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Refining *Trichomonas vaginalis* treatment in women and men: protocol for an open-label randomised comparison of multi-dose oral metronidazole versus single-dose oral secnidazole

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ABSTRACT

Introduction *Trichomonas vaginalis* is estimated to be the most common non-viral sexually transmitted infection (STI) worldwide with 156 million new cases each year. In 2021, the United States Centres for Disease Control and Prevention (CDC) updated their STI Treatment Guidelines to recommend multi-dose oral metronidazole (MTZ) for all *T. vaginalis*-infected women. Although multi-dose oral MTZ 500 mg twice daily was found to be superior to single-dose 2 g oral MTZ in multiple trials in women, multi-dose oral MTZ still had unacceptably high rates of breakthrough infection (9%–11%) at test-of-cure. With approximately 156 million cases of *T. vaginalis* worldwide per year, over 17 million persons per year are estimated to be insufficiently treated with multi-dose oral MTZ. Moreover, past trials only included women, and single-dose 2 g oral MTZ remains the recommended treatment for men. Thus, there is a critical need to further refine *T. vaginalis* treatment in women and men. A single dose of 2 g of oral secnidazole (SEC), a next generation 5-nitroimidazole with a longer half-life than oral MTZ and improved tolerability, may be a good option. This study will examine the effectiveness of multi-dose oral MTZ versus single-dose oral SEC in both men and women infected with *T. vaginalis*.

Methods and analysis This is a multi-centred open-label effectiveness trial comparing oral multi-dose MTZ (500 mg twice daily for 7 days) to 2 g of single-dose oral SEC. This trial aims to enrol 1200 *T. vaginalis*-infected women and men aged 18 years and older at four clinical sites: the University of Alabama at Birmingham (UAB) Sexual Health Clinic and the UAB Gynaecology Clinics in Birmingham, AL, LSU-CrescentCare Sexual Health Centre (LSUHSC-NO) in New Orleans, LA, and HealthCare Clinical Data, Inc. in Miami, FL. Those who are pregnant/lactating, have been treated with a 5-nitroimidazole within the last 28 days, used intra-vaginal boric acid or any other intra-vaginal treatment for *T. vaginalis* within the last 14 days, have a history of a type 1 hypersensitivity reaction to 5-nitroimidazoles, are taking phenytoin and/or warfarin, use any medications which may alter the metabolism of oral MTZ, or have previously been enrolled will be excluded from the study. Participants will be randomised in a 1:1 fashion to either multi-dose oral MTZ or single-dose oral SEC. A test-of-cure (TOC) visit will be performed 4 weeks after completion of treatment (window 1 week before and 2 weeks after scheduled TOC visit).

Ethics and dissemination This protocol is approved through a single Institutional Review Board (IRB) mechanism by the Tulane Human Research Protection Programme (Protocol # 2024–101 SPHTM). External relying sites are the UAB IRB (including both the UAB Sexual Health Research Clinic and Gynaecology Clinics; Protocol ID IRB-300012617), the LSUHSC-NO IRB (LSU-CrescentCare Sexual Health Centre; Protocol ID 6979) and the Advarra IRB (Healthcare Clinical Data Inc; Protocol ID Pro00085531). This study is also approved for referral

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is the first clinical trial to compare oral multi-dose metronidazole (500 mg twice daily for 7 days) to 2 g of single-dose oral secnidazole for the treatment of *T. vaginalis* in women and men.
⇒ Strengths of this study include strong proof-of-concept data, a multi-centred randomised trial approach, and use of nucleic acid amplification testing (NAAT) to assess *T. vaginalis* infection status at enrolment and test-of-cure visits.
⇒ An additional strength is the robust, multi-modal assessment of medication adherence during the trial, including text messaging, surveys and pill counts, which will take place during the course of the trial.
⇒ One limitation is the feasibility of enrolling the large number of participants needed for this trial, particularly *T. vaginalis*-infected men.
⇒ Another limitation is the exclusion of pregnant/lactating women in the trial, resulting from the current lack of safety data regarding oral secnidazole use during pregnancy/lactation.

purposes only by the Research Review Committee at the Jefferson County Department of Health (JCDH) Sexual Health Clinic in Birmingham, AL (JCDH Research Number 2024–03). Study findings will be presented in scientific conferences and peer-reviewed journals, shared with treatment advisory boards, as well as disseminated to providers and patients in communities of interest. The study Data Safety and Monitoring Board (DSMB) will meet twice a year to review patient safety data and study progress and provide recommendations on the study's continuation or modification.

