers of clients counselled and risk scored, diagnostic tests conducted, infections diagnosed and treated, and referrals made; staff time required for each activity; time spent at the clinic for each client trajectory; – Outcomes/impacts: Improvements of access to and quality of services (from client satisfaction survey, staff interviews).
Secondary objectives	Secondary endpoints
1. Compare performance of syndromic management, POCT, and gold standard molecular testing for the diagnosis of NG, CT, TV, BV, and candidiasis.	• Sensitivity, specificity, PPV, and NPV for: – TV, BV: Syndromic vs POCT of everyone vs gold standard – Candidiasis: Syndromic vs gold standard – NG, CT: Syndromic vs POCT after risk scoring vs POCT (= gold standard) of everyone. The POCT test is a molecular test and is considered to be a gold standard in this SAP.

1.2 WISH study population

We enrolled adult women (18 years or older) living in the city of Kigali who were at high risk of HIV/urogenital infections (defined as having had more than one sexual partner OR having been treated for a sexually transmitted infection (STI) in the 12 months prior to enrollment) regardless of

the presence of current urogenital symptoms. Each woman could participate in the WISH study only once. Women were excluded when they were participating in another health intervention study or were unfit for participation as judged by the PI, but they were not excluded when they were known HIV-positive and/or pregnant. Unmarried women aged 18-20 required written informed consent of a parent or guardian (as per Rwandan law) in addition to their own consent; however, this was no longer needed after 7 November 2016 because the age of majority was lowered from 21 to 18 in the Rwandan law.

1.3 WISH study procedures

All participants attended a Main Visit, during which the following procedures were done in the order given: eligibility check, informed consent procedures, assignment of Patient Identification Number (PID), face-to-face interview including CT/NG and syphilis risk scoring, counselling (the participant could choose the topics she wanted to be counselled on herself), and a pelvic and bimanual examination if the participant reported relevant and moderate/severe urogenital symptoms (see paragraph 4.1, section "Pelvic, bimanual and physical examinations performed at Main and Additional Visits", for details).

Participants were offered the following additional services:

a) Voluntary counselling and testing (VCT) for HIV.
b) Urine pregnancy test if indicated.
c) POC testing for UTI if UTI symptoms were present.
d) POC testing for TV and BV regardless of symptoms, and management of vaginal candidiasis based on symptom-reporting and/or signs during a pelvic examination (if applicable).
e) POC testing for syphilis and/or CT/NG if considered at risk by risk scoring (such as being pregnant).
f) Syndromic management of LAP, genital ulcer syndrome (GUD) and inguinal buboes.
g) Treatment and partner notification and treatment as appropriate, and referrals to antenatal, family planning, HIV and cervical cancer screening care.

Services were available for free at RU's research clinic for the duration of the project. Services were generally delivered within one half day. However, women could choose to leave before all results were available, and be contacted by study staff when results were available, which was particularly relevant for women undergoing CT/NG POC testing (this was performed on the Cepheid GeneXpert platform, which takes about 90 minutes).

Additional Visits took place when participants opted not to wait for test results, for partner notification and treatment, if urogenital symptoms did not resolve after treatment, and for other reasons that are summarised in this SAP. Women could notify partners themselves or allow RU staff to contact partners. They could also opt out of partner notification of specific partners, for example, if there was a risk of domestic violence. Participants who developed new urogenital symptoms were referred to local clinics because each woman was allowed to participate in the WISH study only once.

1.4 STI syndromic management: WHO and Rwandan guidelines

The WHO published its STI syndromic management guidelines[1] in 2003 to allow for diagnosis and treatment of STIs in resource-poor settings where laboratory testing is not available and physical examination skills are scarce. The original idea was that each symptom syndrome (vaginal discharge syndrome (VDS), lower abdominal pain (LAP), genital ulcer disease (GUD), etc) would be treated for

[1] World Health Organization, 2003: Guidelines for the Management of Sexually Transmitted Infections.

all organisms that might cause the syndrome. This was later expanded by the addition of physical examinations (if available), and the possibility to tailor the guidelines to local STI epidemics as well as person-centered risk assessments. A next version of the guidelines was published in 2008[2] but the VDS and LAP algorithms for women were unaltered. Flowcharts of the WHO algorithms relevant for the WISH study are shown in appendix 8.1.

The Rwandan STI management guidelines were published in 2010[3] with an update in 2013[4] (see appendix 8.2). Only the treatment guidelines, but not the diagnostic algorithms, were revised in this update. The Rwandan STI management guidelines differ substantially from the WHO guidelines:

- Both guidelines contain two different VDS algorithms: one with and one without a speculum and bimanual examination (and the WHO guidelines also incorporate the possibility of local wet mount or Gram stain microscopy). However, the Rwandan guidelines assume that the clinician can distinguish between mucopurulent cervical discharge and/or cervicitis (which is to be treated for CT/NG/TV) and non-mucopurulent vaginal discharge (which is to be treated for BV/TV/candidiasis). ***We believe that speculum examinations will rarely be available, and when available, will mostly be used to identify PID, GUD, buboes, condylomata, and other visible/palpable pathologies, but cannot be reliably used to distinguish between different types of discharge. In this SAP, we will therefore only use the VDS algorithms in the absence of a speculum and bimanual examination when evaluating algorithm performances.***
- The Rwandan VDS algorithms incorporate a predetermined set of questions for CT/NG risk scoring, as well as CT/NG treatment when a woman's partner has urethritis complaints. The WHO guidelines do provide the possibility for risk scoring but state that risk scoring should be guided by local epidemiology. ***In this SAP, when evaluating the performance of the Rwandan guidelines, we will follow the Rwandan risk scoring as outlined in the algorithm.*** *One of the possible risk factors in the Rwandan guidelines is "2 or more sexual partners" but no time frame is given; we will use 2 or more sexual partners in the past 12 months.* ***When evaluating the performance of the WHO guidelines, we will assume high risk for CT/NG based on the local epidemics in our research communities.***
- In the Rwandan VDS algorithms, candidiasis is diagnosed based on the presence of unusual vaginal discharge and a low CT/NG risk score, while in the WHO guidelines candidiasis is only treated in the presence of typical signs and symptoms (vulval oedema/curd-like discharge, vulval erythema or excoriations). ***In this SAP, we will follow each respective guideline when evaluating the performance of that guideline.***
- In the Rwandan algorithms, all female sex workers (FSWs) without symptoms are to receive presumptive treatment for NG, CT and TV. However, when they do report symptoms, the usual syndromic algorithms are to be used and no presumptive treatment should be given. No definition of FSW is given***. In this SAP, we will define sex work by self-reported exchange of sex for money and/or goods in the past 12 months, and we will follow the Rwandan guidelines.***

Flow diagrams of the WISH algorithms, as described in section 1.3, are shown in appendix 8.3.

2. Participant disposition

The number of participants was dictated by the available budget and no formal statistical power calculations were performed. 705 participants were enrolled in the study.

[2] World Health Organization, 2008: Report of the Expert Consultation and Review of the Latest Evidence to Update Guidelines for the Management of Sexually Transmitted Infections.
[3] Republic of Rwanda – Ministry of Health, 2010: National Guide on the Care of Sexually Transmitted Infections – Manual of the Care Provider.
[4] Republic of Rwanda – Ministry of Health, 2013: National Guidelines for Prevention and Management of HIV, STIs & Other Blood Borne Infections.

Women heard about the study during recruitment activities (recruitment meetings organised by RU staff, leaflets) or word of mouth. From 4 July 2016 to 2 September 2016, RU staff conducted all recruitment activities with the help of three Community Mobilisers (two were former female sex workers; one was a community organizer), as had been done previously in many RU studies. They referred high risk women to recruitment sessions in the community (conducted by RU staff) and handed out leaflets. However, this method attracted too many women who tested positive on the risk scores (mostly because many of them were sex workers). From 5 September 2016 until the week of 13 March 2017, RU staff no longer worked with the Community Mobilisers, but instead, performed the following recruitment activities: providing information and recruitment leaflets at non-governmental women's organizations (such as women's cooperatives), monthly *umuganda* community meetings, district hospitals, local health centers, pharmacies, and at a local family planning clinic. Earlier participants from the WISH study (especially testing negative on risk scores) were also encouraged to refer friends and family. These new strategies did indeed attract fewer women who tested positive on the risk scores. The numbers of women who were approached (at a meeting, by leaflet, or by word-of-mouth); subsequently did or did not attend the RU clinic for a Main Visit; and did or did not proceed to the informed consent procedures are not known. Data were only collected from women who attended the RU clinic after they had given informed consent.

Participants were allowed to voluntarily withdraw from the study for any reason at any time. The PI was also allowed to discontinue participants (for example, if this was deemed in the best interest of the participant). The reason(s) for withdrawal or discontinuation were recorded in the participant's records.

Participant disposition	**N = 705**
N women enrolled	705
N women excluded by PI at the Main Visit	0
N women who completed their Main Visit	705
N women who did not complete their Main Visit	0
N women who withdrew their informed consent after Enrolment	0
Participant disposition	**n (%)** **N = 705**
N Additional Visits attended	
N women who attended one Additional Visit	
N women who attended multiple Additional Visits	
Reasons for Additional Visits[1]: – To withdraw informed consent – To obtain results and/or treatment: left Main Visit prior to receiving all results – For speculum/bimanual exam because this could not be completed at Main Visit – For additional sampling/testing because this could not be completed at Main Visit – For speculum/bimanual exam and/or additional testing because symptoms did not resolve (ongoing untreated infection, re-infection, or treatment failure) – To have a new urogenital symptom investigated or to repeat screening for HIV/STIs or urogenital infections[2] – For couple counselling, potentially in conjunction with HIV testing of a male partner – To report an (S)AE and/or social harm – To ask questions or express concerns – Other, specify [additional categories to be made if necessary]	
N women aged 18-20 who required consent of a parent or guardian[3]	
N women aged 18-20 who did not require consent of a parent or guardian[3]	

Abbreviations: AE = adverse event; PI = Principal Investigator; STI = sexually transmitted infection.

1. May total to more than 100% because one woman could attend Additional Visits for multiple reasons.
2. These women should subsequently be referred to a local clinic.
3. The age of majority in Rwanda changed from 21 to 18 years of age during the study. The % is of all women aged 18-20.

3. Description of the study population

All women participating in the WISH study underwent a face-to-face interview with a clinician during the Main Visit. Questions were asked about sociodemographics, sexual history, reproductive and contraceptive history, and general medical history. All of the data below are self-reported by the participant.

Demographic data	**n (%)** **N = 705**
Kigali sector where participant lives: - Gikondo - Kimihurura - Remera - Muhima - Other: [categories to be made]	
Age in years: median [IQR]	
Marital status: - Never married - Married - Divorced - Widowed	
Highest educational level attained: - No schooling - Primary school not completed - Primary school completed - Secondary school not completed - Secondary school completed - More than secondary school	
Sexual history	**n (%)**
N male sex partners in lifetime: median [IQR]	
N male sex partners in past 12 months: median [IQR]	
N sex partners in past month: median [IQR]	
New sex partner in the past three months	
Currently has a main sex partner	
Reported length of relationship with main sex partner: median [IQR]	*N = xxx*
Currently lives together with main partner: - Yes	*N = xxx*
Main partner is circumcised: - Yes - No - Does not know	*N = xxx*
Knows or suspects that main partner has had other sexual partners in past 12 months: - Yes - No - Does not know	*N = xxx*
N vaginal sex acts in the past two weeks: median [IQR]	

N anal sex acts in the past two weeks: median [IQR]	
Has had anal sex in the past two weeks	
Frequency of condom use during vaginal sex in the past two weeks: - Always - Sometimes but not always - Never	
Used a condom during last vaginal sex act	
Exchanged sex for money or goods in past month	
Exchanged sex for money or goods in past 12 months	
N male sex partners in lifetime if exchanged sex in past 12 months: median [IQR]	*N = xxx*
N male sex partners in past 12 months if exchanged sex in past 12 months: median [IQR]	*N = xxx*
Reproductive and contraceptive history	**n (%)**
N pregnancies in lifetime: median [IQR]	
N deliveries in lifetime: median [IQR]	
N miscarriages/stillbirths in lifetime: median [IQR]	
N induced abortions in lifetime: median [IQR]	
N premature born children (i.e. < 37 weeks) in lifetime: median [IQR]	
N children born alive in lifetime: median [IQR]	
N children alive at visit date: median [IQR]	
Length between visit date and last birth in months: median [IQR]	
Currently breastfeeding	
Has a regular menstrual cycle: - Yes - No, irregular - Amenorrhea due to progestin-only contraception - Amenorrhea due to pregnancy or postpartum period - Amenorrhea due to menopause	
Has ever used a product to prevent pregnancy	
If yes, product(s) used in lifetime[1]: - Combined estrogen/progestin pills [describe brands in footnote] - Progestin-only pills [describe brands in footnote] - Progestin injections [describe brands in footnote] - Progestin implant [describe brands in footnote] - Copper IUD - Participant is sterilised - Other [categories to be made as needed]	
Currently using a product to prevent pregnancy	
If yes, product currently using[1]: - Combined estrogen/progestin pills [describe brands in footnote] - Progestin-only pills [describe brands in footnote] - Progestin injections [describe brands in footnote] - Progestin implant [describe brands in footnote] - Copper IUD - Participant is sterilised - Other [categories to be made as needed]	
General medical history	**n (%)**
Has ever had surgery	
Has a chronic disease [describe in footnote]	

Has long-term medications [describe in footnote]	
Took antibiotic or antifungal treatment in the previous two weeks [describe in footnote]	
Is currently taking an antibiotic or antifungal [describe in footnote]	
Has ever had an allergic reaction to a medication or other commercial product	
Has been tested for HIV in the past	
If yes, number of times tested for HIV: median [IQR]	*N = xxx*
Known to be HIV-positive prior to Main Visit	
Treated for an STI in the past	
If yes, number of times treated for an STI: median [IQR]	*N = xxx*
Has been treated for BV in the past	
If yes, number of times treated for BV: median [IQR]	*N = xxx*
Has been treated for a yeast infection/vaginal candidiasis in the past	
If yes, number of times treated for a yeast infection/vaginal candidiasis: median [IQR]	*N = xxx*
Has been treated for a UTI in the past	
If yes, number of times treated for a UTI: median [IQR]	*N = xxx*

Abbreviations: BV = bacterial vaginosis; IQR = interquartile range; IUD = intra-uterine device; NA = not applicable; STI = sexually transmitted infection; UTI = urinary tract infection.

1. May total to more than 100% because women could report multiple methods.

4. Primary objectives

4.1 Monitoring and evaluation indicators

In this section, the ***activities and outputs indicators*** of the study will be reported. The ***inputs and impacts indicators*** will be reported in Section 7 (feasibility objectives).

Counselling:
All (705) women were offered counselling during the Main Visit. In addition, four women and two male partners received counseling at Additional Visits (these two men are not included in the table below). Women could choose their own counselling topics of interest with the exception of post-HIV test counselling: everyone who was tested for HIV was counselled in accordance with Rwandan VCT guidelines.

	MV n (%) N = 705	**AV n (%) N = 4**
General counselling performed by: - Nurse/counsellor - Physician		
Topics that were discussed during general counselling[1]: – HIV basic facts – STIs basic facts – HIV & STI treatment – HIV & STI prevention – HIV & STIs: Condom use demonstration – BV and vaginal candidiasis basic facts		

– BV and vaginal candidiasis treatment – BV and vaginal candidiasis prevention – UTIs: what it is, consequences if not treated, prevention – Family planning – Domestic violence: including referrals – Other, specify [categories to be made if needed: hepatitis, condylomata?]		
HIV post-test counselling performed: - Nurse/counsellor - Physician		
Topics that were discussed during HIV post-test counselling: – Negative result for HIV test – Positive or equivocal result for HIV test		

Abbreviations: AV = additional visit; BV = bacterial vaginosis; MV = main visit; STI = sexually transmitted infection; UTI = urinary tract infection.

1. May total to more than 100% because women could choose multiple topics.

Risk scoring for CT/NG and syphilis:

All women were risk-scored for CT/NG and syphilis. Each of the two risk scores consisted of four questions based on the face-to-face interview and findings during speculum and bimanual examination (if applicable). GeneXpert CT/NG testing was only offered if the participant was positive for the CT/NG risk score and syphilis testing was only offered if the participant was positive for the syphilis risk score. However, a sample for GeneXpert testing was taken from all participants (a vaginal sample with the option of a urine sample if the participant refused vaginal sampling) so that we would have a CT/NG GeneXpert result for all participants at the end of the study. Participants who had a negative CT/NG risk-score but tested positive on the GeneXpert later on in the study were contacted for treatment at an Additional Visit.

CT/NG risk score	**n (%) N = 705**
Currently pregnant	
Exchanged sex for money or goods in the past 12 months	
New sex partner in the past three months	
Abnormal cervicovaginal discharge during speculum exam and/or cervical motion/adnexal tenderness during bimanual exam (if pelvic/bimanual not done, the answer was no)	
Final CT/NG risk score[1]: - Positive - Negative	
Syphilis risk score	**n (%)**
Currently pregnant	
Exchanged sex for money or goods in the past 12 months	
New sex partner in the past three months	
Genital ulcers/blisters/sores visible during pelvic exam (if pelvic/bimanual not done, the answer was no)	
Final syphilis risk score[1]: - Positive - Negative	

Abbreviations: CT = *Chlamydia trachomatis*; NG = *Neisseria gonorrhoeae*.

1. The risk score was positive if at least one of the four criteria was positive. If a speculum/bimanual examination was not done, the answer was no for that question.

Urogenital symptoms reported spontaneously and after structured questioning at Main Visits:

During the face-to-face interview, participants were asked the following two questions in the order given:

- "Do you experience, or did you experience in the past 2 weeks, any urogenital symptoms?" We

will refer to these as ***spontaneously reported symptoms***.

- "Do you experience, or did you experience in the past 2 weeks, any of the urogenital symptoms below?", followed by a list of symptoms that were read out loud to the participant. We will refer to these as ***structurally reported symptoms***.

In the table below, we report the spontaneously and structurally reported symptoms, as well as the overlap in answers between the two questions. Each column contains n (% of 705).