Trial registration number NCT06261840.

INTRODUCTION

Trichomonas vaginalis is estimated to be the most common non-viral sexually transmitted infection (STI) worldwide with 156 million new cases annually.[1] *T. vaginalis* is highly prevalent, causes considerable and costly perinatal/reproductive morbidity,[2–4] disproportionately affects persons of colour (POC),[5] and can amplify HIV transmission.[6–8] For several decades, the Centres for Disease Control and Prevention (CDC) has recommended single-dose 2 g oral metronidazole (MTZ) as the treatment of choice for *T. vaginalis* infection in women and men.[9] Discovery of high breakthrough rates with this regimen in women placed this guidance into question.[10] We subsequently completed two randomised controlled trials (RCTs) of single-dose 2 g oral MTZ versus multi-dose oral MTZ 500 mg twice daily for 7 days in both HIV-infected and HIV-uninfected women, respectively, and found that the multi-dose regimen was superior to single-dose in both studies.[11 12] This led to the CDC updating their recommendations in the 2021 STI Treatment Guidelines to use multi-dose oral MTZ for all *T. vaginalis*-infected women.[13] Since neither trial included men and there are few such data in men, single-dose 2 g oral MTZ remains the recommended treatment for men.[9] In both female trials, even though multi-dose oral MTZ was found to be superior to single-dose oral MTZ, multi-dose oral MTZ still had unacceptably high rates of breakthrough infection at test-of-cure (9%–11%).[11 12] With approximately 156 million cases of *T. vaginalis* worldwide per year,[1] over 17 million persons per year are estimated to be insufficiently treated with multi-dose oral MTZ. Thus, there is a critical need to refine *T. vaginalis* treatment recommendations, as well as to harmonise the treatment regimen in women and men. Single-dose oral secnidazole (SEC), a next generation 5-nitroimidazole, may be a good option.[14]

Our recent phase 3, randomised, double-blind, placebo-controlled, delayed-treatment trial found that single-dose 2 g oral SEC was superior to placebo in *T. vaginalis*-infected women with an efficacy of 92.2%.[15] This study, along with studies in Europe and Brazil,[15–17] led to U.S. FDA approval of single-dose 2 g oral SEC for *T. vaginalis* treatment in both women and men in 2021. Oral SEC has multiple benefits compared with multi-dose oral MTZ, including a longer half-life and improved tolerability.[18] Single-dose oral SEC poses less burden on the patient[19 20] and it is the only single-dose oral medication FDA-approved for the treatment of bacterial vaginosis (BV),[21 22] a common comorbidity among women with *T. vaginalis* infection.[23] On the other hand, oral MTZ is far less costly and can be given during pregnancy/lactation, in contrast to oral SEC, for which pregnancy data are limited.[24] However, no studies have directly compared multi-dose oral MTZ to single-dose oral SEC for *T. vaginalis* treatment in both women and men, which is our primary aim.

With this in mind, we aim to conduct a multi-centred, randomised trial to examine the effectiveness of oral multi-dose MTZ versus oral single dose SEC for *T. vaginalis*-infected women and men. Our secondary aims are as follows: 1) to examine if BV co-infection interferes with *T. vaginalis* treatment as was found in one study[12] but not another,[11] 2) to examine if oral SEC is superior to oral MTZ for the treatment of BV, 3) to examine participant preferences for the test-of-cure visit (in clinic or via telemedicine), and 4) to further examine the natural history of *T. vaginalis* infection, as several small studies, including ours, have found spontaneous clearance in a proportion of men,[25–27] placing the significance of treatment in all men into question.