Urogenital symptoms n (% of 705) in each column[1]	**Sponta-neous total**	**Structural total**	**Spontaneous but not structural**	**Structural but not spontaneous**
Any reported				
Burning when passing urine				
Frequent urination/urge				
Blood in urine				
Genital burning				
Genital itching				
Postcoital/intermenstrual bleeding				
Pain during sex				
Lower abdominal pain				
Unusual VDS, curdlike				
Unusual VDS, offensive smell				
Unusual VDS, other[2]				
Ulcers/blisters/sores genital/anal				
Warts genital/anal				
Swelling/bubo inguinal area				
Other[3]				

Abbreviations: VDS = vaginal discharge syndrome

1. May total to more than 100% because the participant could report multiple symptoms.
2. These will be described in a footnote.
3. Additional categories may be added on to this list if certain other symptoms were mentioned frequently. Symptoms that were infrequently reported will be described in a footnote.

Other urogenital symptom-related questions	**n (%) N = 705**
Already receiving treatment for her current symptoms by another medical doctor or nurse	
Already took traditional medicine for her current symptoms	
At least one of the symptoms is ongoing	
At least one of participant's male partners has symptoms of urethritis *(this question was asked because it is part of the Rwandan STI guidelines)* - Yes - No - Does not know - NA	
At least one of participant's male partners has symptoms of swelling or tumefaction of the scrotum that did not start all of a sudden *(this question was asked because it is part of the Rwandan STI guidelines)* - Yes - No - Does not know - NA	

Abbreviations: IQR = interquartile range; NA = not applicable

Pelvic, bimanual and physical examinations performed at Main and Additional Visits:
At the Main Visit, speculum and bimanual examinations were only performed if the participant reported relevant and moderate/severe urogenital symptoms. If she only had UTI-related symptoms (burning when passing urine, frequent urination or urge to urine, or blood in urine), a speculum and bimanual examination was not offered, and UTI testing and treatment were offered based on symptom-reporting. In the case of candidiasis-related symptoms (curdlike unusual vaginal discharge and genital itching), a speculum and bimanual examination was done at the discretion of the study physician; the protocol allowed the study physician to treat the participant based on the reported symptoms alone. If a pelvic and bimanual examination was performed, and no signs of vaginal candidiasis were seen, no treatment for vaginal candidiasis was given.

During Additional Visits, a pelvic and bimanual examinations were only performed if the participant had not had an examination at the Main Visit (for example, because she was menstruating), or if her symptoms had not resolved after having received treatment.

Speculum, bimanual, and physical examinations	**MV n (%) N = 705**	**AV n (%) N = 705**
N women who underwent a speculum exam		
Reason for speculum exam[1]: - To evaluate symptoms - At the participant's request - Another reason, specify [additional categories to be made if needed]	*N = xxx*	*N = xxx*
Any abnormalities observed by physician during speculum exam	*N = xxx*	*N = xxx*
If yes, which one(s)[1]: - Enlarged/tender inguinal lymph nodes - Abnormal (genital) odour - Warts or condylomata (any location genitalia) - Ulcers/blisters/sores suggestive of STI in vulva - Vulvitis - Any other lesion on vulva - Vaginal mass (polyp, myoma, etc.) - Ulcers/blisters/sores suggestive of STI in vagina - Vaginitis - Any other lesion on vaginal epithelium - Cervicitis - Any other lesion on cervical epithelium - Abnormal vaginal or cervical discharge/pus - Other, specify [additional categories to be made if needed]	*N = xxx*	*N = xxx*
N women who underwent a bimanual exam		
Any abnormalities observed by physician during bimanual exam	*N = xxx*	*N = xxx*
If yes, which one(s)[1]: - Uterine mass - Adnexal mass on the right - Adnexal mass on the left - Uterine tenderness - Adnexal tenderness on the right - Adnexal tenderness on the left - Cervical motion tenderness	*N = xxx*	*N = xxx*

- Others, specify [additional categories to be made if needed]		
N women who underwent a physical exam by a physician		
Reason for physical exam n (%)[1]: - [Described in a footnote and/or categories to be made]	*N = xxx*	*N = xxx*
Abnormalities observed by physician during physical exam: - [Described in a footnote and/or categories to be made]	*N = xxx*	*N = xxx*

Abbreviations: STI = sexually transmitted infection.

1. May total to more than 100% because there could have been multiple reasons or findings.

Services offered and opted out of, and results/referrals/treatments received at Main Visits:
Participants were offered services as outlined in the background. Some services (such as HIV, BV, and TV testing) were offered to everyone. Others were only offered to a subset of participants: UTI testing was only offered in the case of reported UTI symptoms; CT/NG testing was only offered in the case of a positive CT/NG risk score; syphilis testing was only offered in the case of a positive syphilis risk score; and a speculum and bimanual examination was only offered in the case of relevant symptom reporting. Participants were subsequently asked if they wanted to opt-out of any service offered. The plan was to give participants their test results and referrals and/or treatments (if applicable) the same day, but this may not always have been possible. Also, in the case of GeneXpert CT/NG testing, participants were given the option to receive their results later on because the test takes 90 min. The table below summarises the services offered and accepted/declined at Main Visits, as well as whether results, referrals, and treatments were indeed delivered on the same day, at some other time, or not at all. ***In this table, we will not yet take into account whether any mistakes were made by study staff along this pathway.***

Services (n/705; %)[1]	**Offered**	**Declined**	**Reasons for declining[2]**	**Sample taken**	**Received result the same day**	**Received tx or referral same day**
HIV test[3]			- Known HIV+: - Other: - NA - Missing	- EDTA blood: - Fingerstick: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:
Pregnancy test[4]			- Known pregnant: - Other: - NA - Missing	- Urine: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:
UTI test[5]				- Urine: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:
Vaginal pH for BV				- pH swab: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:
TV test				- Kit swab: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:
CT/NG test[6,7]				- Kit swab: - Urine: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:	- Yes: - No, other time: - Not at all: - NA: - Missing:
Syphilis test[6]				- EDTA blood:	- Yes:	- Yes:

				- Fingerstick: - NA: - Missing:	- No, other time: - Not at all: - NA: - Missing:	- No, other time: - Not at all: - NA: - Missing:
Speculum/ bimanual[5]				NA	Done same day? - Yes: - No, other time: - Not at all: - NA: - Missing:	NA
Counselling				NA	NA	NA
Male condoms				NA	NA	NA

Other sampling questions	**n (% of 705)**
Two extra vaginal swab collected for storage	- Yes: - No: [reasons why not will be described in footnote]
Did the participant agree to clinician-sampling or did she request self- sampling of vaginal samples?	- Clinician: - Self: - Declined all vaginal sampling:
Menstruating at the time of sampling	- Yes
Willing to wait for CT/NG results (women whose risk score was positive and who did not opt-out of testing)	*N = xxx* - Yes, wanted to wait for the results: - No, wanted to come back for results later: - No, wanted to receiv results by text/phone/letter: - Never received results

Abbreviations: BV = bacterial vaginosis; CT = *Chlamydia trachomatis*; NA = not applicable; NG = *Neisseria gonorrhoeae*; TV = *Trichomonas vaginalis*; UTI = urinary tract infection.

1. Each column contains n and % of 705. In most columns, the numbers should add to 705 (including NA and missing) except for 2.
2. May total to more than 100% because multiple answers possible. When no categories or 'other' are listed, (additional) categories will be made as needed.
3. PID 50, 58, 63, 81 and 125 were not offered HIV testing because they were known HIV-positive.
4. PID 14, 55 and 97 were not offered a pregnancy test as they were visibly pregnant.
5. Only offered in the case of reported relevant symptoms (if symptoms were clearly UTI or vaginal candidiasis-related, a speculum examination was not necessarily offered).
6. Only offered in the case of a positive risk score.
7. This does not include samples taken from participants who had a negative risk score for testing later on in the study. That was done to enable test performance calculations, but was not part of the WISH clinical algorithms.

Additional Visits: sociodemographic data, symptoms, procedures, and additional services offered

Additional Visits took place for various reasons as reported in section 2 (Participant Disposition). We recorded the reasons for the Additional Visits for all visits. However, additional data were collected, and services offered, only to women with suspected ongoing untreated infection, re-infection or treatment failure. These data are reported in the table below. One woman could have had multiple Additional Visits. We will summarise the data from all women who had at least one Additional Visit. If the Additional Visit was related to a suspected ongoing untreated infection, re-infection or treatment failure of an infection that was originally diagnosed at the Main Visit, we will describe the sequence of events at each visit for these women. In the tables that follow, we have only counted each of these women once, and we have combined the data from all of her Additional Visits (for example, if she had surgery between AV1 and AV2, the answer to the question if she had surgery since her Main Visit was yes).

	n (%) N = xxx[1]
Had surgery since the MV [details in footnote]	
Was diagnosed with new chronic diseases since the MV [details in footnote]	
Started new long-term medications since the MV [details in footnote]	
Received antibiotic/antifungal treatment by non-RU providers since MV [details in footnote]	
If yes, was still taking this treatment at her (last) AV	*N = xxx*
Reported a new allergic reaction since the MV [details in footnote]	
Reported a urogenital symptom at the first AV (spontaneously reported)[2]	
Reported a urogenital symptom at the first AV (assessed structurally by reading the list)[3] - Burning when passing urine - Frequent urination or need to urinate - Blood in urine - Genital burning - Genital itching - Postcoital or intermenstrual bleeding - Pain during sex - Lower abdominal pain - Unusual vaginal discharge, curdlike - Unusual vaginal discharge, offensive smell - Unusual vaginal discharge, other: [specifications will be described in footnote] - Ulcers/blisters/sores in the genital and/or anal area (including buttocks) - Warts in the genital and/or anal area - Swelling in the inguinal area / inguinal bubo - Other, specify: [specifications will be described in footnote] - None of the above	
If any symptoms reported, is at least one of them the same as the ones reported at the MV?	*N = xxx*
If any symptoms reported, is at least one of them reported again at subsequent AVs? - Yes - NA (only had one AV)	*N = xxx*
At any of the woman's AVs, at least one of the participant's current male partners has symptoms of urethritis - Yes - No - Does not know - NA	
At any of the woman's AVs, at least one of the participant's current male partners has symptoms of swelling or tumefaction of the scrotum that did not start all of a sudden - Yes - No - Does not know - NA	

Abbreviations: Additional Visit = AV; MV=Main Visit; NA = not applicable

1. The number of women who had at least one AV due to a suspected ongoing untreated infection, re-infection or treatment failure. If one woman had multiple AVs related to a suspected ongoing untreated infection, re-infection or treatment failure, the data from these visits were combined.
2. While women had to specify their symptoms, we will not report them here but use the list of structurally assessed symptoms instead.
3. May total to more than 100%.

Pelvic/bimanual examinations and/or POC testing were only offered to women with suspected ongoing untreated infection, re-infection or treatment failure. Vaginal swabs for storage were not taken. During Main Visits, we reported whether results and/or treatment were given the same day or later. This information is not available for the Additional Visits and is therefore not reported in the text below.

Services: n (% of xxx)[1]	Offered	Declined	Reasons for declining[2]	Sample taken
HIV test			- Known HIV+: - Other: - NA: - Missing:	- EDTA blood: - Fingerstick: - NA: - Missing:
Pregnancy test			- Known pregnant: - Other: - NA: - Missing:	- Urine: - NA: - Missing:
UTI test				- Urine: - NA: - Missing:
Vaginal pH for BV				- pH swab: - NA: - Missing:
TV test				- Kit swab: - NA: - Missing:
CT/NG test				- Kit swab: - Urine: - NA: - Missing:
Syphilis test				- EDTA blood: - Fingerstick: - NA: - Missing:
Speculum/ bimanual exam				NA
Counselling				NA
Male condoms				NA
Other sampling questions			**n (%) of xxx**	
Was menstruating at time of sampling				

Abbreviations: BV = bacterial vaginosis; CT = *Chlamydia trachomatis*; NA = not applicable; NG = *Neisseria gonorrhoeae*; TV = *Trichomonas vaginalis*; UTI = urinary tract infection.

1. Each column contains n and % of the total number of women who had at least one AV due to a suspected ongoing untreated infection, re-infection or treatment failure. If one woman had multiple AVs related to a suspected ongoing untreated infection, re-infection or treatment failure, the data from these visits were combined.
2. May total to more than 100%. When 'other' reasons are listed, (additional) categories may be made as needed.

Syndromic diagnoses made at Main Visits and Additional Visits:

Syndromic diagnoses made by a study physician	MV[1] n (%) N = 705	AV[1,2] n (%) N = xxx	Total[1,3] n (%) N = 705
- None - Genital warts/condylomata - Vaginal candidiasis			

- VDS – not vaginal candidiasis, tested negative for BV/TV/CT/NG - LAP (with or without VDS) - no tenderness during bimanual[3] - LAP (with or without VDS) - tenderness during bimanual (PID) - Genital ulcers/blisters/sores with or without inguinal buboes - tested negative for syphilis - Inguinal buboes without genital ulcers - Dysuria testing negative for UTI - Other, specify: [additional categories to be made if needed] - Missing			

Abbreviations: AV = Additional Visit; BV = bacterial vaginosis; CT = *Chlamydia trachomatis*; LAP = Lower abdominal pain; MV = Main Visit; NG = *Neisseria gonorrhoeae*; PID = pelvic inflammatory disease; TV = *Trichomonas vaginalis*; UTI = urinary tract infection; VDS = vaginal discharge syndrome.

1. May total to more than 100% because one woman could have multiple syndromic diagnoses.
2. The denominator is the number of women who attended at least one AV related to a suspected ongoing untreated infection, re-infection or treatment failure. If one woman attended multiple AVs, the data from these AVs were combined. The reasons why a diagnosis was not made at the MV but at an AV will be reported in footnotes. Diagnoses made at AVs that are based on newly reported symptoms will not be included because these participants should have been referred to a local health centre.
3. Diagnoses that are reported at both the MV and at one or more AVs for the same woman will be reported as one diagnosis but each case will be described in a footnote. This column therefore lists the proportion of the 705 women who received a syndromic diagnosis at least once regardless of whether the diagnosis was first made at the MV or an AV.

<u>POCT results at Main Visits and Additional Visits</u>:

All POCTs described here were offered during the Main Visit to women who qualified per protocol. However, participants may have received results at Additional Visits if they were not available at the Main Visit (participant may have chosen to go home before all test results were available or for other reasons). Additional POCTs may have been offered at Additional Visits but only to women with suspected ongoing untreated infection, re-infection or treatment failure.

Laboratory diagnoses	**MV** **n (%)** **N = 705**	**AV[1,2]** **n (%)** **N = xxx**	**Total[3]** **n (%)** **N = 705**
HIV algorithm result[4]: - Positive - Negative - 2x equivocal (to be repeated in the future) - Testing not offered - Testing declined - Missing			
HIV algorithm result of participants who were not previously known as HIV-positive[4]: - Positive - Negative - 2x equivocal (to be repeated in the future) - Testing not offered - Testing declined - Missing - NA (HIV positive)			
Pregnancy result[5]:			

- Positive - Negative - Testing not offered (obviously pregnant) - Testing declined and no pregnancy result available[6] - Missing			
Vaginal pH result[7]: - 4.0 - 4.5 - 5.0 - 5.5 - 6.0 - 6.5 - 7.0 - 7.5 - Testing not offered - Testing declined - Missing			
Vaginal pH result[7]: - pH < 5.0 - pH ≥ 5.0 - Testing not offered - Testing declined - Missing			
TV result[8]: - Positive - Negative - Testing not offered - Testing declined - Missing			
CT result[9]: - Positive - Negative - Testing not offered - Testing declined - Missing			
NG result[9]: - Positive - Negative - Testing not offered - Testing declined - Missing			
Syphilis algorithm result[10]: - Positive - Negative - Testing not offered and no syphilis result available - Testing declined - Missing			
UTI result[11]: - Positive - Negative - Testing not offered and no UTI result available			

- Testing declined - Missing			
Other results, specify: [additional categories to be made if needed]			

Abbreviations: AV = additional visit; BV = bacterial vaginosis; CT = *Chlamydia trachomatis*; MV = main visit; NA = not applicable; NG = *Neisseria gonorrhoeae*; TV = *Trichomonas vaginalis*; UTI = urinary tract infection.

1. The denominator is the number of women who attended at least one AV related to a suspected ongoing untreated infection, re-infection or treatment failure. If one woman attended multiple AVs, the data from these AVs were combined.
2. Only includes POCT results that were reported at an AV but still relate to symptoms reported at the MV. The reasons why the POCT results were not available at the MV will be reported in footnotes. AV POCT results that are based on newly reported symptoms will not be included because these participants should have been referred to a local health centre.
3. POCT results that are reported at both the MV and at one or more AVs for the same woman and for the same infection will be reported as one result but each case will be described in a footnote. This column therefore lists the proportion of the 705 women who received a certain POCT result at least once, regardless of whether the result was received at the MV or an AV.
4. Determine HIV 1/2 rapid test (Alere, Waltham, USA), followed by Trinity Biotech Uni-gold HIV rapid test (Trinity Biotech, Bray, Ireland) if reactive, and Vironostika ELISA (Biomerieux, Marcy, France; performed at the National Reference Laboratory in Rwanda) as a tie-breaker if needed. All women were offered HIV testing, even if they had had a previous positive HIV result.
5. Pregnancy was tested for with the locally available hCG-based urine dipstick Nova test (Atlast Link Technology Co. Beijing, China). Testing was offered to all women except when obviously pregnant.
6. The vaginal pH was measured with the EcoCare pH swab (Merete Medical, Luckenwalde, Germany); the swab consists of 0.5 increments ranging from 4.0 to 7.5. A pH of 5.0 or above was treated for BV regardless of symptoms. All women were offered testing.
7. TV OSOM rapid test (Sekisui Diagnostics, Lexington, USA). All women were offered testing.
8. GeneXpert CT/NG assay (Cepheid, California, USA). Only women with a positive risk score for CT/NG were offered testing. Stored samples from all other participants were also tested later on in the study; those results are reported in section 5.1.
9. Alere Determine Syphilis rapid test (Alere, Waltham, USA) confirmed by RPR SpinReact test (SpinReact, Girona, Spain). Only women with a positive risk score for syphilis were offered testing.
10. Urinalysis dipstick tests (Acon, San Diego, USA). Testing was only offered to women with typical UTI symptoms.

Treatments dispensed by a study physician at Main Visits and Additional Visits:

Participants were treated for all laboratory-confirmed and syndromic diagnoses that were available during their Main Visit. Some preferred to go home and receive POCT results later, either by text/phone message or by making an appointment for an Additional Visit. Some participants received treatment at Additional Visits because their results had not yet been available during the Main Visit, or because their symptoms had not resolved or reappeared (suspected ongoing untreated infection, re-infection or treatment failure).

Results reporting and reinfections/treatment failures	**n (%)** **N = 705**
When and how did women receive their positive POCT results *(GeneXpert CT/NG counts as one result and is considered positive if at least one test was positive)*: - Had no positive results - Received all her positive results at the MV - Received all her positive results at an AV - Received all her positive results by phone/text - Received some at MV and at least one at AV; none by phone/text - Received some at MV and at least one by phone/text; none at AV - Other [details in footnote] - Missing	
Had at least one suspected ongoing untreated infection, symptomatic at AV but not at MV [each case to be described in footnote]	
Had at least one suspected ongoing untreated infection, symptomatic at both AV and MV	

[each case to be described in footnote]			
Had at least one suspected re-infection after having received appropriate treatment [each case to be described in footnote]			
Had at least one suspected treatment failure because of inappropriate treatment [each failed drug regimen-infection combination to be described in footnote]			
Had at least one suspected treatment failure because of suspected poor adherence [each failed drug regimen-infection combination to be described in footnote]			
Had at least one suspected treatment failure for other reasons [each failed drug regimen-infection combination to be described in footnote]			
Had at least one suspected treatment failure in total			
Treatments (or prescriptions) given by a study physician	**MV[1] n (%) N = 705**	**AV[1,2,3] n (%) N = xxx**	**Total[1,4] n (%) N = 705**
- None - Metronidazole 7 days po for BV and/or TV - Metronidazole single dose po for BV and/or TV[5] - Fluconazole single dose po for vaginal candidiasis - Clotrimazole vaginal pessaries 3 nights for vaginal candidiasis - Antibiotic for UTI, PID, CT, NG, syphilis or genital ulcers / inguinal buboes [categories to be specified] - Antibiotic for another reason: [categories to be specified] - Acyclovir 5-7 days po for genital ulcers/herpes - Other [categories to be specified]			

Abbreviations: AV = additional visit; BV = bacterial vaginosis; CT = *Chlamydia trachomatis*; MV = main visit; NG = *Neisseria gonorrhoeae;* po = per os; PID = pelvic inflammatory disease; TV = *Trichomonas vaginalis*; UTI = urinary tract infection.

1. May total to more than 100% because one participant could have received multiple treatments.
2. The denominator is the number of women who attended at least one AV related to a suspected ongoing untreated infection, re-infection or treatment failure. If one woman attended multiple AVs, the data from these AVs were combined.
3. Only includes treatments that were reported at an AV but still relate to symptoms reported at the MV. The reasons why the treatments were not given at the MV will be reported in footnotes. Treatments given at AVs that were based on newly reported symptoms will not be included because these participants should have been referred to a local health centre.
4. Treatments that are reported at both the MV and at one or more AVs for the same woman and for the same infection will be counted as one woman/treatment combination but each case will be described in a footnote. This column therefore lists the proportion of the 705 women who received a certain treatment at least once, regardless of whether the treatment was first dispensed at the MV or an AV.
5. The Rwandan STI guidelines list 7-day Metronidazole course as the preferred option. However, some women opted for a 2g single dose due to frequent alcohol ingestion and associated side-effects.

Referrals made at Main and Additional Visits:

Active referrals by physician letter were made when a diagnosed infection/condition (e.g. HIV, pregnancy, PID) could not be treated at RU. All participants who had not had a previous or recent cervical cancer screening in the past were given a passive referral (information about where to go but no physician letter), as cervical cancer screening was not offered at RU. Other passive referrals were made as deemed appropriate by the clinic staff or requested by the participant.

Referrals made	**MV[1] n (%) N = 705**	**AV[1,2,3] n (%) N = xxx**	**Total[1,4] n (%) N = 705**
Active referrals made by a study physician: - Because of new HIV diagnosis - Because of new pregnancy - For further gynaecological evaluation/treatment			

- Because of wish to start/change family planning method - Other: For other medical specialist diagnosis & treatment - Other: For starting ARV treatment of previously known HIV infection - At least one referral offered but declined - No referrals were needed - Missing			
Active referral to: - Local public health center close to participant's home - Other local public health center - Private clinic - Hospital (public or private) - ARBEF family planning clinic - Psychosocial referral site - Other, specify: [categories to be specified] - At least one referral offered but declined - No referrals were needed - Missing			
Passive referrals made by a study nurse or physician[1]: - Because of new HIV diagnosis - Because of new pregnancy - For cervical cancer screening - For further gynaecological evaluation/treatment [details in footnote] - Because of wish to start/change family planning method - None; no further services required - Missing			

Abbreviations: AV = Additional Visit; ARV = antiretroviral treatment; MV = Main Visit.

1. May total to more than 100% because one participant could have received multiple referrals.
2. The denominator is the number of women who attended at least one AV related to a suspected ongoing untreated infection, re-infection or treatment failure. If one woman attended multiple AVs, the data from these AVs were combined.
3. Only includes referrals that were reported at an AV but still relate to symptoms reported at the MV. The reasons why the referrals were not made at the MV will be reported in footnotes. Referrals made at AVs that were based on newly reported symptoms will not be included because these participants should have been referred to a local health centre.
4. Referrals that are reported at both the MV and at one or more AVs for the same woman and for the same condition will be reported as one referral. This column therefore lists the proportion of 705 women who received a referral at least once regardless of whether it was first made at the MV or an AV.

Partner notifications at Main and Additional Visits:

Positive laboratory results for STIs and data from the sexual history of the participant were used to identify partners to be notified in the window periods of the relevant STIs.

Partners requiring notification (identified at any visit)	**n (%)**
Number of women who had at least one partner requiring notification during the study[1] - Yes - No - Missing	*N = 705*
Number of partners requiring partner notification per woman: - One - Two - Three - More than three [additional categories to be made as needed] - NA: no partner notification required (no infection, partner already treated, outside window) - Missing	*N = 705*

Number of women who agreed to: - All of the identified partners being notified - Some of the identified partners being notified - No partners being notified - NA: no partner notification required - Missing	*N = 705*
Preferred partner notification method: - Chose to notify all partners herself - Chose to have RU staff notify all partners (in agreed-upon manner for each partner) - Chose to notify some partners herself and some by RU staff - Other, specify: [categories to be specified] - NA: No partner notification required - NA: Did not want to notify any partners - Missing	*N = 705*
Total number of partners requiring notification per protocol N Median number of partners requiring notification per woman with an infection N (IQR) Total numbers of partners that the women consented to being notified N Total number of partners who came for a treatment visit N	
Partner treatment at AVs	**N = xxx[2] n (%)**
Diagnosis of the index case that precipitated this partner notification[2,3]: - CT - NG - TV - PID - Syphilis - GUD: chancroid, granuloma inguinale - Other, specify: [categories to be specified]	
Male partner reported to have had urogenital symptoms himself in the last month	
Symptoms reported by the male partner (structurally assessed)[1,2]: - Burning when passing urine - Frequent urination or urgent need to urinate - Blood in urine - Genital burning / urethritis - Genital itching - Urethral discharge - Ulcers/blisters/sores in the genital/anal area - Warts/condylomata in the genital/anal area - Swelling in the inguinal area / inguinal bubo - Swelling / tumefaction of the scrotum that did not start all of a sudden - Other, specify: [categories to be specified] - Did not report any symptoms - Missing	
Are these symptoms ongoing: - Yes - No - Did not report any symptoms - Missing	
Treatment given to male partner[1]: - Metronidazole single dose for TV - Metronidazole 7 days for TV	

- Antibiotic for CT, NG, PID, syphilis or GUD: [categories to be specified] - Antibiotic for another reason: [categories to be specified] - Other, specify: [categories to be specified] - None [reasons why in footnote] - Missing	
Physician requested additional testing of the male partner: - Yes, specify: [tests to be specified] - NA: no additional testing requested	
Physician made an active referral - Yes, specify: [referrals to be specified] - NA: no active referrals made	
Physician/nurse made a passive referral - Yes, specify: [referrals to be specified] - NA: no passive referrals made	

Abbreviations: AV = additional visit; CT = *Chlamydia trachomatis*; GUD = genital ulcer disease; MV = main visit; NA = not applicable; NG = *Neisseria gonorrhoeae;* PID = pelvic inflammatory disease; TV = *Trichomonas vaginalis.*

1. The number of partners who actually attended an AV for partner treatment.
2. May total to more than 100%.

Overall participant trajectories:

Participant trajectories	**n (%) N = 705**
Women with no diagnoses[1] at MV and all procedures completed at MV	
Women with no diagnoses at MV and procedures completed at an AV	
Women with no diagnoses at MV and procedures never completed [details in footnote]	
Women with one diagnosis at MV and all procedures completed at MV	
Women with one diagnosis at MV and procedures completed at an AV	
Women with one diagnosis at MV and procedures never completed [details in footnote]	
Women with two or more diagnoses at MV and all procedures completed at MV	
Women with two or more diagnoses at MV and procedures completed at an AV	
Women with two or more diagnoses at MV, procedures never completed [details in footnote]	

Abbreviations: AV = additional visit; MV = main visit.

1. Both POCT diagnoses and syndromic management diagnoses are counted.

In the following table, participant trajectories will be reported from the point of view of the different possible laboratory diagnoses made during Main Visits and Additional Visits to show at which stage the disease was diagnosed, treated, and partner notification and/or referrals were done (if applicable).

Diagnosis n (%) of 705[1]	**Diagnosis at: n (%) of xxx[2]**	**Treatment at: n (%) of xxx[2]**	**Partner notification initiated[3] at: n (%) of xxx[2]**	**Active referral at: n (%) of xxx[2]**
BV by pH≥5:	- MV: - AV:	- MV: - AV: - None:	NA	NA
TV:	- MV: - AV:	- MV: - AV: - None:	- MV: - AV: - None done: - None required:	NA
CT[4]:	- MV: - AV:	- MV: - AV: - None:	- MV: - AV: - None done:	- MV: - AV: - Not done:

			- None required:	- Not required:
NG[4]:	- MV: - AV:	- MV: - AV: - None:	- MV: - AV: - None done: - None required:	- MV: - AV: - Not done: - Not required:
HIV[5]:	- MV: - AV: - Status known	NA	- MV: - AV: - None done: - None required:	- MV: - AV: - Not done: - Not required:
PID:	- MV: - AV:	- MV: - AV:	- MV: - AV: - None done: - None required:	- MV: - AV: - Not done: - Not required:
Syphilis:	- MV: - AV:	- MV: - AV:	- MV: - AV: - None done: - None required:	- MV: - AV: - Not done: - Not required:
UTI:	- MV: - AV:	- MV: - AV:	NA	- MV: - AV: - Not done: - Not required:

Abbreviations: AV = Additional Visit; BV = bacterial vaginosis; CT = *Chlamydia trachomatis*; MV = Main Visit; NA = not applicable; NG = *Neisseria gonorrhoeae;* PID = pelvic inflammatory disease; TV = *Trichomonas vaginalis;* UTI = urinary tract infection.

1. This column lists the proportion of 705 women who received the particular POCT diagnosis at least once regardless of whether it was first made at the MV or an AV. If a woman had a positive POCT test for the same infection multiple times it was only counted once.
2. The denominator is the total number of women who received each specific POCT diagnosis at least once at an MV or AV. This is the n in the first column. Totals may be more than 100%.
3. One woman may have had multiple partners in the window period and she may have consented for all, some or none to be notified. If at she consented to at least one partner to be notified, she is included in the MV or AV category. If there were partners but a deliberate choice not to notify (any of them), she is included in the 'none done' category. If she had an infection but no partner notification was required per protocol, she is included in the 'not required' category.
4. Not including diagnoses made in participants who had a negative risk score and whose samples tested positive later on in the study.
5. During the time of the WISH study, Rwandan health clinics were still in the process of actively enrolling known HIV-infected patients into antiretroviral treatment programs regardless of their CD4 count. Study physicians therefore referred newly diagnosed HIV infections but not known untreated HIV infections (these were expected to be contacted by their local HIV clinic in due course) or women who were already on ART.

4.2 Gold standard test results at Main Visits

Gold standard testing was performed for CT, NG, BV, TV and *Candida albicans* on samples taken during the Main Visit as follows:

- CT/NG: For those participants scoring negative on the CT/NG risk score, a GeneXpert swab was stored and tested by GeneXpert in the onsite Rinda Ubuzima laboratory later during the study. This was to permit comparisons between syndromic management alone, CT/NG testing after risk scoring, and CT/NG testing on everyone. We did not perform a commercial CT/NG PCR test because the GeneXpert platform is a PCR-based platform with proven high sensitivity and specificity. We therefore considered the GeneXpert results to be gold standard results in our analyses.
- BV, TV, *Candida albicans:* Two vaginal polyester swabs per participant were collected at the Main Visit (but not at Additional Visits). In the lab, the swab head was cut using sterile scissors, stored in RNALater (ThermoFisher Scientific, Waltham, USA) at -80 degrees Celsius. Gold

standard qPCR tests were performed at the Institute of Tropical Medicine in Belgium, Antwerp, after study completion. For BV, we conducted qPCRs for *Gardnerella vaginalis*, *Atopobium vaginae*, and *Lactobacillus* genus, and we will use a vaginal health score as follows: [$\log_{10}$ geq/ml (*Lactobacillus* genus) - $\log_{10}$ geq/ml (*G. vaginalis* + *A. vaginae*)]. This vaginal health score correlated well with the Nugent score in a large vaginal microbiota study in three African countries[5]. We used validated in-house qPCR assays for TV and *C. albicans*.

Gold standard test results using Main Visit samples	**n/N[1] (%)**
CT by GeneXpert (POCT performed on everyone)	
NG by GeneXpert (POCT performed on everyone)	
Lactobacillus genus qPCR $\log_{10}$ meq/ml: median [IQR]	
Gardnerella vaginalis qPCR $\log_{10}$ meq/ml: median [IQR]	
Atopobium vaginae qPCR $\log_{10}$ meq/ml: median [IQR]	
BV by vaginal health score	
Trichomonas vaginalis by qPCR	
Candida albicans by qPCR	

Abbreviations: AV = *Atopobium vaginae*; BV = bacterial vaginosis; CT = *Chlamydia trachomatis*; GV = *Gardnerella vaginalis*; IQR = interquartile range; NG = *Neisseria gonorrhoeae*; qPCR = quantitative polymerase chain reaction.

1. The denominator is the number of women who provided Main Visit samples that were tested and produced a valid test result. The denominator may differ slightly per infection due to missing samples and invalid test results.

4.3 Adverse events and social harms

No serious adverse events were reported during the study. Two adverse events were reported during study follow-up, and both were adverse reactions to metronidazole that are included in the package insert:

- PID 283 had a mild allergic reaction following metronidazole ingestion. She reported an itchy skin rash, nausea and vomiting that resolved without intervention. The event occurred on 25 October 2016 and was reported on 27 October 2016.
- PID 569 had pruritus, angio-oedema and urticaria immediately after metronidazole ingestion. The event occurred on 7 February 2017 and was reported on 8 February 2017. Intramuscular hydrocortisone was given due to persistence of symptoms.

No social harms or other safety concerns were reported or observed during the study.

5. Secondary objectives

In this section, we will use information of the WISH study, the face-to-face interviews, the POCT results and the laboratory gold standard results, to evaluate the performance of the POCT tests performed. We will make a hypothetical comparison between syndromic management procedures (both the WHO and the Rwandan guidelines) versus the WISH study procedures; we will also compare syndromic management and WISH study procedures versus gold standard testing.

5.1 Definitions of gold standard in the WISH Study and diagnostic approaches made

For some of the STI outcomes of the WISH study, gold standard tests are available:

Infection	Definition of gold standard
CT	CT GeneXpert test performed on everyone
NG	NG GeneXpert test performed on everyone

[5] Further explained in the article by Jespers V, Crucitti T, van de Wijgert J et al. "A DNA tool for early detection of vaginal dysbiosis in African women." Res Microb 167.2 (2016): 133-41.

TV	qPCR test for *Trichomonas vaginalis*
UTI	No gold standard available
BV	qPCR vaginal health DNA tool for BV[1]
Syphilis	No gold standard available
Candidiasis	qPCR test for *Candida albicans*
HIV	No gold standard available[2]

Abbreviations: BV = bacterial vaginosis; CT = *Chlamydia trachomatis*; NG = *Neisseria gonorrhoeae*; TV = *Trichomonas vaginalis*; UTI = urinary tract infection.

1. (As calculated by Log_{10}(*Lactobacillus* genus) – Log_{10}(*G. vaginalis* + *A. vaginae*). This DNA tool has a sensitivity and specificity comparable to the Nugent score. Further explained in the article by Jespers V, Crucitti T, van de Wijgert J et al. "A DNA tool for early detection of vaginal dysbiosis in African women." Res Microb 167.2 (2016): 133-41.
2. HIV rapid testing is already commonplace in health clinics in Rwanda.

The following table describes, per possible infection, in what case treatment must be given per protocol. As mentioned before, the Rwandan guidelines include VDS algorithms that do not use risk scoring but use a pelvic examination to distinguish between mucopurulent cervical discharge and/or cervicitis (which is to be treated for CT/NG/TV) and non-muco-purulent vaginal discharge (which is to be treated for BV/TV/Candidiasis). We have decided to not take these algorithms into account.