OBJECTIVES

The primary aim of the study is to examine the optimal treatment for *T. vaginalis* infection in women and men by conducting an open-label, randomised, multi-centred, parallel, phase IV clinical trial comparing multi-dose oral MTZ (500 mg twice daily for 7 days) to 2 g single-dose oral SEC in *T. vaginalis*-infected women and men. We hypothesise that *T. vaginalis* repeat infection rates at test of cure (TOC) will be 1.75 times lower in the 2 g single-dose oral SEC arm versus the multi-dose oral MTZ arm.[11 12] The secondary aims are as follows: 1) To examine the influence of BV co-infection on the treatment of *T. vaginalis* among women. In our prior RCTs, treatment effects varied by BV status for HIV-infected women[12] but not for HIV-uninfected women.[11 12] We will examine if clinically diagnosed BV at baseline influences treatment effectiveness by arm. We hypothesise that BV will be highly prevalent but will not interfere with *T. vaginalis* treatment in either arm. 2) To examine if oral SEC is superior to multi-dose oral MTZ for the treatment of BV as measured by the OSOM BV Blue test (Sekisui Diagnostics, Burlington, MA)[28] at TOC. 3) To evaluate participant preference for the TOC visit (in clinic or via telemedicine). To increase accessibility for select participants, including men and asymptomatic women who would otherwise have difficulty returning to clinic for their TOC visit, we are offering the option of returning to clinic for the TOC visit or conducting this visit via telemedicine with home specimen collection for repeat *T. vaginalis* testing. 4) To further examine the natural history of *T. vaginalis* in women and men. Persons who previously tested positive for *T. vaginalis* by wet mount,[8] OSOM trichomonas test (Sekisui Diagnostics, Burlington, MA),[29] nucleic acid amplification test (NAAT), urinalysis and Pap smear[8] will

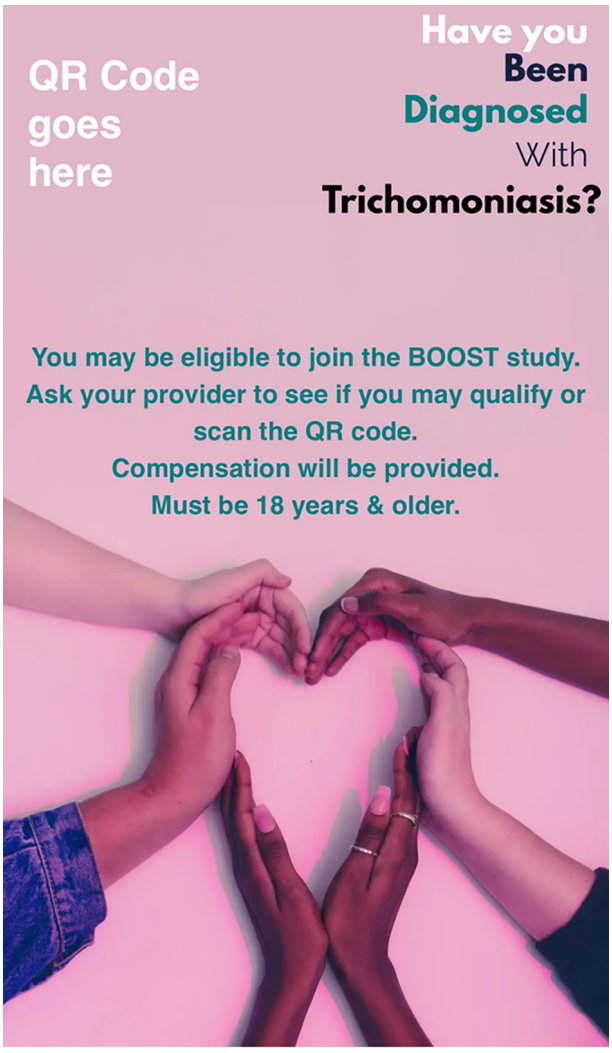

Figure 1 Clinical Flyer A.

be retested by NAAT at study enrollment. The rate of and time to early spontaneous resolution will be calculated. We hypothesise that men will clear infection at a higher rate than women.[25 30] We will also be obtaining and storing *T. vaginalis* clinical isolates for future 5-nitroimidazole drug susceptibility testing and research regarding drug resistance mechanisms in *T. vaginalis*. In addition to these secondary aims, we are collecting and banking *T. vaginalis* cultures on women for a future examination of 5-nitroimidazole resistance.