Treatment given for:	WHO Syndromic Management	Rwandan Syndromic Management	WISH procedures	Gold standard procedures
CT	Given with VDS and high risk / high local prevalence[1]; given with PID (after LAP)[2]	Given with VDS and positive risk score[3]; given with PID (after LAP)[2]; given as presumptive FSW treatment if asymptomatic[4]	Positive for CT GeneXpert test performed after risk-scoring[5]	Positive CT GeneXpert test (test performed on everyone)
NG	Given with VDS and high risk / high local prevalence[1]; given with PID (after LAP)[2]	Given with VDS and positive risk score[3]; given with PID (after LAP)[2]; given as presumptive FSW treatment if asymptomatic[4]	Positive for NG after GeneXpert test performed after risk-scoring[5]	Positive NG GeneXpert test (test performed on everyone)
TV	Given with VDS; covered with PID (after LAP)[2]	Given with VDS no matter the risk score[3]; covered with PID (after LAP)[2]; given as presumptive FSW treatment if asymptomatic[4]	TV OSOM test	Positive qPCR test for *Trichomonas vaginalis*
UTI	NA	Treated based on reported symptoms	Positive urine dipstick test after reported symptoms[6]	ND
BV	Given with VDS; covered with PID (after LAP)[2]	Given with VDS and negative risk score[3]; covered under VDS with positive risk score and PID (after LAP)[2]	EcoCare pH swab (all pH ≥ 5.0 results treated)	Positive vaginal health qPCR DNA tool for BV[7]
Syphilis	Given with GUD	Given with GUD (with	Positive syphilis	ND

	on examination[8]	or without notion of recurrence) on examination	algorithm after risk-scoring[9]	
Candidiasis	Given with VDS and typical signs and symptoms	Given with VDS and negative risk score[3]	Given with typical signs and symptoms	Positive qPCR test for *Candida albicans*
HIV	HIV rapid test with confirmatory tests	HIV rapid test with confirmatory tests	HIV rapid test with confirmatory tests	ND

Abbreviations: BV = bacterial vaginosis; CT = *Chlamydia trachomatis*; FSW = female sex worker; GUD = genital ulcer disease; LAP = lower abdominal pain; NA = not applicable; ND = not done; NG = *Neisseria gonorrhoeae*; PID = pelvic inflammatory disease; TV = *Trichomonas vaginalis*; UTI = urinary tract infection; VDS = vaginal discharge syndrome.

1. In our analyses, it was presumed that all women participating in our study were at high risk for CT/NG due to high local prevalence.
2. Lower abdominal pain (with or without vaginal discharge) requires an abdominal and pelvic examination. If cervical motion, uterine, or adnexal tenderness is present, the participant is treated for pelvic inflammatory disease (and thus for CT/NG included). Hospital referral is required in the presence of alarming symptoms. When the participant reports both LAP and VDS, and is not diagnosed with PID, the VDS algorithm is followed.
3. If the participant reports vaginal discharge and (one of) her partner(s) has urethritis or she is positive for a risk score (2 or more positive of: age < 21; being single; 2 or more sexual partners in the past 12 months; new sexual partner in the last 3 months), the participant is to be treated for CT/NG/TV. If the participant reports vaginal discharge, none of her partners have urethritis, and she has a negative risk score (0 or 1 positive of: age < 21; being single; 2 or more sexual partners; new sexual partner in the last 3 months), the participant is to be treated for BV/TV/candidiasis
4. Under the Rwandan guidelines, presumptive treatment for CT/NG/TV is given at the STI-related first visit if the patient is a female sex worker, but only in the absence of symptoms. If symptomatic, the normal algorithms are followed and the presumptive treatment is not given.
5. GeneXpert CT/NG testing was offered to the participant if she was positive for a CT/NG risk score (1 or more positive of: participant is pregnant; exchanged sex for money or goods in the past 12 months; has had a new sexual partner in the past 3 months; abnormal cervicovaginal discharge present during the speculum exam and/or cervical motion / adnexal tenderness present during the bimanual exam).
6. UTI POCT was performed if the participant reported typical symptoms. The dipstick was considered positive if it had at least 1+ leucocytes or was nitrite-positive, per Rwandan guidelines.
7. As calculated by Log_{10}(*Lactobacillus* genus) – Log_{10}(*G. vaginalis* + *A. vaginae*). This DNA tool has a sensitivity and specificity comparable to the Nugent score, and is further explained in the article: Jespers V, Crucitti T, van de Wijgert J et al. "A DNA tool for early detection of vaginal dysbiosis in African women." Res Microb 167.2 (2016): 133-41.
8. The WHO algorithm states in a note that only women with a positive RPR and no recent treatment should be treated. We hypothesized that no RPR results are available, which is often the case in Rwanda.
9. Syphilis testing was offered to the participant if she was positive for a Syphilis risk score (1 or more positive of: participant is pregnant; exchanged sex for money or goods in the past 12 months; has had a new sexual partner in the past 3 months; genital ulcers/blisters/sores were visible during the gynaecological exam).

5.2 Syndromic diagnoses based on spontaneously and structurally reported symptoms

We will use data from the sociodemographic interview and the pelvic and bimanual examinations to reconstruct hypothetical syndromic diagnoses, in the case rapid testing had not been available. Hypothetical reconstructions according to both the WHO and the Rwandan syndromic management guidelines will be reported. In this section, the symptoms that were spontaneously reported by participants, as well as the symptoms structurally reported by the participants during the face-to-face-interview, will be considered separately. The latter mimics real-life syndromic management, as in practice, clinicians ask exploratory questions on related symptoms after participants report suffering from a certain symptom. The following assumptions will be made:

- All women who report urogenital symptoms during the WISH study (spontaneously or structurally) would have sought treatment at local clinics (to be treated by syndromic management).
- All women reporting vaginal discharge of any kind will be considered at high risk of CT/NG due to high local prevalence (relevant for the WHO guidelines).
- All asymptomatic FSWs would have been regularly followed by local health clinics had they not participated in the WISH study (relevant for the Rwandan guidelines).

- All women with GUD would be treated for syphilis (relevant for the WHO guidelines which stipulate only to treat if a positive RPR is available and the patient has not been recently treated for syphilis; RPR testing is not commonplace in Rwanda).

WHO guidelines – based on spontaneously reported symptoms	**n (%)** **N = 705**
WHO syndromic diagnoses[1]: - None - VDS (with or without LAP[2]) • Vaginal candidiasis - GUD without inguinal buboes - Inguinal bubo without signs of GUD - LAP (with or without VDS)[2] • PID	
Rwandan guidelines – based on spontaneously reported symptoms	**n (%)** **N = 705**
Rwandan syndromic management diagnoses[1]: - None - VDS (with or without LAP[2]); with risk factors for CT/NG[3] - VDS (with or without LAP[2]); without risk factors for CT/NG[3] - GUD - Inguinal bubo - LAP (with or without VDS)[2] • PID - Condylomata acuminata - Presumptive treatment for asymptomatic FSW[4] - UTI symptoms	

Abbreviations: FSW = female sex worker; GUD = genital ulcer disease; LAP = lower abdominal pain; PID = pelvic inflammatory disease; UTI = urinary tract infection; VDS = vaginal discharge syndrome.

1. Totals may be more than 100%.
2. Lower abdominal pain (with or without vaginal discharge) requires an abdominal and pelvic examination. If cervical motion, uterine, or adnexal tenderness is present, the participant is treated for pelvic inflammatory disease (and thus for CT/NG included). Hospital referral is required in the presence of alarming symptoms. When the participant reports both LAP and VDS, and is not diagnosed with PID, the VDS algorithm is followed.
3. If the participant reports vaginal discharge and (one of) her partner(s) has urethritis or she is positive for a risk score (2 or more positive of: age < 21; being single; 2 or more sexual partners in the past 12 months; new sexual partner in the last 3 months), the participant is to be treated for chlamydia/gonorrhea/*Trichomonas vaginalis*. If the participant reports vaginal discharge, none of her partners have urethritis, and she has a negative risk score (0 or 1 positive of: age < 21; being single; 2 or more sexual partners; new sexual partner in the last 3 months), the participant is to be treated for bacterial vaginosis/*Trichomonas vaginalis*/candidiasis.
4. Under the Rwandan guidelines, presumptive treatment for chlamydia/gonorrhea/*Trichomonas vaginalis* is given at the STI-related first visit if the patient is a female sex worker, but only in the absence of symptoms. If symptomatic, the normal algorithms are followed and the presumptive treatment is not given.

WHO guidelines – based on structurally reported symptoms	**n (%)** **N = 705**
WHO syndromic diagnoses[1]: - None - VDS (with or without LAP[2]) • Vaginal candidiasis - GUD without inguinal buboes - Inguinal bubo without signs of GUD - LAP (with or without VDS)[2] • PID	

Based on these syndromic diagnoses, participant would have received treatment covering the following urogenital infections[1]: - None - CT/NG - TV/BV - Syphilis - Candidiasis	
Rwandan guidelines – based on structurally reported symptoms	**n (%)** **N = 705**
Rwandan syndromic management diagnoses[1]: - None - VDS (with or without LAP[2]); with risk factors for CT/NG[3] - VDS (with or without LAP[2]); without risk factors for CT/NG[3] - GUD - Inguinal bubo - LAP (with or without VDS)[2] • PID - Condylomata acuminata - Presumptive treatment for asymptomatic FSW[4] - UTI symptoms	
Based on these syndromic diagnoses, participant would have received treatment covering the following urogenital infections[1]: - None - CT/NG - TV/BV - Syphilis - Candidiasis - UTI	

Abbreviations: BV = bacterial vaginosis; CT = *Chlamydia trachomatis*; FSW = female sex worker; GUD = genital ulcer disease; LAP = lower abdominal pain; NG = *Neisseria gonorrhoeae*; PID = pelvic inflammatory disease; TV = *Trichomonas vaginalis*; UTI = urinary tract infection; VDS = vaginal discharge syndrome.

1. Totals may be more than 100%.
2. Lower abdominal pain (with or without vaginal discharge) requires an abdominal and pelvic examination. If cervical motion, uterine, or adnexal tenderness is present, the participant is treated for pelvic inflammatory disease (and thus for CT/NG included). Hospital referral is required in the presence of alarming symptoms. When the participant reports both LAP and VDS, and is not diagnosed with PID, the VDS algorithm is followed.
3. If the participant reports vaginal discharge and (one of) her partner(s) has urethritis or she is positive for a risk score (2 or more positive of: age < 21; being single; 2 or more sexual partners in the past 12 months; new sexual partner in the last 3 months), the participant is to be treated for CT/NG/TV. If the participant reports vaginal discharge, none of her partners have urethritis, and she has a negative risk score (0 or 1 positive of: age < 21; being single; 2 or more sexual partners; new sexual partner in the last 3 months), the participant is to be treated for BV/TV/candidiasis.
4. Under the Rwandan guidelines, presumptive treatment for CT/NG/TV is given at the STI-related first visit if the patient is a female sex worker, but only in the absence of symptoms. If symptomatic, the normal algorithms are followed and the presumptive treatment is not given.

5.3 Comparisons syndromic management vs. WISH procedures vs. gold standard testing

In this section, all hypothetical syndromic management (under WHO guidelines) individual algorithms and presumed treatments of STIs will be compared to the POCT results as performed during the WISH study, and to the gold standard results. For each outcome, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) will be reported (see next page).

Procedure 1	Procedure 2 (reference)	N pos/pos (= TP)	N pos/neg (= FP)	N neg/pos (= FN)	N neg/neg (= TN)	OR (95% CI)[1] Fisher's p	Sens.[2] (%)	Spec.[2] (%)	PPV[2] (%)	NPV[2] (%)
Syndromic (WHO)	*WISH procedures*									
Any VDS (with or without LAP, typical or not for candidiasis)	CT/NG (after RS)[3] by POCT, TV/BV by POCT, or treated for candidiasis									
Any VDS (with or without LAP, typical or not for candidiasis)	CT/NG (after RS)[3] by POCT, TV/BV by POCT									
Any VDS (with or without LAP, typical or not for candidiasis)	CT/NG (after RS)[3] by POCT									
Any VDS (with or without LAP, typical or not for candidiasis)	CT (after RS)[3] by POCT									
Any VDS (with or without LAP, typical or not for candidiasis)	NG (after RS)[3] by POCT									
Any VDS (with or without LAP, typical or not for candidiasis)	TV/BV by POCT									
VDS (with or without LAP, typical for candidiasis)	Treated for candidiasis									
PID (with or without VDS, after LAP)	CT/NG (after RS)[3] by POCT, TV/BV by POCT									
PID (with or without VDS, after LAP)	CT/NG (after RS)[3] by POCT									
PID (with or without VDS, after LAP)	TV/BV by POCT									
GUD	Syphilis algorithm (after RS)[4]									
Would have received treatment for CT/NG[5]	CT/NG (after RS)[3] by POCT									
Would have received treatment for TV/BV[5]	TV/BV by POCT									

Procedure 1	Procedure 2 (reference)	N pos/pos (= TP)	N pos/neg (= FP)	N neg/pos (= FN)	N neg/neg (= TN)	OR (95% CI)[1] Fisher's p	Sens.[2]	Spec.[2]	PPV[2]	NPV[2]
Syndromic (WHO)	*Gold standard*									
Any VDS (with or without LAP, typical or not for candidiasis)	CT/NG (on everyone) by POCT, or TV/BV[6]/CA by qPCR									
Any VDS (with or without LAP, typical or not for candidiasis)	CT/NG (on everyone) by POCT, or TV/BV[6] by qPCR									
Any VDS (with or without LAP, typical or not for candidiasis)	CT/NG (on everyone) by POCT									
Any VDS (with or without LAP, typical or not for candidiasis)	CT (on everyone) by POCT									
Any VDS (with or without LAP, typical or not for candidiasis)	NG (on everyone) by POCT									
Any VDS (with or without LAP, typical or not for candidiasis)	TV/BV[6] by qPCR									
VDS (with or without LAP, typical for candidiasis)	CA by qPCR									
Would have received treatment for CT/NG[5]	CT/NG (on everyone) by POCT									
Would have received treatment for TV/BV[5]	TV/BV[6] by qPCR									
Syndromic (Rwanda)	*WISH procedures*									
Any VDS (with or without LAP, regardless of risk score[7])	CT/NG (after RS)[3] by POCT, TV/BV by POCT, or treated for candidiasis									
Any VDS (with or without LAP, regardless of risk score[7])	TV/BV by POCT									
VDS (with or without LAP, positive risk score[7])	CT/NG (after RS)[3] by POCT, TV/BV by POCT									
VDS (with or without LAP, positive risk score[7])	CT/NG (after RS)[3] by POCT									
VDS (with or without LAP, positive risk score[7])	TV/BV by POCT									

Procedure 1	Procedure 2 (reference)	N pos/pos (= TP)	N pos/neg (= FP)	N neg/pos (= FN)	N neg/neg (= TN)	OR (95% CI)[1] Fisher's p	Sens.[2]	Spec.[2]	PPV[2]	NPV[2]
VDS (with or without LAP, negative risk score[7])	TV/BV by POCT, or treated for candidiasis									
VDS (with or without LAP, negative risk score[7])	TV/BV by POCT									
VDS (with or without LAP, negative risk score[7])	Treated for candidiasis									
Asymptomatic FSW[8]	CT/NG (after RS)[3] by POCT, TV/BV by POCT									
Asymptomatic FSW[8]	CT (after RS)[3] by POCT									
Asymptomatic FSW[8]	NG (after RS)[3] by POCT									
Asymptomatic FSW[8]	TV by POCT									
GUD	Syphilis algorithm (after risk-scoring)[4]									
Typical UTI symptoms	Urinary dipstick (after reporting typical UTI symptoms)									
Would have received treatment for CT/NG[9]	CT/NG (after RS)[3] by POCT									
Would have received treatment for TV/BV[9]	TV/BV by POCT									
Syndromic (Rwanda)	*Golden standard*									
Any VDS (with or without LAP, regardless of risk score[7])	CT/NG (on everyone) by POCT, TV/BV[6]/CA by qPCR									
Any VDS (with or without LAP, regardless of risk score[7])	CT/NG (on everyone) by POCT, TV/BV[6] by qPCR									

Procedure 1	Procedure 2 (reference)	N pos/pos (= TP)	N pos/neg (= FP)	N neg/pos (= FN)	N neg/neg (= TN)	OR (95% CI)[1] Fisher's p	Sens.[2]	Spec.[2]	PPV[2]	NPV[2]
VDS (with or without LAP, positive risk score[7])	CT/NG (on everyone) by POCT, TV by qPCR									
VDS (with or without LAP, positive risk score[7])	CT (on everyone) by POCT									
VDS (with or without LAP, positive risk score[7])	NG (on everyone) by POCT									
VDS (with or without LAP, positive risk score[7])	TV by qPCR									
VDS (with or without LAP, negative risk score[7])	TV/BV[6]/CA by qPCR									
VDS (with or without LAP, negative risk score[7])	TV/BV[6] by qPCR									
VDS (with or without LAP, negative risk score[7])	CA by qPCR									
Asymptomatic FSW[8]	CT/NG (on everyone) by POCT, TV by qPCR									
Asymptomatic FSW[8]	CT/NG (on everyone) by POCT									
Asymptomatic FSW[8]	TV by qPCR									
Would have received treatment for CT/NG[9]	CT/NG (on everyone) by POCT									
Would have received treatment for TV/BV[9]	TV/BV[6] by qPCR									
WISH procedures	*Gold standard*									
CT/NG (after RS)[3] by POCT	CT/NG (on everyone) by POCT									
CT (after RS)[3] by POCT	CT (on everyone) by POCT									

Procedure 1	Procedure 2 (reference)	N pos/pos (= TP)	N pos/neg (= FP)	N neg/pos (= FN)	N neg/neg (= TN)	OR (95% CI)[1] Fisher's p	Sens.[2]	Spec.[2]	PPV[2]	NPV[2]
NG (after RS)[3] by POCT	NG (on everyone) by POCT									
Treated for PID (under WISH procedures)	CT/NG (on everyone) by POCT, TV/BV[6] by qPCR									
TV by POCT	TV by qPCR									
BV by POCT	BV[6] by qPCR									
Treated for candidiasis	CA by qPCR									

Abbreviations: BV = bacterial vaginosis; CA = *Candida albicans*; CI = confidence interval; CT = *Chlamydia trachomatis*; FN = false negative; FP = false positive; FSW = female sex worker; GUD = genital ulcer disease; LAP = lower abdominal pain; NA = not applicable; NG = *Neisseria gonorrhoeae*; NPV = negative predictive value; OR = odds ratio; PID = pelvic inflammatory disease; POCT = point of care test; PPV = positive predictive value; RS = risk scoring; Sens. = sensitivity; Spec. = specificity; TN = true negative; TP = true-positive; TV = *Trichomonas vaginalis*; UTI = urinary tract infection; VDS = vaginal discharge syndrome.