Methods and analysis

Study design

How participants will be identified

All potentially eligible individuals testing positive for *T. vaginalis* as part of routine care at any of the study sites will be informed about the study. Additionally, potential participants will be recruited using study flyers (figures 1 and 2), social media campaigns (figures 3 and 4), word-of-mouth and referrals from local partnering clinics (including the UAB 1917 HIV Clinic and the Jefferson County Health Department Sexual Health Clinic in Birmingham, AL) and emergency departments (ie, the

Figure 2 Clinic Flyer B.

UAB emergency department). Enrolled participants will also be encouraged to refer their male and female sex partners to the study.

Intervention to be measured

This is an open-label, randomised, multi-centred, parallel, phase IV clinical trial comparing multi-dose oral MTZ

Figure 3 Social Media Flyer C.

Figure 4 Social Media Flyer D.

(500 mg twice daily for 7 days) to 2 g single-dose oral SEC for the treatment of *T. vaginalis* among infected women and men. The study will include two visits: a baseline enrolment visit and a 4 week post completion of treatment visit (window 1 week before and 2 weeks after scheduled TOC visit) TOC visit. The TOC visit will not take place before 3 weeks after the end of treatment to prevent the possibility of false positive results on repeat *T. vaginalis* NAAT testing.[31]

This intended sample size is 1200 women and men aged 18 years and older with a positive *T. vaginalis* rapid antigen test (OSOM trichomonas test, Sekisui Diagnostics, Burlington, MA),[32] positive wet mount microscopy with motile trichomonads,[8] positive urinalysis for *T. vaginalis*,[8] positive *T. vaginalis* nucleic acid amplification test (NAAT) or positive Pap smear[8] for *T. vaginalis* within 2 weeks of available results who have not yet been treated for this infection. Additionally, participants must be willing and able to provide written informed consent and HIPAA attestation to comply with the study protocol, have a reliable method of contact (phone, email or social media), and be willing to be randomised. Participants will be excluded from the study if they are pregnant/lactating or seeking to become pregnant, have been treated with a 5-nitroimidazole (ie, MTZ, tinidazole (TDZ) or SEC) within the last 28 days, used intravaginal boric acid or any other intravaginal treatment for *T. vaginalis* within the last 14 days, have a history of a type 1 hypersensitivity reaction to 5-nitroimidazole medications, are taking phenytoin and/or warfarin due to drug-drug interactions with oral MTZ, are taking medications which may alter the metabolism of MTZ including lithium and barbiturates (amobarbital, butalbital, methohexital, phenobarbital, pentobarbital, primidone and secobarbital) or have been previously enrolled in the study.

Once study staff have screened potential participants for eligibility, those who are eligible will be invited to join the study and written informed consent will be obtained. After consent, women will be asked to provide a urine specimen for pregnancy testing. Those found to be pregnant will be dropped from the study (ie, screen failure) and referred to prenatal care. This will be followed by a computer-assisted, self-administered survey (CASI) including sociodemographic data, current genital symptoms, STI history data and sexual behaviour data by partner. Then baseline genital specimen collection (table 1) will take place including self-collected vaginal specimens for women and a first catch urine for men. Women will obtain three self-collected vaginal specimens for *T. vaginalis* NAAT, OSOM BV Blue testing and *T. vaginalis* culture. Only the UAB and LSUHSC-NO clinical sites will be collecting a vaginal specimen from women for *T. vaginalis* culture as Healthcare Clinical Data, Inc. does not have the capacity to perform *T. vaginalis* culture. The urine specimen obtained from men will be used for *T. vaginalis* NAAT.

Treatment randomisation

Randomisation envelopes were prepared prior to the study start by our study statistician using the randomizer.org website. A blocked scheme (by site) was used to avoid 'runs' in the randomisation process.[33] Arm was written on a card, sequentially numbered and then the envelope was sealed. Staff are required to take the next envelope in sequence. Adherence to the sequence is checked on REDCap monthly by our Data Manager and at annual site visits by checking the randomisation cards in the patient's study record. The Data Centre retains a sealed list of randomisation to check for accuracy.