1. By binary logistic regression.
2. As calculated by: sensitivity = TP / (TP + FN); specificity = TN / (TN + FP); positive predictive value = TP / (TP + FP); negative predictive value = TN / (TN + FN).
3. GeneXpert CT/NG testing was only offered if the participant was positive for the CT/NG risk score. The risk score was positive if at least one of the four following criteria was positive: 1) participant is currently pregnant 2) exchanged sex for money and/or goods in the past 12 months 3) reported a new sex partner in the last 3 months 4) abnormal cervicovaginal discharge during speculum exam and/or cervical motion/adnexal tenderness during bimanual exam. If a speculum/bimanual examination was not done, the last criterion was considered negative.
4. Syphilis testing was only offered if the participant was positive for the syphilis risk score. The risk score was positive if at least one of the four following criteria was positive: 1) participant is currently pregnant 2) exchanged sex for money and/or goods in the past 12 months 3) reported a new sex partner in the last 3 months 4) genital ulcers/blisters/sores visible during pelvic exam. If a pelvic examination was not done, the last criterion was considered negative.
5. Participant would have been received treatment covering CT/NG/TV/BV if she is positive for VDS (with or without LAP) and/or PID under the WHO guidelines. In the case of VDS, this is assuming all of our participants are at risk of CT/NG infection due to high local prevalence.
6. Further explained in the article by Jespers V, Crucitti T, van de Wijgert J et al. "A DNA tool for early detection of vaginal dysbiosis in African women." Res Microb 167.2 (2016): 133-41.
7. If the participant reports vaginal discharge and (one of) her partner(s) has urethritis or she is positive for a risk score (2 or more positive of: age < 21; being single; 2 or more sexual partners in the past 12 months; new sexual partner in the last 3 months), the participant is to be treated for CT/NG/TV. If the participant reports vaginal discharge, none of her partners have urethritis, and she has a negative risk score (0 or 1 positive of: age < 21; being single; 2 or more sexual partners; new sexual partner in the last 3 months), the participant is to be treated for TV/BV/candidiasis.
8. Under the Rwandan guidelines, presumptive treatment for CT/NG/TV is given at the STI-related first visit if the patient is an FSW, but only in the absence of symptoms. If symptomatic, the normal algorithms are followed and the presumptive treatment is not given.
9. Participant would have received treatment covering CT/NG if she had VDS (with or without LAP) with a positive risk score as described under (8) and/or PID, or if she was an asymptomatic FSW. Participant would have received treatment covering TV/BV if she had VDS (with or without LAP), regardless of the result of the risk score described under (7), and/or PID, or if she was an asymptomatic FSW.

5.4 Overview syndromic management and WISH procedures vs. gold standard testing

An overview table will be made to compare WHO and Rwandan syndromic management, and the procedures of the WISH study, with gold standard testing.

Outcome / treated for N = 705	WHO syndromic management						Rwandan syndromic management						WISH procedures						Gold standard	
	TP[1] N	FP[1] N	FN[1] N	TN[1] N	Sens.[1] %	Spec.[1] %	TP[1] N	FP[1] N	FN[1] N	TN[1] N	Sens.[1] %	Spec.[1] %	TP[1] N	FP[1] N	FN[1] N	TN[1] N	Sens.[1] %	Spec.[1] %	Negative N	Positive N
CT[2]																				
NG[2]																				
CT and/or NG[2]																				
TV[3]																				
BV[3]																				
BV and/or TV[3]																				
Candidiasis[4]																				
Syphilis[5]																				
UTI[6]																				

Abbreviations: BV = bacterial vaginosis; CT = *Chlamydia trachomatis*; FN = false negative; FP = false positive; FSW = female sex worker; GUD = genital ulcer disease; LAP = lower abdominal pain; NA = not applicable; NG = *Neisseria gonorrhoeae*; PID = pelvic inflammatory disease; POCT = point of care test; Sens. = sensitivity; Spec. = specificity; TN = true negative; TP = true-positive; TV = *Trichomonas vaginalis*; UTI = urinary tract infection; VDS = vaginal discharge syndrome.

1. Compared to gold standard testing (CT, NG, TV, BV, candidiasis) or WISH procedures reference test (Syphilis, UTI). Sensitivity calculated by TP / (TP + FN); specificity calculated by TN / (TN + FP).
2. Under WHO syndromic management, the participant is treated for CT/NG if she is positive for VDS (with or without LAP) and/or PID. Under Rwandan syndromic management, the participant is treated for CT/NG if she is positive for VDS and (one of) her partner(s) has urethritis or she is positive for a risk score (2 or more positive of: age < 21; being single; 2 or more sexual partners in the past 12 months; new sexual partner in the last 3 months), if she has PID, or if she is an asymptomatic FSW. Under WISH procedures, the participant is offered GeneXpert CT/NG POCT testing if she is positive for the WISH CT/NG risk score previously described, and treated based on the test results. Gold standard is defined as GeneXpert CT/NG POCT performed on everyone.
3. Under WHO syndromic management, the participant is treated for BV/TV if she is positive for VDS (with or without LAP) and/or PID. Under Rwandan syndromic management, the participant is treated for BV/TV is she is positive for VDS (no matter the Rwandan CT/NG risk score described under (2)), if she has PID, or if she is an asymptomatic FSW. Under WISH procedures, the participant is offered TV OSOM POCT testing and treated based on the test results, and is offered BV by pH testing and treated based on the test results (a pH of 5.0 or higher is treated, regardless of symptoms) . Gold standard testing is defined as TV qPCR, and BV qPCR vaginal health score, as explained in section 5.1
4. Under WHO syndromic management, the participant is treated for BV if she is positive for VDS (with or without LAP) and has typical signs/symptoms of candidiasis present. Under Rwandan syndromic management, the participant is treated for BV is she is positive for VDS and has a negative Rwandan risk score as described under (3).
5. Under both Rwandan and WHO syndromic guidelines, the participant is treated for syphilis if there are ulcerations observed during the examination. Under WISH procedures, syphilis testing is offered if the participant is positive for WISH syphilis risk score previously described, and treated based on the test results. No gold standard test is available for this outcome, and the WISH procedures are considered the reference standard.
6. Under Rwandan guidelines, all women complaining of typical UTI symptoms are treated. Under WISH procedures, all women complaining of UTI symptoms were tested using a urinary dipstick; as per Rwandan guidelines, all dipsticks with at least 1+ leucocytes and/or nitrite-positive were treated for UTI. No gold standard test is available for this outcome, and the WISH procedures are considered the reference standard.

5.5 *Primary and secondary objective outcomes based on gold standard tests*

In this section, we will examine the influence of false-negative and false-positive POCT results on the WISH study primary and secondary outcomes. The CT/NG GeneXpert tests of the women scoring negative on the risk score came available relatively quickly after their Main Visit; if their CT/NG GeneXpert test performed later came back positive, participants were called back for treatment and partner notification procedures. This was all done when the WISH study was still active, and will not be reported here. If the TV OSOM test turned out to be false-negative (compared to the gold standard qPCR TV test), participants were urged by cell phone text message to seek diagnosis/treatment elsewhere. The other gold standard tests performed (BV, Candidiasis) do not require partner treatment nor referrals, and thus are not likely to have changed most outcomes except for treatment.

Abbreviations: BV = bacterial vaginosis; TV = *Trichomonas vaginalis*.

1. May be lower than total number of false-negatives due to same treatment given for other infections.

Results at Main Visit – false-negative and false-positive TV POCT test	**N = 705**
False-negative TV OSOM result N	
False-positive TV OSOM result N	
Number of partners that should have been notified based on window period and false-negative results N	
Over-treatment given due to false-positive TV OSOM result[1] n (%): - Metronidazole single dose - Metronidazole 7 days - other, [categories to be made]	
Number of women that should have been treated for false-negative TV OSOM result[2] N	
Results at Main Visit – false-negative and false-positive BV POCT test	**N = 705**
False-negative BV by pH testing results N	
False-positive BV by pH testing results N	
Over-treatment given due to false-positive BV result[1] n (%): - Metronidazole single dose - Metronidazole 7 days - other, [categories to be made]	
Number of women that should have been treated for false-negative BV result[2] N	
Results at Main Visit – false-negative and false-positive candidiasis diagnosis	**N = 705**
False-negative Candidiasis diagnoses N	
False-positive Candidiasis diagnoses N	
Over-treatment given due to false-positive Candidiasis diagnosis n (%): - Fluconazole single dose for vaginal candidiasis - Clotrimazole pessaries 3 nights for vaginal candidiasis.	
Number of women that should have been treated for false-negative Candidiasis result N	

2. May be lower than total number of false-positives due to same treatment given for other infections.

5.6 *Mistakes made in clinic flow and diagnosis & care procedures*

We will highlight mistakes made during the study in table below; for each mistake, we will try to investigate at what point in the clinic flow the mistake was made (at clinician-level, laboratory-level or diagnosis and care-level). The WISH procedures results will be taken as a reference, as these were the ones dictating the clinic flow. Where necessary, specifications of the mistakes committed will be made in footnotes.

General	**N = 705**
POC tests erroneously ordered from laboratory by clinician N - UTI tests erroneously requested N	

- Syphilis tests erroneously requested N - Pregnancy test erroneously requested N	
POC tests erroneously not ordered from laboratory by clinician N - UTI tests erroneously not requested N - Syphilis tests erroneously not requested N - Pregnancy test erroneously not requested N	
Sample erroneously not taken by clinician N - EcoCare pH swab erroneously not taken N	
POC tests erroneously performed by laboratory (while not ordered by clinician) N - UTI test erroneously performed - Pregnancy test erroneously performed	
POC tests erroneously not performed by laboratory (while requested by clinician) N - UTI test erroneously not performed - Pregnancy test erroneously not performed	
Treatment erroneously given N - Ciprofloxacin 500 mg single dose given	
Treatment erroneously not given N - No treatment given for BV diagnosis - No treatment given for candidiasis diagnosis	
Partner notifications missed N	
Partner notifications performed incorrectly N	
Referrals erroneously made N	
Referrals erroneously not made N	

Abbreviations: POC test = point of care test.

6. Additional laboratory results

Additional tests were performed on vaginal swabs and urine to perform sensitivity analyses and to gather more data for hypothesis-generating exploratory analyses; however, these tests are not gold standard tests. As previously described, unless opted out for, all women handed in two vaginal swabs for sensitivity analyses and (again unless opted out for) long-term storage. After performing UTI and/or pregnancy testing during the Main Visit, urine was centrifuged and the pellet was stored in two cryovials of 2 ml each, at -80 degrees Celsius. Participants who did not undergo any urine testing did not have urine stored.

Vaginal swab results	**n (%)** **N = xxx**
Mycoplasma genitalium qPCR result: - Positive	
Mycoplasma hominis qPCR result [If performed by ITM] n (%): - Positive	
Urine results	**n (%)** **N = xxx**
E. coli qPCR result n (%): - Positive	
P. mirabilis qPCR result n (%): - Positive	
Lactobacillus genus qPCR $\log_{10}$ meq/ml: median [SD]	
Lactobacillus crispatus qPCR $\log_{10}$ meq/ml: median [SD]	

7. Feasibility endpoints

To show it is possible to implement improved urogenital infection care service, in this section, we will report M&E indicators such as inputs (procurement experiences, infrastructure/training experiences) and outcomes/impacts (improvements of access to and quality of services).

7.1 Infrastructure/training/procurement: requirements and challenges

The RU clinic was already in place prior to beginning the study, and had experience offering urogenital care to Rwandan at-risk women. To implement the WISH procedures, several changes in infrastructure and training had to be implemented.

Topic	Already in place	Had to be established	Challenges experienced	Comments
Infrastructure & laboratory	- Equipped basic air-conditioned laboratory - Fully equipped clinic rooms - -80° C freezers for storage, fridges already available	- Installation of GeneXpert platform with desk computer - Internal quality control measures had to be devised to test POCT - Pharmacy-like room at RU's premises to store medications dispensed	- GeneXpert can only be installed with help of technician - All POCT have been validated, but which degree of quality control to perform is debatable	- Installation of GeneXpert is included in price - Most Rwandan health centres have a pharmacy on premises - Quality control could also be organized centrally (at LNR) if WISH procedures were to be implemented - -80° C freezers only used for research-specific procedures
Consumables	- HIV testing materials all available locally - All clinic consumables are available locally - All types of medication used in WISH are available in local pharmacies	- GeneXpert CT/NG cartridges had to be imported - TV OSOM test and syphilis POCT could be ordered locally (but are imported) - EcoCare pH swab had to be ordered abroad and imported	- TV OSOM test can only be ordered in bulk (450 or more) - No adequate pH strip for BV testing available locally; cannot currently be ordered in Rwanda	- HIV rapid testing is already commonplace in Rwanda - Procurement problems did not lead to a delay in participant enrolment & testing - Ordering pH strips from Rwanda might be possible in government setting
SOPs	- Clinic-specific SOPs were in place (used in RU's previous studies), such as counselling, partner notification, STI management guidelines.	- Existing SOPs had to be updated - SOPs had to be (re)written for all POCTs including GeneXpert testing - STI treatment SOP was updated to incorporate WISH procedures	- Difficulty establishing best-practice partner notification due to little experience locally - Window periods of STIs (for partner notification) taken from international literature but sometimes difficult to identify partners	- STI management SOPs now incorporate how to treat depending on method of diagnosis (POCT, syndromic management). - More research evidence is needed to improve partner notification programs

Training	- RU staff had experience with most clinic procedures - RU staff had some experience with partner notification but success in past was low	- RU laboratory staff needed training in POCT procedures, including GeneXpert - RU clinic staff needed training in clinic flow, sample collection and sample handling	- Clinic flow took a few months to implement correctly - Speed in clinic flow (especially informed consent procedures and interview) remained a problem throughout study	- Full training for procedures took about 3-4 weeks in total; - CT/NG GeneXpert training for laboratory technicians took 2 days - Procedures were well implemented throughout study
(Local) STI guidelines	- WHO and Rwandan STI guidelines are available and in place - Rwandan STI guidelines offer possibility of presumptive STI treatment for asymptomatic FSWs	- RU physicians had to be trained to correctly identify syndromic management diagnoses	- While local STI guidelines are in place, some parts of algorithms (e.g. CT/NG risk scoring) are open to - STI guidelines contain little information on how to identify and notify partners	- No system currently in place to monitor antibiotic resistance and treatment success - Ability of Rwandan clinics in reaching asymptomatic FSWs is unknown but likely low - Rwandan VDS guidelines presume ability to distinguish cervical from vaginal discharge, which is unlikely to be possible
Recruitment	- General recruitment SOP was in place but not specific to WISH study - RU had a network of community mobilizers that help with recruitment and sensitizing	- Recruitment plan was written to be able to recruit at least 500 participants during study follow-up	- First recruitment sessions resulted in high number of FSWs - Recruitment plan had to be amended twice to obtain a good sample of Kigali's population	- Recruitment was successful, with 705 participants included in less than a year - See, for more information, section 7.2

Abbreviations: CT = *Chlamydia trachomatis*; FSW = female sex worker; LNR = national reference laboratory of Rwanda; NG = *Neisseria gonorrhoeae* STI = sexually transmitted infection; SOP = standard operating procedures; TV = *Trichomonas vaginalis*; VDS = vaginal discharge syndrome.

7.2 Recruitment challenges

705 participants were enrolled in the WISH study between July 2016 to March 2017. Some challenges were observed by the RU Outreach Manager and the PI during the recruiting period. These include:

- Most women interviewed are not aware that urogenital infections can be asymptomatic as well. Moreover, there is not a culture of seeking preventive care; it is only when women have (severe) symptoms that they seek care.
- Some women avoid care due to long waiting times at local clinics; some go to pharmacies directly to request treatment, without getting diagnosed.
- Women complain that their urogenital symptoms often do not resolve (due to misdiagnoses, re-infection or treatment failure). Therefore, they decide not to return to the clinic.
- Some women may believe that traditional medicine provides a better cure rate than "Western"

medicine.

- Despite free diagnostics and treatment provided at RU, some women struggled with high transport cost and/or time lost due to not being able to work.
- Specific to clinical research, recruitment was sometimes difficult do to misconceptions about study participation and rumours spread in local communities.
- Taboos related to sexual care and sex in general; more specifically, women might be blamed when informing their partner(s) of diagnosed STIs and therefore either not participate in the study, or, when participating, to be inclined not to notify their partner(s).

Even though some of these challenges are specific to the situation of RU, some problems might be faced by urogenital clinics and health clinics in other parts of sub-Saharan Africa as well. In general, we have shown it is feasible to recruit women who are asymptomatic, or who have symptoms but who have not presented to local health clinics. However, the experiences during the WISH study do show that it is essential to provide good counselling, and to seek support from community mobilizers and authorities to reach the women at (high) risk for STIs.

7.3 Overall costs

The overall salary costs of the RU personnel, the costs of clinic supplies, laboratory supplies, and the overhead costs will be synthesized to estimate costs of the procedures as performed during the WISH study.

	Rwandan Francs	**Euros**
Exchange rate used (per xx/xx/xxxx)		
Salary per month of physician		
Salary per month of nurse		
Salary per month of laboratory staff		
Salary per month of receptionist		
Medication		
Ciprofloxacin 500 mg, single oral dose		
Ciprofloxacin 1000 mg, single oral dose		
Ciprofloxacin 500 mg, twice per day, 3-day course		
Ciprofloxacin 500 mg, twice per day, 7-day course		
Doxycycline 100 mg, twice per day, 7 day-course		
Doxycycline 100 mg, twice per day, 14 day-course		
Doxycycline 100 mg, twice per day, 21 day-course		
Metronidazole 2 grams, single oral dose		
Metronidazole 500 mg, twice per day, 7 day-course		
Metronidazole 500 mg, twice per day, 14-day course		
Ceftriaxon 250 mg, single im dose		
Fluconazole 150 mg, single oral dose		
Clotrimazole 200 mg pessaries, 3 day-course		
Benzathine benzyl penicilline, 2.4m IU, single im dose		
Benzathine benzyl penicilline, 2.4m IU, three im doses		
Acyclovir 400 mg, thrice per day, 7 day-course		

Clinic and laboratory supplies		
Glove, price per unit		
Gloves, price used per participant (3 x 2 gloves)		
Vacutainer EDTA tubes 4.5 ml, per participant		
Vacutainer needles, per participant		
Urine container, per participant		
HIV Rapid Test Determine, per participant		
HIV Rapid Test Unigold, per participant		
HIV ELISA (at LNR), per participant		
Determine Syphilis Rapid Test, per participant		
Syphilis RPR (SpinReact), per participant		
NOVA pregnancy test, per participant		
NOVA urine dipstick, per participant		
GeneXpert machine (2 slots), including desktop		
GeneXpert CT/NG cartridge, per participant		
TV OSOM test, per participant		
Merete vaginal pH swabs, per participant		

The overall costs will be used for cost-effectiveness comparisons of syndromic management versus WISH procedures. These will be reported separately, in a tertiary SAP.

7.4 Timing of procedures

25 Main Visits were meticulously timed to assess how long it took the nurses, counsellors, physicians and laboratory technicians during the WISH study to perform certain procedures. Of these timings, 5 concerned laboratory procedures only. Some procedures that were timed correspond to study specific-situations, such as the informed consent procedures. These findings are interesting for other studies, but are not relevant to implementing WISH procedures in a normal clinical setting.

Care was taken to have the same amount of observations per study nurse to account for intra-personal differences in timing; there was only one physician present at RU at the time of the procedure timings, and the laboratory technicians worked together on all tests. The timings were performed by the UoL Project Manager (n = 3) and an external consultant (n = 22).

The following will be assessed:

- Median time for face-to-face interviews, physical examination(s), counselling, laboratory and treatment procedures
- Median time for WISH procedures without CT/NG testing per participant: participant doesn't wait for CT/NG results at clinic, or is negative for the CT/NG risk score
- Median time for WISH procedures with CT/NG testing per participant: participant waits for CT/NG results at clinic
- Estimated time for WISH procedures (overall), and estimated time for WISH procedures while subtracting research-specific procedures such as informed consent

	N	Time in median minutes [IQR]
Time difference between scheduled time and arrival at RU		
Duration of procedures at reception		
Time difference between finishing reception procedures with being called in by nurse to start informed consent procedures		
Time difference between arrival at RU and starting informed consent procedures		
Duration of informed consent procedures plus writing down personal contact detail		
Duration of face-to-face interview		
Duration of counselling		
Duration of blood collection		
	N	**Time in median minutes [IQR]**
Duration of vaginal swab collection		
Duration of urine collection		
Duration of pelvic examination		
Duration of bimanual examination		
Time in waiting room between handing in last sample at laboratory and being called back for results		
Time in waiting room between handing in last sample at laboratory and being called back for results (immediate CT/NG testing)		
Time in waiting room between handing in last sample at laboratory and being called back for results (no CT/NG testing)		
Time difference between last sample arrived at laboratory and time at which RU physician received results from laboratory		
Time difference between last sample arrived at laboratory and time at which RU physician received results from laboratory (immediate CT/NG testing)		
Time difference between last sample arrived at laboratory and time at which RU physician received results from laboratory (no CT/NG testing)		
Duration of diagnosing and counselling by RU physician		
Duration of treatment and partner notification procedures by RU physician		
Duration of client satisfaction survey		
Duration of HIV Determine rapid testing		
Duration of HIV Unigold confirmatory testing		
Duration of Syphilis Determine rapid testing		
Duration of Syphilis RPR confirmatory testing		
Duration of CT/NG GeneXpert testing		
Duration of TV OSOM testing		
Duration of pregnancy testing		
Duration of UTI dipstick testing		
	N	**Time in median minutes [IQR]**
Total duration spent at RU clinic with nurse		
Total duration spent at RU clinic with physician		
Total duration for laboratory testing		
Total duration spent at RU		

Total duration spent at RU clinic if CT/NG risk-score negative or chose not to wait for CT/NG results		
Total duration spent at RU clinic if CT/NG risk-score positive and chose to wait for CT/NG results		
Total duration spent at RU (with time for informed consent procedures and client satisfaction survey being substracted)[1]		
Total duration spent at RU (with time for informed consent procedures and client satisfaction survey being substracted)[1] if CT/NG risk-score negative or chose not to wait for CT/NG results		
Total duration spent at RU (with time for informed consent procedures and client satisfaction survey being substracted)[1] if CT/NG risk-score positive and chose to wait for CT/NG results		

Abbreviations: CT = *Chlamydia trachomatis*; IQR = inter-quartile range; NA = not applicable; NG = *Neisseria gonorrhoeae*; RU = Rinda Ubuzima; TV = *Trichomonas vaginalis*; UTI = urinary tract infection.

1. These procedures are study-specific and would not be performed in real clinic situations.

The overall costs will also be used for cost-effectiveness comparisons of syndromic management versus WISH procedures; this will be done to compare total numbers of participants that can be seen under syndromic management per time period versus total numbers of participants that can be seen under clinics that would follow WISH study procedures (while substracting study-specific components such as informed consent). These will be reported separately.

7.5 Procedure observations and clinic flow problems observed

During two monitoring visits performed by the UoL Project Manager, multiple participants were followed to observe whether procedures were performed correctly and what possible issues arose.
Some remarks or issues during these observations were:

- The informed consent procedures, writing down of personal contact details, and the face-to-face interviews all took a long time. Anecdotal information given by participants indicates that this is no different from local health clinics, where long waiting times are also common.
- The informed consent procedures were well done.
- Some questions seemed to be difficult to understand for participants; especially questions related to time frame (e.g. “how many sex partners have you had in the last 12 months”) had to be explained several times until the participant understood.
- The counselling procedures were well done; the participants seemed to appreciate that they could choose counselling topics themselves.
- Pelvic, bimanual and physical examinations were performed adequately.
- Sample collection was performed correctly and in accordance with the SOPs.
- The laboratory procedures were performed meticulously and correctly. No problems were observed during the usage of the GeneXpert platform. The number of invalid GeneXpert tests corresponded with those estimated by the manufacturer (< 5% of total).
- The diagnoses and treatment provided were in accordance to the POCT results, and in accordance to the SOPs.
- Partner notification was difficult as women often opted out for notification of their male partners. According to the RU physicians, many state not knowing who and/or where their partners are; others state that their partners went abroad.

In general, it was observed that the clinic flow was - albeit sometimes slow - performed well and that there were no major bottlenecks.

7.6 Client satisfaction survey

A Client Satisfaction Survey (CSS) was held among a random sample of the participants. 107 surveys were

conducted. They were conducted in a private space and by a clinician who had not interviewed them before and did not perform the normal WISH procedures, to ensure a lower social desirability bias.

	n (%) N = 107
Agreed with the following statements: - "I felt welcome at Rinda Ubuzima" - "The study staff were friendly" - "The instructions I received along the way were clear" - "The medical services I received were of good quality" - "The medical services I received were useful" - "The counselling/information I received was of good quality" - "The counselling/information I received was useful"	
Found (venous) blood sampling: - Very comfortable - Somewhat comfortable - Not comfortable at all - Not done	
Found fingerstick sampling: - Very comfortable - Somewhat comfortable - Not comfortable at all - Not done	
Found urine sampling: - Very comfortable - Somewhat comfortable - Not comfortable at all - Not done	
Found self-sampling of vaginal swabs: - Very comfortable - Somewhat comfortable - Not comfortable at all - Not done	
Found clinician-sampling of vaginal swabs: - Very comfortable - Somewhat comfortable - Not comfortable at all - Not done	
Found the speculum and bimanual examination: - Very comfortable - Somewhat comfortable - Not comfortable at all - Not done	
Found the face-to-face interviewing: - Very comfortable - Somewhat comfortable - Not comfortable at all - Not done	
Found the general counselling: - Very comfortable - Somewhat comfortable - Not comfortable at all - Not done - Missing	
Found the post HIV-test counselling: - Very comfortable - Somewhat comfortable - Not comfortable at all - Not done	
Estimated time participant spent at the clinic: median minutes [IQR]	

Estimated time participant spent at the clinic (positive CT/NG risk score): median minutes [IQR]	
Estimated time participant spent at the clinic (positive CT/NG risk score, and participant chose to wait in clinic for results): median [IQR]	
Estimated time participant spent at the clinic (positive CT/NG risk score, and chose to receive results later without waiting in clinic): median minutes [IQR]	
Estimated time participant spent at the clinic (negative CT/NG risk score): median minutes [IQR]	
Feelings about the clinic visit duration: - Thought it was fine - Was bothered by it but not much - Thought it was very long, but worth it due to all the services received - Thought it was much too long and would not do it again	
Comparison of experience at RU during study visit, compared to other places where HIV/STI/women's issues-related services are given: - Liked RU better - All services are similar - Liked the other services better - Has never been to other places	
	n (%) **N = 107**
Reasons for preferring RU over other clinics, in categories[1]: [categories to be made as needed]	*N = xxx*
Reasons for thinking services are similar, in categories[1]:	*N = xxx*
Reasons for preferring other clinics over RU, in categories[1]:	*N = xxx*
Indicates willingness to be tested in future, even without complaints: Yes	
Intended frequency of being tested on STIs: - Less than once a year - Once a year - Twice a year - Thrice a year - Four times a year - Five or more times a year - NA - Missing	*N = xxx*
Indicates being willing to pay for services such as those offered at RU: - Yes	*N = xxx*
If willing to pay, amount willing to pay, in Rwandan Francs: median [IQR]	*N = xxx*
If willing to pay, amount willing to pay, in Euros (1 euro = 950 Rwandan Francs): median [IQR]	*N = xxx*
Reported reasons what participants liked about services provided at RU[1]: [categories to be made as needed]	
Reported reasons what participant didn't like about services provided at RU[1]: [categories to be made as needed]	

Abbreviations: CT = *Chlamydia trachomatis*; IQR = interquartile range; NA = not applicable; NG = *Neisseria gonorrhoeae*; STIs = sexually transmitted infections.

1. Multiple answers possible; totals may be more than 100%.

7.7 Staff survey

A staff survey was held with all the RU personnel directly involved in the WISH study, to inquire about their opinions of the services procedures offered during the WISH study, and whether there were improvements to make. The interviews were held by an external consultant who was not part of the RU team nor worked

at the Sponsor institution (UoL), to minimize social desirability bias. The survey was semi-structured; the consultant was allowed to inquire more in-depth after the initial answer was given.

	n (%) N = 8
Role at RU during WISH study: - Study physician - Research nurse - Laboratory technician - Outreach manager/data manager/receptionist	
In opinion of interviewee, type of women that were recruited into the WISH study after actively stopping targeting sex workers[1]: [categories to be made as needed]	
Whether women that were seen during the WISH study were hard to find (according to opinion of interviewee)[1]: [categories to be made as needed]	
If recruitment could start again, issues that could have been improved according to interviewee[1]: [categories to be made as needed]	
	n (%) N = 8
If the Ministry of Health in Rwanda decided to provide rapid STI testing on a larger scale, places where interviewee would make the service available, and reasons[1]: [categories to be made as needed]	
Estimated time that participant spent at RU for a Main Visit: shortest time in median minutes [IQR]	
Estimated time that participant spent at RU for a Main Visit: average time in median minutes [IQR]	
Estimated time that participant spent at RU for a Main Visit: longest time in median minutes [IQR]	
Factors mentioned that were important in determining the duration of a participant's study visit[1]: [categories to be made as needed]	
Number of women complaining to interviewee / other RU staff about the long duration of Main Visit or other things related to WISH study: [categories to be made as needed]	
If the participants complained, topics they typically complained about[1]: [categories to be made as needed]	
Time limit after which women started complaining[1]: [categories to be made as needed] - NA; no or almost no contact with participants	
Reasons why women did not complain: [categories to be made as needed] - NA; no or almost no contact with participants	
Most popular counselling topics during counselling sessions[1]: [categories to be made as needed]	
Least popular counselling topics during counselling sessions[1]: [categories to be made as needed] - NA	
Advantages of letting women choose their own counselling topics: [categories to be made as needed]	

- NA	
Disadvantages of letting women choose their own counselling topics[1]: [categories to be made as needed] - NA / not answered	
Advantagesof risk scoring for CT/NG and syphilis[1]: [categories to be made as needed] - NA	
Disadvantages of risk scoring for CT/NG and syphilis: [categories to be made as needed] - NA	
	n (%) **N = 8**
Examples of negative experiences with risk scoring: [categories to be made as needed] - No negative experiences - NA	
Estimated number of women who opted out for a certain service and reasons: [categories to be made as needed] - NA	
Most popular choice for participants when it comes to receiving CT/NG results (in case of positive risk score): - To wait at least 90 minutes for test result - To schedule additional visit at RU to obtain test result) - To receive a text message (and only follow-up in case of positive result) - To receive a call (and only follow-up in case of positive result) - 50% waited, 50% chose for a call back - NA	
Estimated number of women who underwent a pelvic examination (as a proportion of total study participants): - No women - Few women - Less than half of the women - More than half of the women - Most of the women - All women - NA	
Estimation that this number of pelvic examinations conducted appropriate, too many, or too few: [categories to be made as needed] - NA	
Choice between self-sampling and clinician-sampling for vaginal testing: how many women opted out for clinician-sampling, and reasons why[1]: [categories to be made as needed] - NA	
Feedback about clinical procedures during the WISH study: [categories to be made as needed] - NA	
Feedback about laboratory procedures during the WISH study[1]: [categories to be made as needed] - NA	
What the study physician would choose between syndromic management, risk	*N = 2*

scoring followed by POC testing, or POC testing for all women in clinic: [categories to be made as needed]	
Aspects of POC testing that study physician considered difficult to do / interpret or difficult to communicate with patient: [categories to be made as needed]	*N = 2*
Whether physician trusted POC test results: [categories to be made as needed]	*N = 2*
Advantages and disadvantages of communicating with women via text message[1]: [categories to be made as needed]	
Whether interviewee heard of any breaches of confidentiality: [cases to be described as needed] - None reported	
	n (%) **N = 8**
Estimated ratio of sexual partners reached by partner notification: - No partners - A few partners - Less than half of the partners - More than half of the partners - Most of the partners - All of the partners - NA / doesn't know	
Most popular methods of partner notification: - [categories to be made as needed] - NA	
Ideal partner notification program[1]: [categories to be made as needed] - NA	
Procedures of WISH study that could be improved[1]: [categories to be made as needed]	
Any other comment by interviewee[1]: [categories to be made as needed]	

Abbreviations: CT = *Chlamydia trachomatis*; FSW = female sex worker; IQR = interquartile range; NA = not applicable; NG = *Neisseria gonorrhoeae*; RU = Rinda Ubuzima; STIs = sexually transmitted infections.

1. Multiple answers possible; totals may be more than 100%.

7.8 Electronic participant identification register data

During the WISH study, participants could choose what forms of contact attempts they wanted in the case they had to be contacted for test results, treatment to be taken, missing information, to encourage partner treatment, and others. Unlike previous studies conducted at RU, we also added text messages to their mobile number in this.

	n (%) **N = 705**
Contact permissions given by participant[1]: - Text message to own mobile phone - Phone call to own mobile phone - Phone call to emergency contact - Phone call to other mobile number - Email to participant - Letter to own address - Home visit to own address	
Preferred method of follow-up:	

- Text message to own mobile phone - Phone call to own mobile phone - Phone call to emergency contact - Phone call to other mobile number - Email to participant - Letter to own address - Home visit to own address - Missing	
Number of contact attempts during entire WISH study follow-up, per reason[1]: - Outcome after treatment - To ask to come to RU to receive treatment - To ask to come to RU to receive results - To ask to come to RU for a lacking pelvic & bimanual exam - To collect missing information on the source document / to correct data - To communicate about problems with consent forms - To ask about or encourage partner treatment - As a reminder to come for an Additional Visit - To communicate results - To provide an explanation about medication - To answer questions about symptoms the participant has	
	n (%) **N = 705**
Reasons for making an appointment for an additional visit in the ePIR[1]: - To receive treatment - To receive laboratory results - To perform a pelvic & bimanual exam that could not be performed at Main Visit - To come together with partner for partner notification and treatment - NA: no appointment made for additional visit	

Abbreviations: ePIR = electronic participant identification register; NA = not applicable.

1. Multiple answers possible; totals may be more than 100%.

7.9 Potential alternative risk score for Chlamydia and Gonorrhea

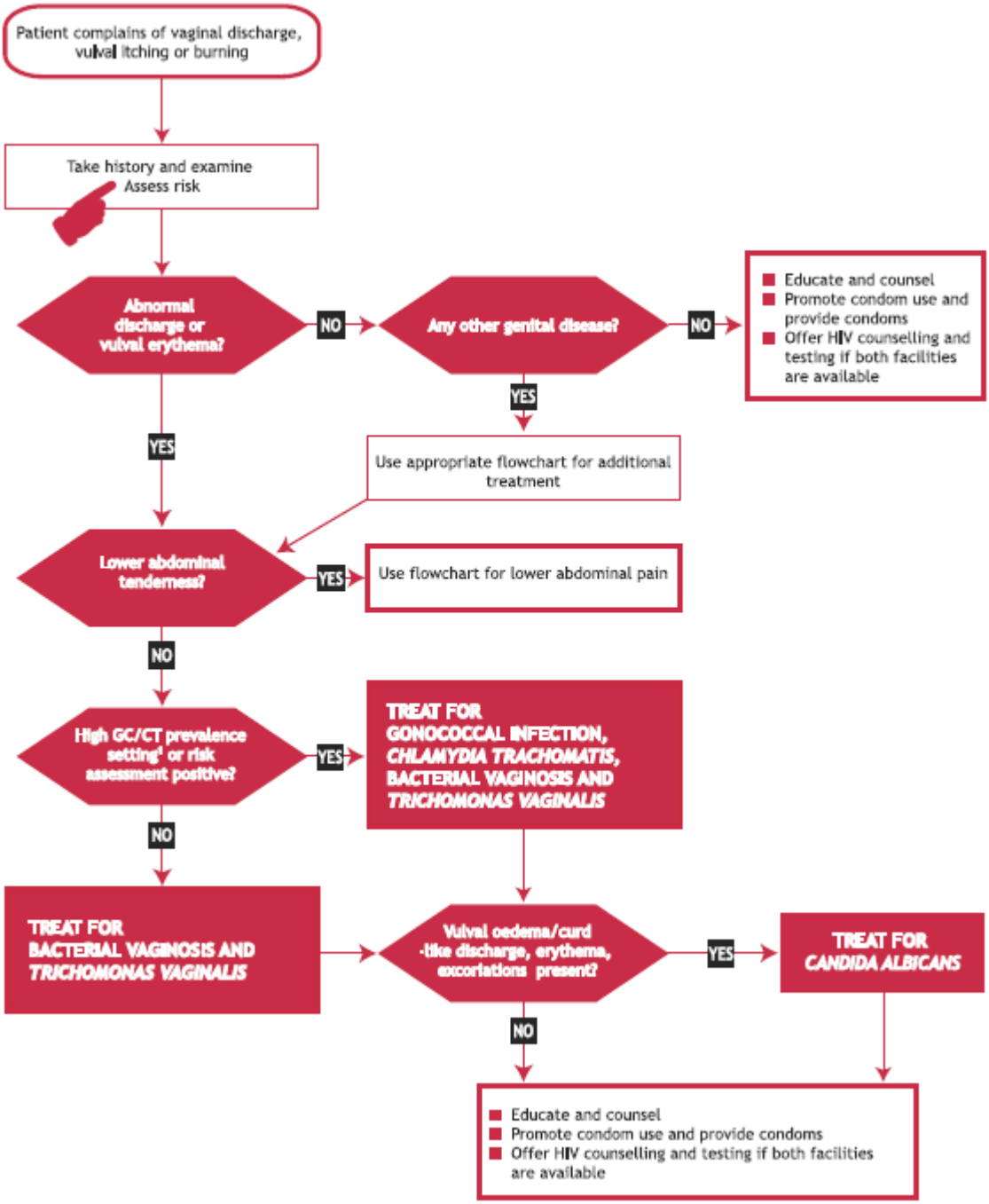
The performance of the CT/NG risk score is one of the secondary objectives of the WISH study (see section 1.1). Momentarily, the GeneXpert CT/NG assay is quite expensive; moreover, it is useful to use risk-scoring to avoid false-positive testing, especially in populations with low CT/NG prevalence. Therefore, a well-functioning CT/NG risk score is important.