After the collection of enrolment specimens, participants will be randomised to one of the treatment arms (multi-dose oral MTZ or single-dose oral SEC) and will be counselled to avoid interval sexual activity while on treatment and to refer all sexual partner(s) during the past 60 days for STI testing and treatment as a contact to *T. vaginalis*. All participants randomised to the oral multi-dose MTZ arm will receive the first dose of the medication while in the clinic. All participants randomised to the oral SEC arm will receive the single dose of oral SEC while in the clinic. As 2 g of oral SEC comes in a granular formulation, a single dose will be mixed in one serving of applesauce, pudding or yoghurt, and participants will be instructed to consume the entire serving followed by drinking a glass of water. All participants will be observed for 30 min after medication administration. Participants who vomit before the 30-min observation period following medication administration will be re-dosed with the same medication if they are agreeable. If they vomit again in the next 30 min, they will be withdrawn from the study and treated according to the standard of care. Participant contact information will then be obtained

Table 1 Study Data Collection Schedule

	Source	Pre-screen	Enrollment visit	2 days after enrollment	7 days after enrollment	TOC visit
Prior positive T. vaginalis test in the last 2 weeks. (This is done as standard of care at referring clinics and includes: wet mount, OSOM trichomonas test, *T. vaginalis* NAAT test, urinalysis, and/or Pap smear	Self-collected or provider-collected vaginal swab and/or urine (female) and urine (male)	X				X
Written informed consent/ HIPAA (REDCap or paper)	Computer/ research staff		X			
Specimen collection for study procedures	Women: urine for pregnancy test and three self-collected vaginal specimens: *T. vaginalis* InPouch culture (LSUHSC, and UAB clinical sites only), OSOM BV test*, *T. vaginalis* Men: urine for *T. vaginalis* NAAT		X			X
Survey (REDCap)	Computer survey		X			X
Randomisation	Envelope		X			
Medication instruction and counselling	Provider or research staff		X			
Dispense medication/30 min observation period	Provider or research staff		X			
Complete contact information form/ Scheduling TOC visit	Computer		X			
Adverse Events Assessment	Computer		X	X	X	X
Twice daily text messages (multi-dose oral MTZ arm only)	Computer survey			X	X	
Participant Reimbursement	Provider or research staff		X			X
Scale/pill counts (multi-dose oral MTZ arm only)[34]	Computer/provider					X

*BV testing at the TOC visit is only being performed for women who have a positive BV test at enrollment or who have symptoms at the TOC visit.
LSUHSC, LSU-Crescent Care Sexual Health Centre; MTZ, metronidazole; NAAT, nucleic acid amplification testing; TOC, test-of-cure; UAB, the University of Alabama at Birmingham .

and they will be given an appointment for their TOC visit 4 weeks after completion of treatment (window 1 week before and 2 weeks after the scheduled visit). Participants randomised to oral multi-dose MTZ will be instructed to bring their pill bottle back to the clinical site for their TOC visit (or show their pill bottle to research personnel if doing a telemedicine TOC visit) for a pill count.

Methods to increase retention

The TOC visit will be scheduled for 4 weeks after completion of treatment, thus 4 weeks for SEC arm and 5 weeks for MTZ arm. Participants are given an appointment card and receive a text reminder several days before the visit and are called to reschedule if they do not attend the scheduled visit. All participants will be compensated with $75 for their participation at the enrolment visit.

Adherence to the multi-dose oral MTZ arm in three ways during the course of the trial: (1) a daily text message assessment for the 7 days that participants will be on the medication, (2) an assessment of adherence using components of the Morisky, Green, Levine scale[34] on the

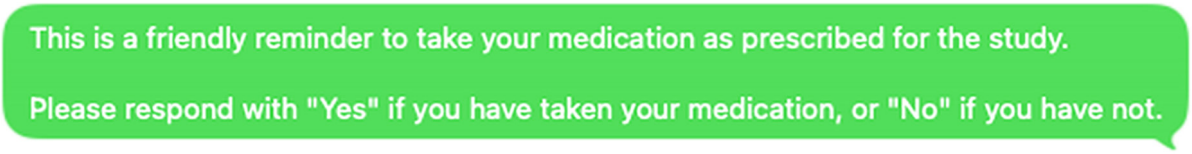

Figure 5 Reminder Text for Multi-Dose Oral MTZ Arm.

TOC survey,[34] and (3) a pill count at the TOC visit. If a participant indicates that they did not take their medication during this 7 day period, they will receive a text message asking if they took their medication (figure 5) and, if not, ask them why, as depicted in figure 6.

Clinical *T. vaginalis* isolates to be obtained for future research (with written participant permission) will be grown using the *T. vaginalis* InPouch (BioMed Diagnostics, White City, OR) culture system. Once the InPouch culture is inoculated with one of the self-collected female vaginal specimens, it will be immediately incubated at 37 °C at each of the respective clinical sites and subsequently transferred on the same day to the UAB and LSUHSC-NO STI research laboratories, respectively, where it will continue to be incubated at 37 °C. The InPouch culture will be read under the microscope for positivity for 5 out of 7 days (barring weekends).[35] Positive *T. vaginalis* cultures will subsequently be frozen back at –80 °C and stored for future research.

At the TOC visit, participants will complete a brief CASI survey that elicits information on interval sexual exposure, medication adherence, alcohol consumption, interim treatment, partner treatment and medication side effects. Women will provide three self-collected vaginal specimens for *T. vaginalis* NAAT, OSOM BV Blue and *T. vaginalis* culture. Men will provide a urine specimen for *T. vaginalis* NAAT. All participants will be compensated with $75 at all sites except LSU-CrescentCare, which compensates $50 for their participation in the TOC visit. Participants who will not or cannot return to clinic for the TOC visit will be given a home testing kit with a pre-paid mailer at enrolment and a telemedicine TOC visit will be scheduled and conducted. All the same procedures as a face-to-face TOC visit will be performed at the telemedicine TOC visit. Participants will be told to mail the testing kit at the nearest post office. Study staff will call the participant the day after the telemedicine TOC visit to confirm their specimen has been mailed.

As one of the secondary aims is to compare the effectiveness of multi-dose oral MTZ to oral SEC for the treatment of BV, all women will be tested for BV at enrolment using the OSOM BV Blue test and those who tested positive at enrolment will be retested using the OSOM BV Blue test at the TOC visit.

Study setting

We aim to enrol 1200 participants during a 4 year time period (2025–2029) at four clinical sites: (1) 400 participants at the UAB SHRC Clinic (2) 200 participants at the UAB Gynaecology Clinics, (3) 200 participants at the LSU-CrescentCare Sexual Health Centre, and (4) 400 participants at Healthcare Clinical Data, Inc. The UAB Gynaecology Clinics and Healthcare Clinical Data, Inc. only see women, thus men will only be enrolled at the UAB SHRC and LSU-CrescentCare clinical sites. Tulane University will be the data management centre for this clinical trial.

Data sources and variables

REDCap (Research Electronic Data Capture) will be the primary data collection and database management system for this study. Data from all study questionnaires and case report forms (CRFs) will be stored on REDCap and monitored by the Data Manager at Tulane University. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.[36 37]

Study questionnaires at the enrolment and TOC visits will be administered via the REDCap mobile application on a study device at each of the clinical sites. Data Access Groups (DAGs) will be used to prevent cross-site data access and facilitate each site's access to its own data. Participants enrolled in the study on the multi-dose oral MTZ arm will receive text messages to remind them to take their medication on a twice daily basis for 7 days and

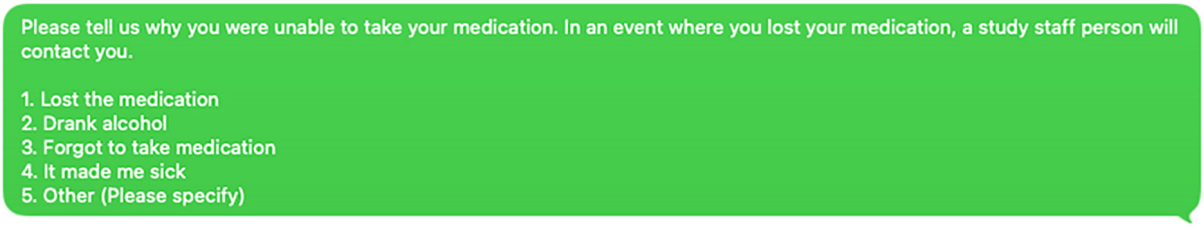

Figure 6 Text Message to Elicit Reasons Why Participants May Not Have Taken Their Oral MTZ.