Depending on the sensitivity and specificity of the CT/NG risk score, an alternative risk score will be devised. If performed, this alternative risk score is only intended as a tertiary analysis. Its SAP will be presented in a separate document. To make an alternative risk score, the best performing risk factors for CT/NG will be identified, and will be used individually and together; ROC curves will be made for these risk factors, both individually and put together, to find the risk score that provides the best sensitivity and specificity compared to gold standard testing of CT/NG (i.e., CT/NG GeneXpert test on everyone).

8. Appendices

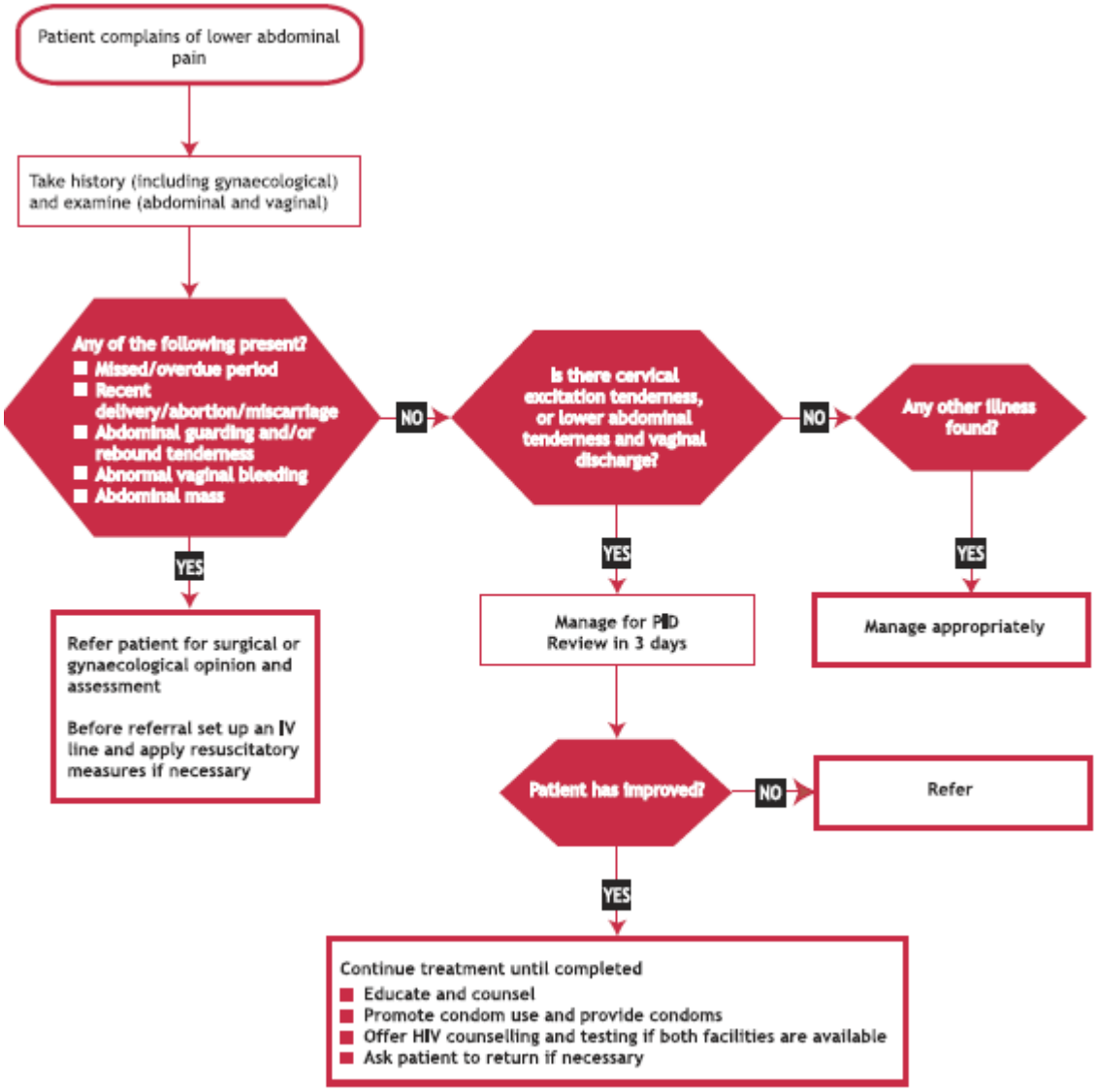
8.1 WHO Syndromic Management Algorithms

WHO: VAGINAL DISCHARGE SYNDROME (WITHOUT SPECULUM OR BIMANUAL EXAMINATION)
[A second algorithm is available for VDS with speculum/bimanual exam but is not included here].

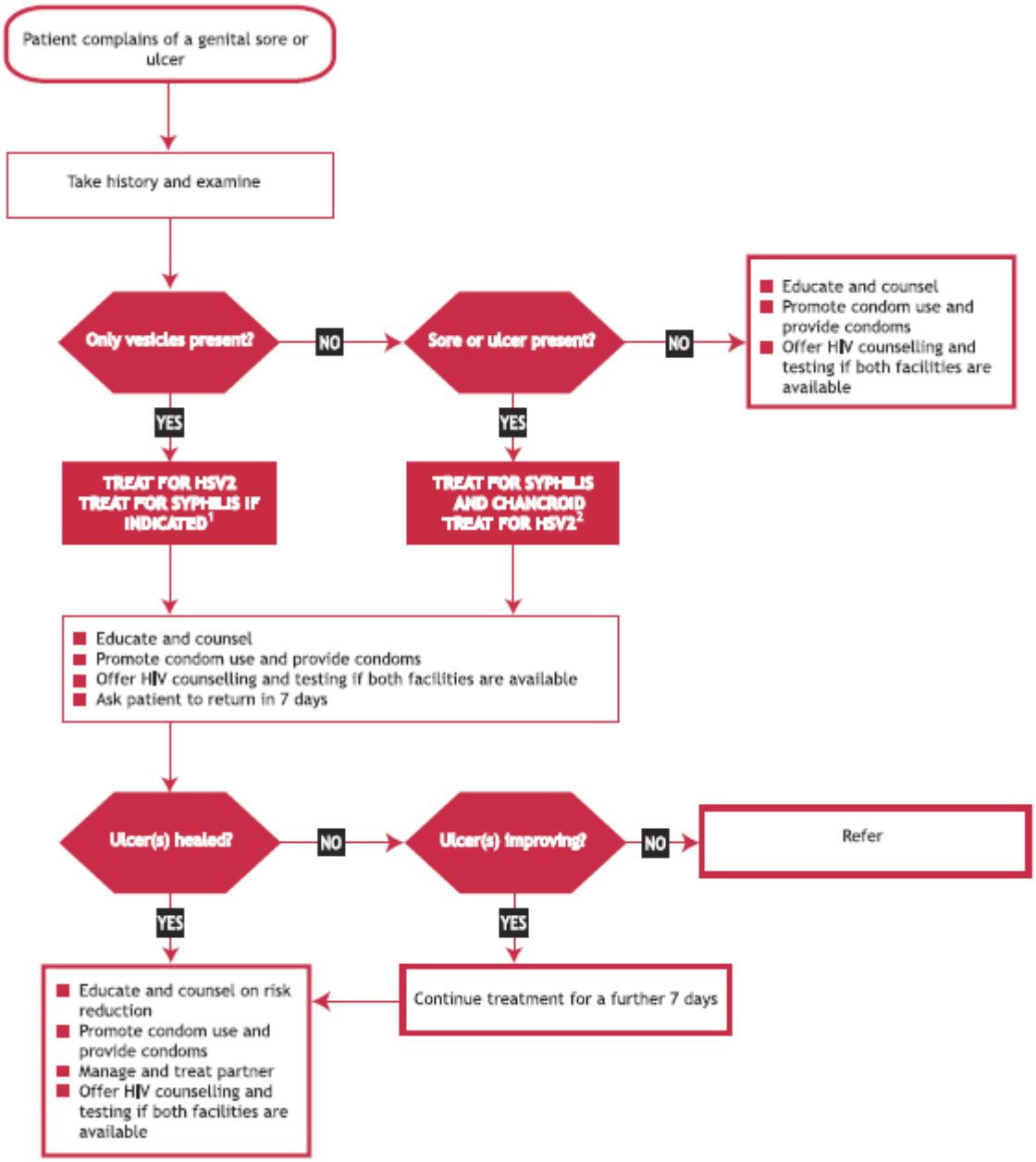


Abbreviations: GC = Gonococcal cervicitis; CT = *Chlamydia trachomatis*.
1. The definition of high prevalence levels, and potential risk assessments, are to be decided upon locally.

WHO: LOWER ABDOMINAL PAIN (WITH OR WITHOUT VAGINAL DISCHARGE)

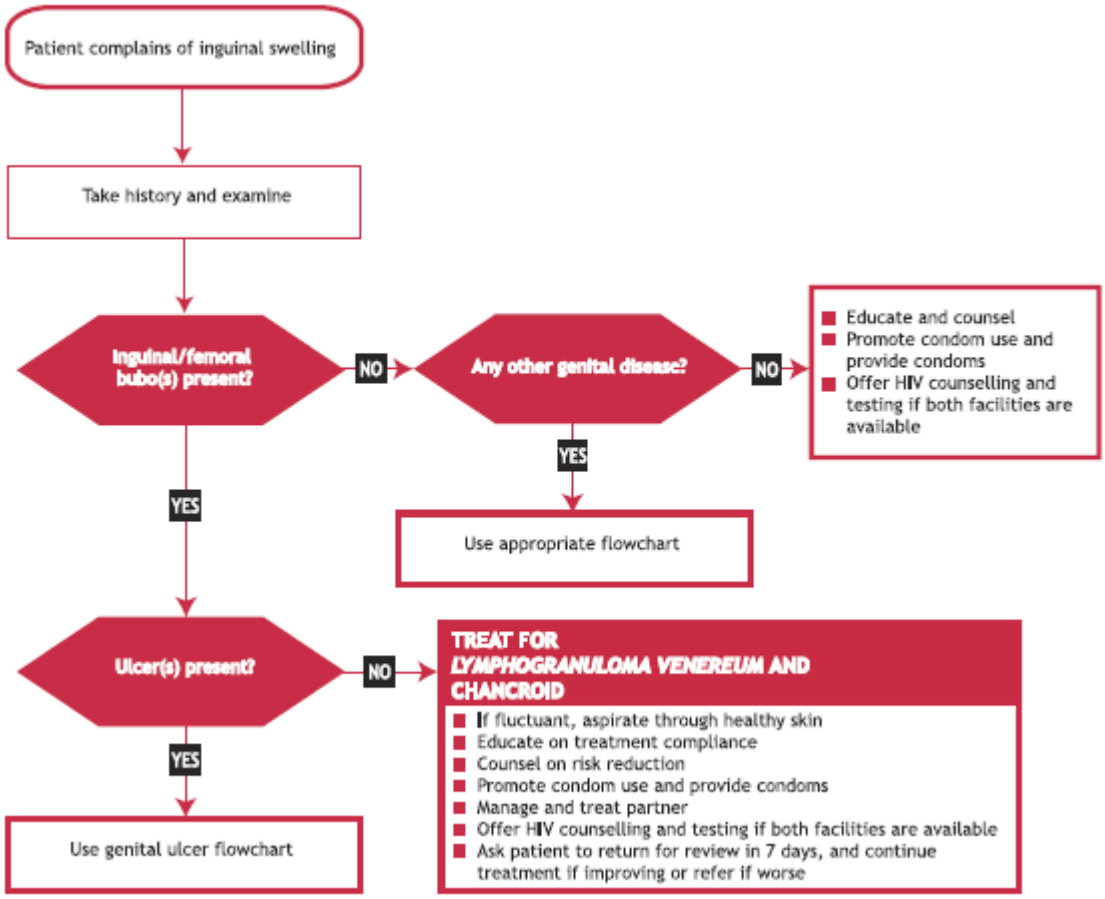


WHO: GENITAL ULCER DISEASE



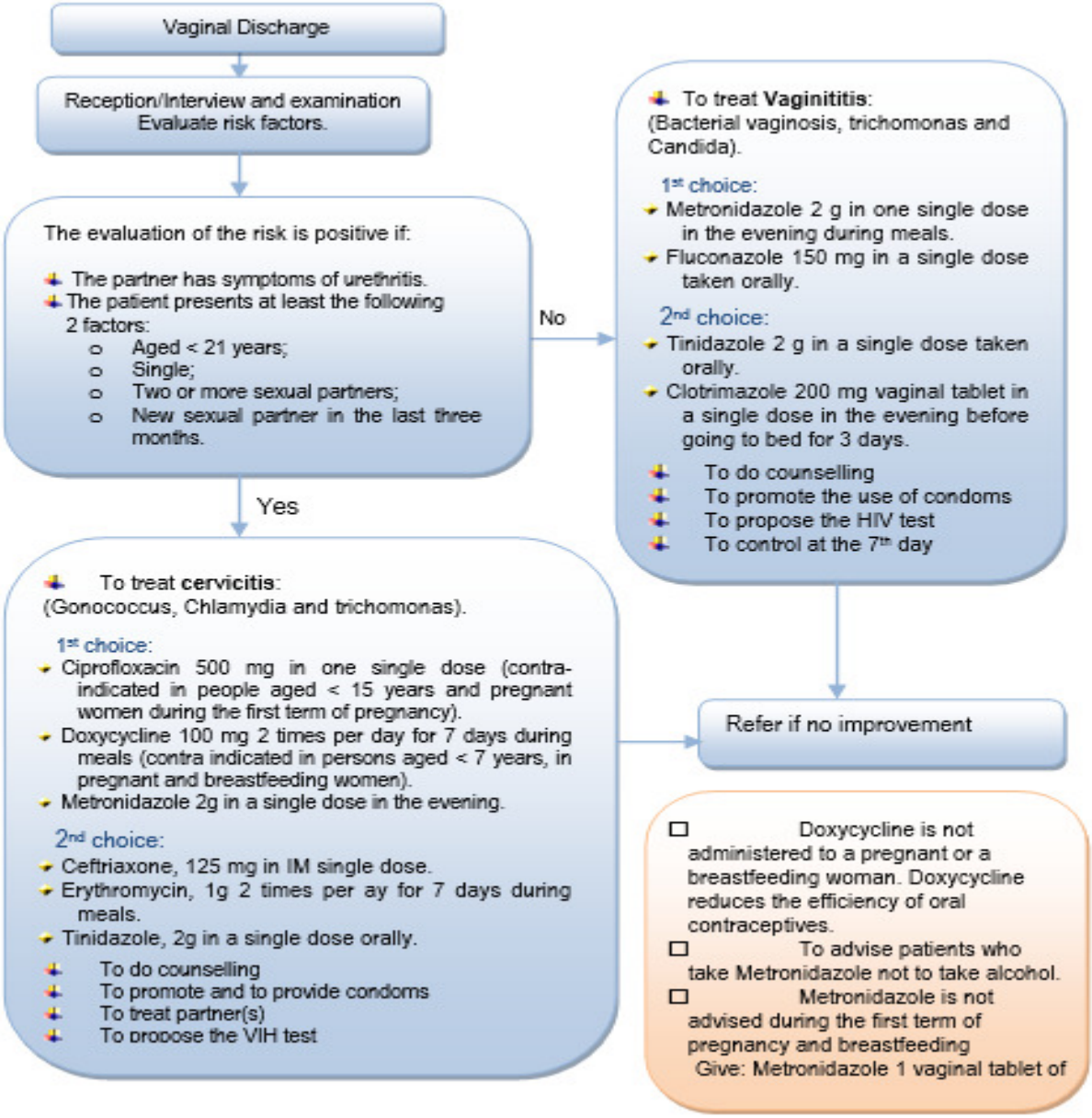
Abbreviations: HSV2 = herpes simplex virus type II.
1) To be treated for syphilis if RPR is positive and participant has not been treated for syphilis recently.
2) Treat for HSV2 where prevalence is 30% or higher, or adapt to local conditions.