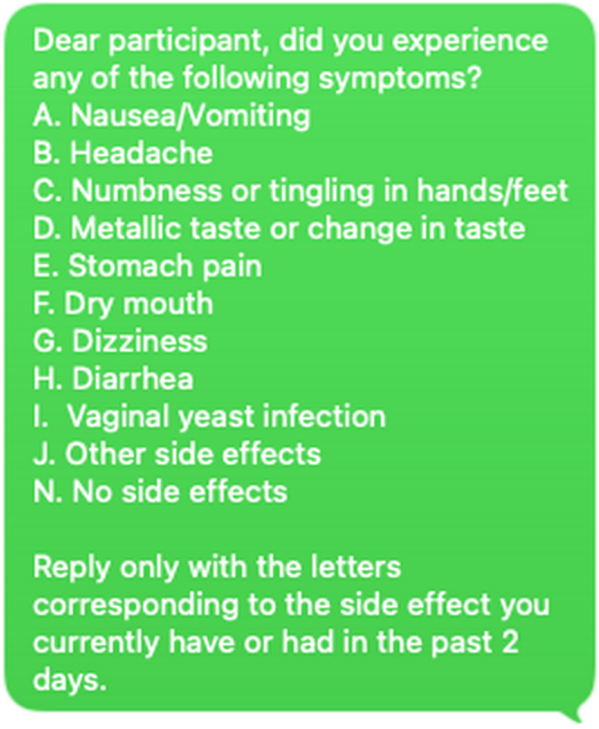

Figure 7 Text message for side effect assessment for all participants on study days 2 and 7.

to inquire whether they have experienced any adverse effects after taking their medication (Days 2 and 7) (figure 7). Participants on the single dose oral SEC arm will also receive text messages on days 2 and 7 to inquire whether they have experienced any adverse effects after taking the medication. The device on which this service operates is a secure, password-protected device accessible only by authorised study personnel. If a participant does not answer the medication adherence or side effect text message questions, a study staff member from the site where the participant was enrolled will attempt to contact the participant and record the information on both paper CRFs and in the REDCap database.

If a participant declines to enrol in the study, the reason for refusal will be recorded in a study refusal log CRF. Refusal logs are sent to the Data Manager at the Tulane Data Centre on a monthly basis and will be entered onto a Qualtrics database.

Bias

While participants may experience social desirability bias while answering enrolment and TOC visit survey questions, the surveys are self-administered, which should mitigate this bias. Other potential threats to validity are if we encounter any issues with enrolling the intended sample size, if we experience a greater than anticipated (ie, 15%) loss-to-follow-up, or greater than anticipated spontaneous clearance of *T. vaginalis*. As minimal research has been conducted on *T. vaginalis* among men, we are uncertain how many men we will enrol. As such, we may not be able to do analyses stratified by sex for hypothesis testing but will examine gender differences by arm in a more descriptive manner.

Statistical power

Our most recent RCT comparing single-dose 2 g oral MTZ to multi-dose oral MTZ 500 mg twice daily for 7 days found a 11% breakthrough rate at TOC among women on the multi-dose oral MTZ arm.[11] In contrast, two contemporary studies that included the use of 2 g oral SEC for the treatment of *T. vaginalis* in women found an average 6% breakthrough rate at TOC.[15 17] Thus, we hypothesise that single-dose oral SEC will be superior to multi-dose oral MTZ for the treatment of *T. vaginalis*-infected women and men in our study. At a power of 0.80, alpha-0.05, and a 1:1 allocation, we will need 480 participants in each arm. We have inflated this number for a potential 15% of participants that will be administratively withdrawn for various reasons (ie, pregnancy at enrolment, negative repeat baseline *T. vaginalis* NAAT at enrolment, or other reasons discovered after randomisation) and 15% will be lost to follow-up at the TOC visit. Thus, we will need to enrol a total of 1200 participants in this clinical trial (figure 8).