WHO: INGUINAL SWELLING



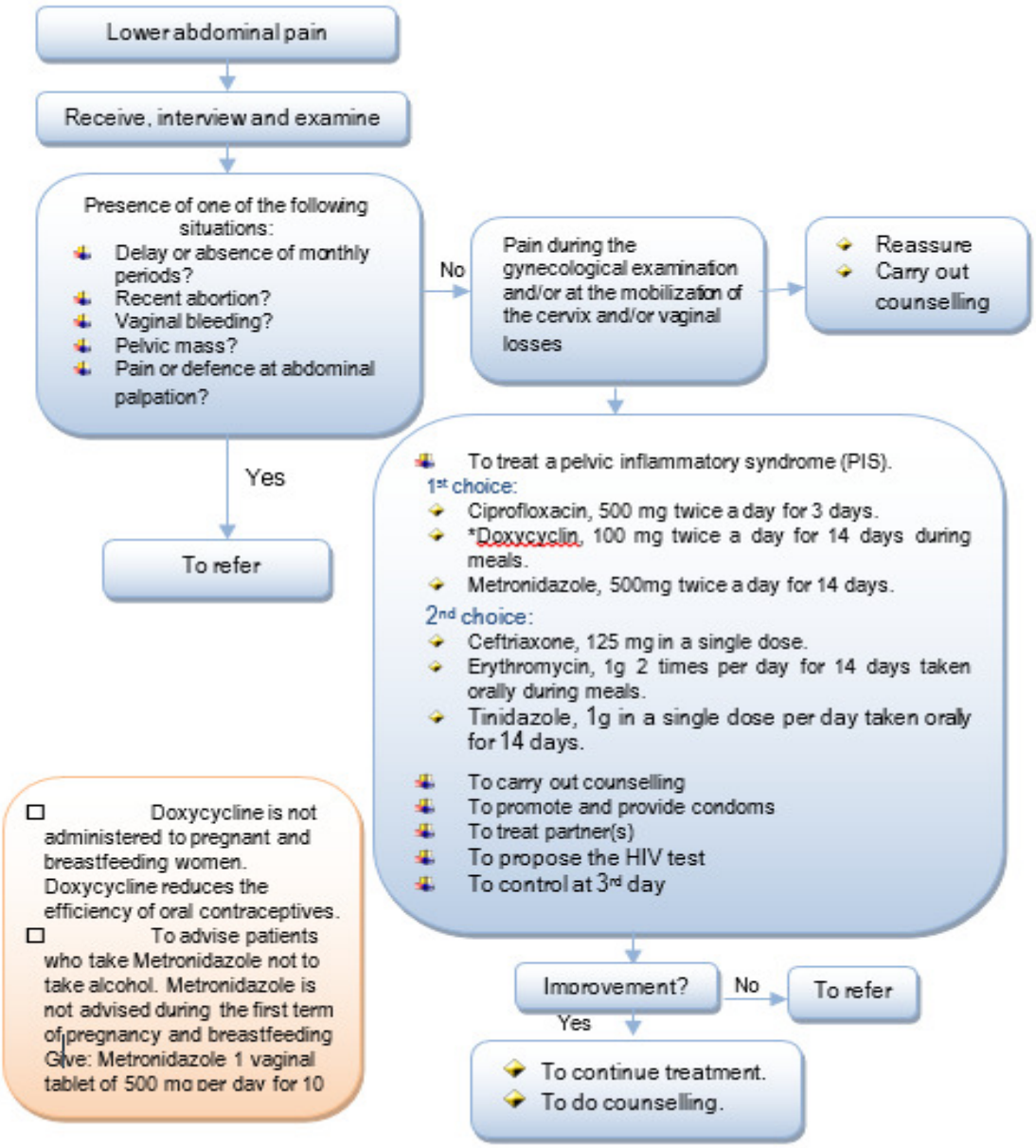
8.2 Rwandan Syndromic Management Algorithms

RWANDA: VAGINAL DISCHARGE SYNDROME (WITHOUT SPECULUM OR BIMANUAL EXAMINATION)
[A second algorithm is available for VDS with speculum/bimanual exam but is not included here].

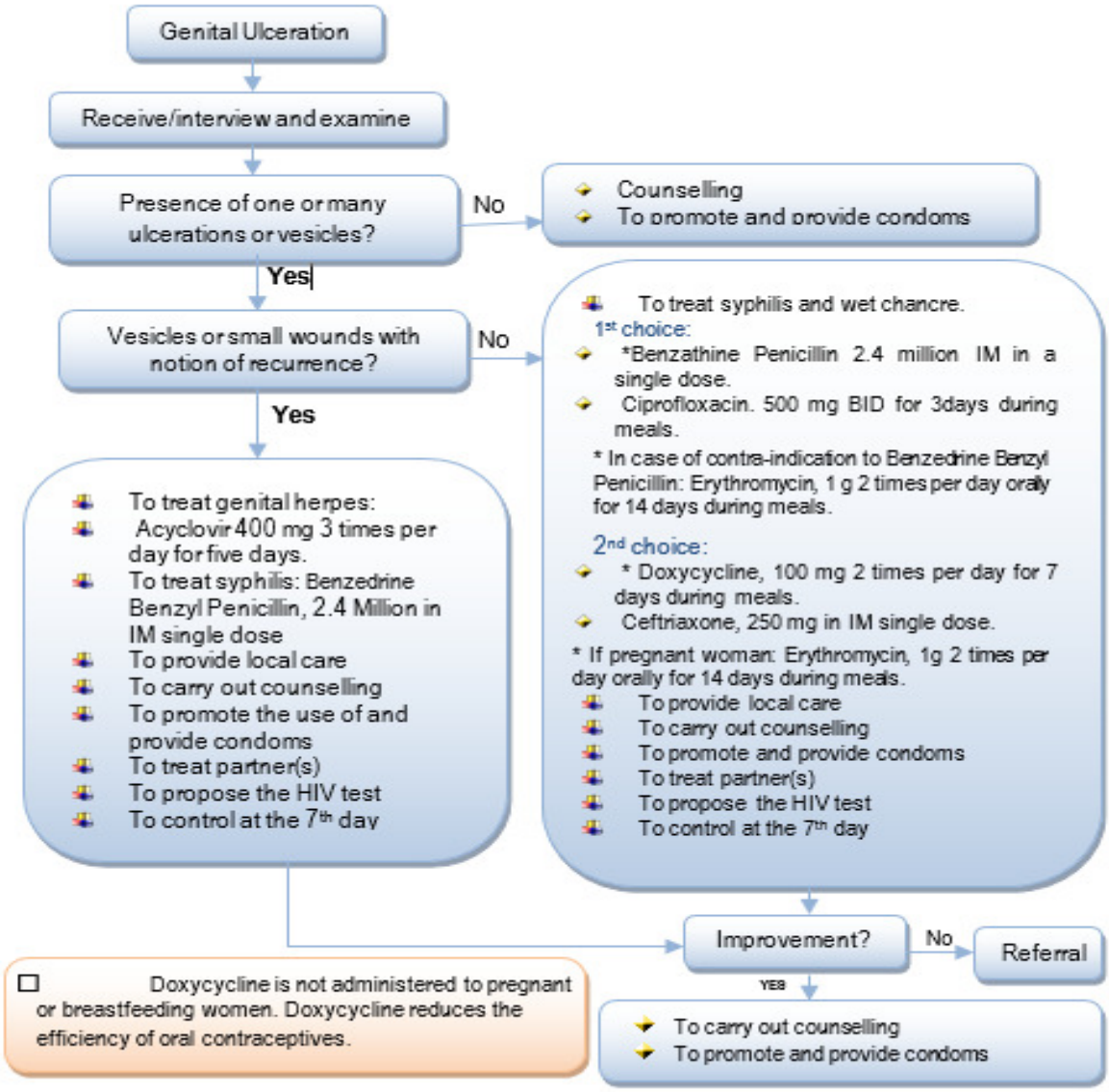


Abbreviations: IM = intramuscular; VIH = HIV

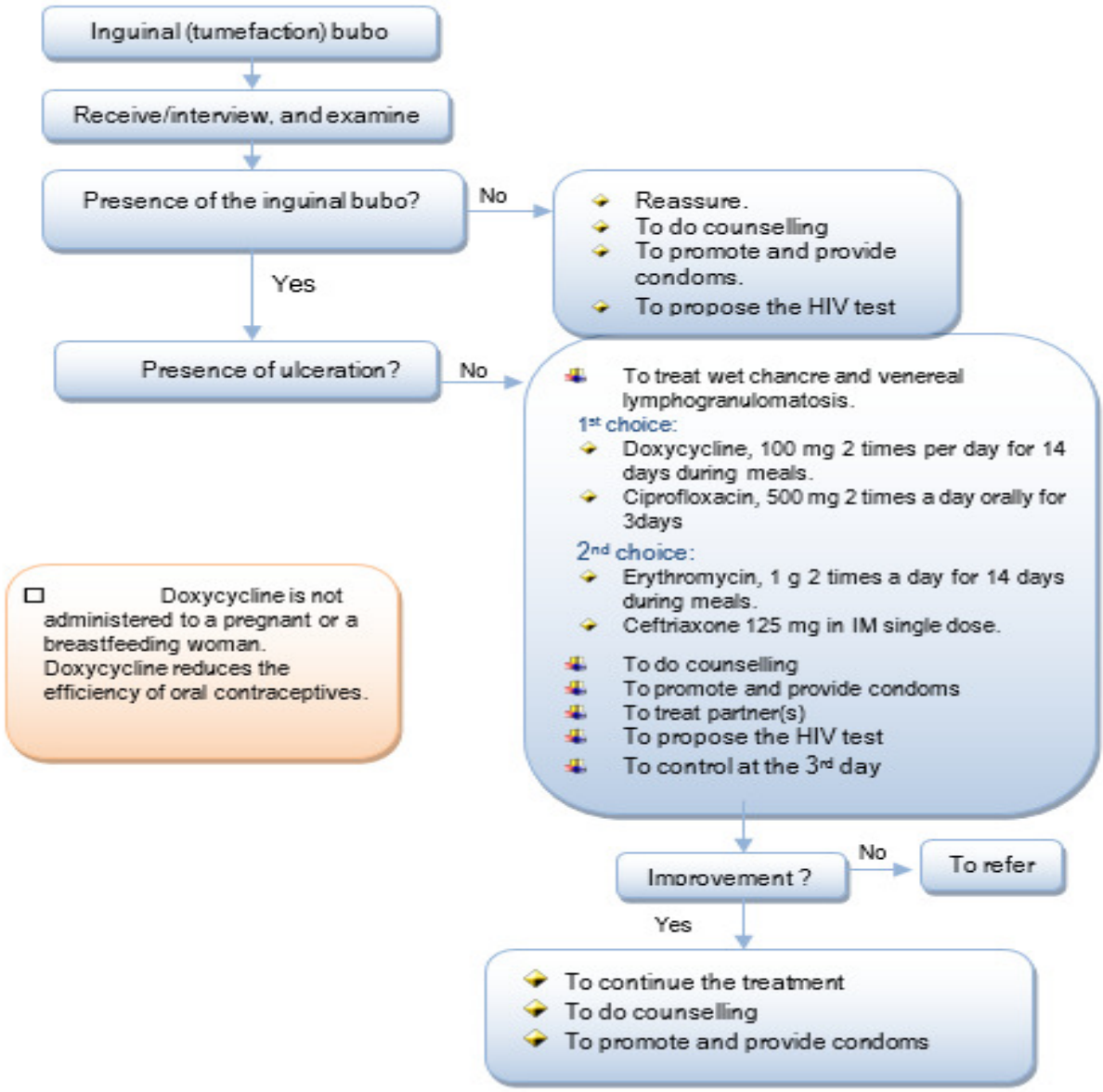
RWANDA: LOWER ABDOMINAL PAIN



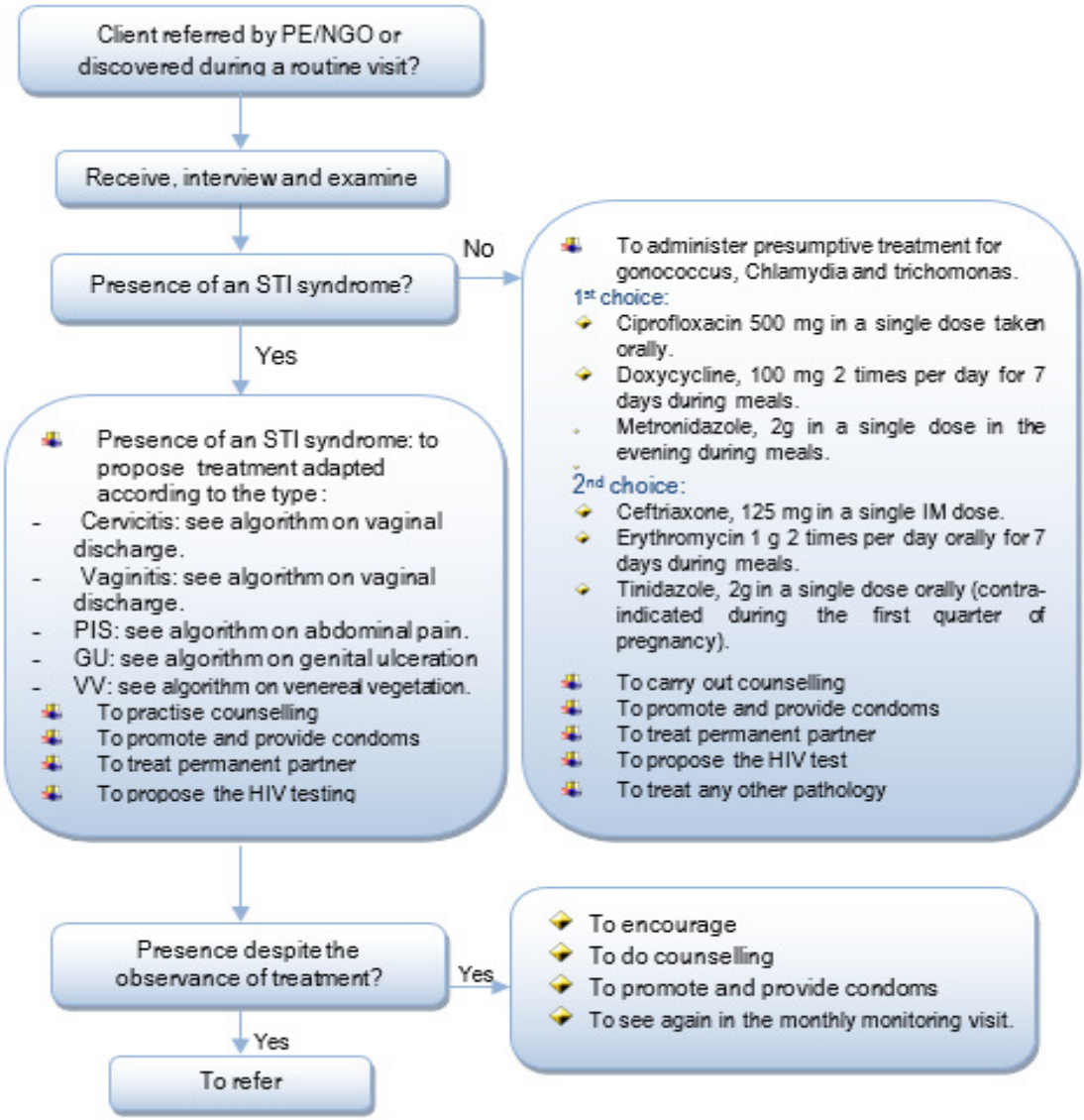
RWANDA: GENITAL ULCER SYNDROME



RWANDA: INGUINAL BUBO

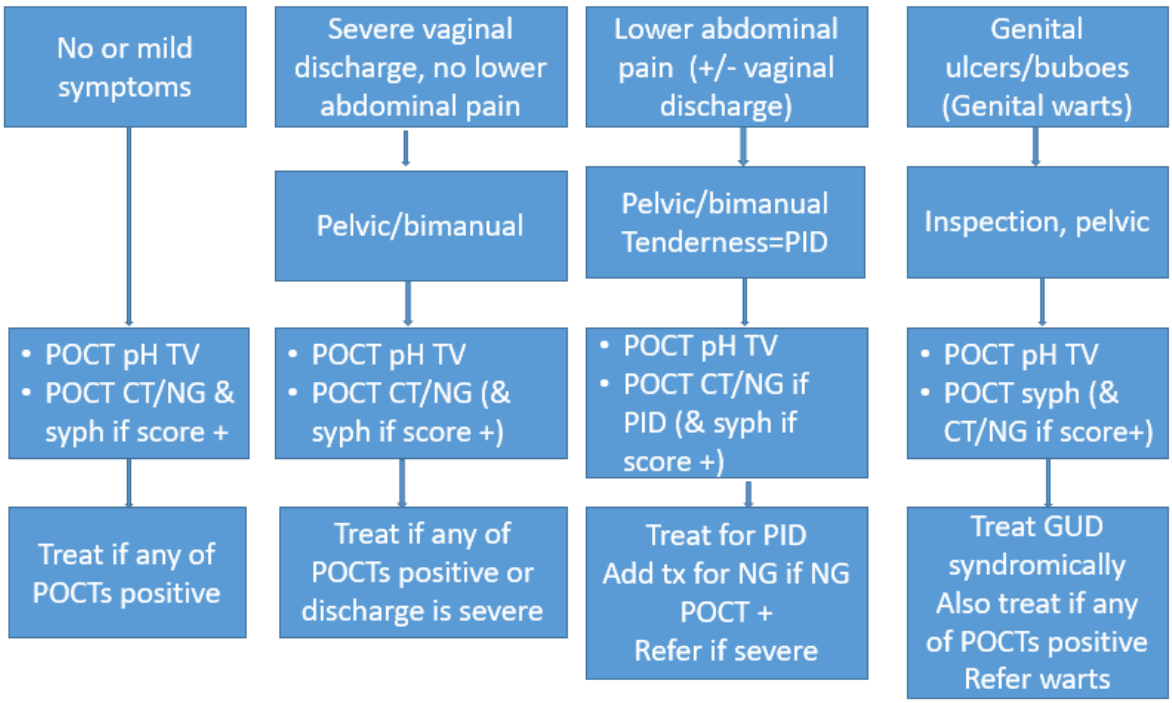


RWANDA: FEMALE SEX WORKERS



Abbreviations: GU = genital ulceration; IM = intramuscular; NGO = non-governmental organisation; PE = ?; PIS = pelvic inflammatory syndrome; STI = sexually transmitted infection; VV = venereal vegetation.

8.3 WISH Algorithms



In addition: UTI POC testing when relevant symptoms were reported; voluntary counselling and testing for HIV in accordance with the Rwandan national HIV testing algorithm; and syphilis RPR testing if the POCT was positive to determine if the infection was active.

Abbreviations: CT = *Chlamydia trachomatis*; GUD = genital ulcer disease; NG = *Neisseria gonorrhoeae*; PID = pelvic inflammatory disease; POCT = Point of Care test; TV = *Trichomonas vaginalis*.