Statistical analysis

Statistical analyses will be conducted by the study statistician at Tulane University using an a priori designed

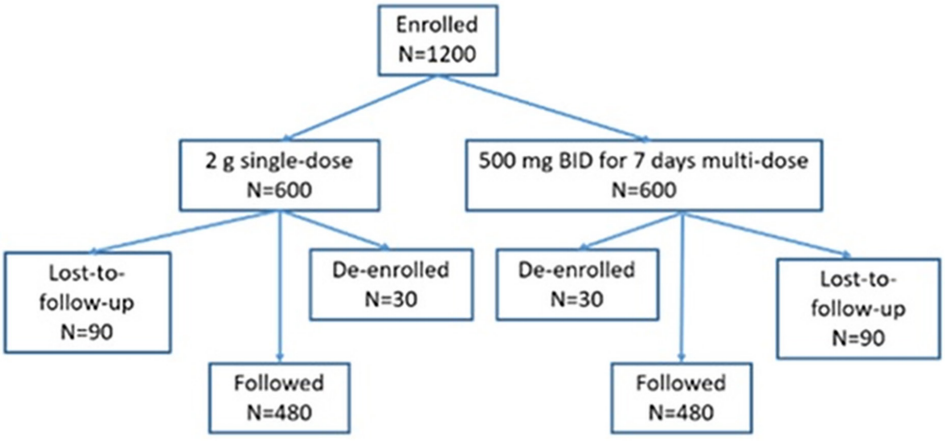

Figure 8 Participant randomisation scheme and study flow.

analytic plan. These analyses are independent of the funder (NIH). The outcome of interest for our primary aim (*T. vaginalis* infection rate at TOC) will be examined by arm (multi-dose oral MTZ vs single-dose 2 g oral SEC) at the TOC visit using two independent proportions (binomial) test or χ^2/exact test. As this is a phase IV open-label effectiveness study, we will not do an interim analysis (unless our Data Safety and Monitoring Board (DSMB) decides it is necessary). Statistical analysis of the data will follow the intent-to-treat principle, analysing each participant as randomly assigned, regardless of compliance with treatment. We expect a 15% loss to follow-up, and another 15% will be administratively de-enrolled for various reasons (as detailed previously).

Assessment of missing data

To assess if loss to follow-up and administrative withdrawals have produced bias in the analytic sample, we will examine select socio-demographic, clinical and behavioural (including medication adherence and sexual re-exposure) factors by follow-up status using χ^2 tests, t-tests and multivariable analyses. If there are differences between the baseline and follow-up datasets, we will conduct a series of sensitivity analyses, as we did in our recent RCT among *T. vaginalis*-infected women,[31] including multiple imputation for missing data and multivariable analyses. Point estimates and CIs will be compared from the complete case and multiple imputation analyses.[38] Additionally, we will discern if participants with a repeat positive *T. vaginalis* NAAT test at TOC are due to lack of adherence (for those on the multi-dose oral MTZ arm) or re-infection from an untreated sexual partner. We will reclassify the outcome accordingly and examine that in an additional sensitivity analysis. We expect the effect measures from the sensitivity analyses to be similar to the main analysis.

All analyses, summaries and listings will be performed using SAS software (version 9.4 or higher in a Windows environment). Analyses will be conducted by the Data Manager under the direction of Drs. Kissinger, Muzny and Srivastav (study statistician) in an intent-to-treat manner with variables categorised per protocol. For secondary aim 1), we will conduct a stratified analysis of TOC NAAT results by arm by enrolment BV status at trial enrolment. For secondary aim 2), we will conduct a similar analysis and sensitivity analyses as for the main analysis, but we will examine BV by arm as the main analyses. For secondary aim 3), we will compare those who choose a home telemedicine visit for their TOC visit compared with an in-person clinic visit by demographic and behavioural characteristics using bivariate and multivariable analyses. For secondary aim 4), we will conduct time to event analysis to examine the rate of early spontaneous resolution of *T. vaginalis* (ie, negative enrolment *T. vaginalis* NAAT test), stratified by sex.

Data management and confidentiality

Drs Kissinger and Muzny will serve as the study co-PIs and all co-investigators will be accountable to them. They will be overseen by the DSMB and the National Institutes of Allergy and Infectious Diseases (NIAID) Project Officer. Tulane University will serve as the Data Management Site. The Data Manager at Tulane University will be supervised by Drs. Kissinger, Muzny and Srivastav. As previously mentioned, there will be four clinical sites enrolling in this study: the UAB Sexual Health Research Clinic (SHRC), the UAB Gynaecology Clinics, LSU-CrescentCare Sexual Health Centre and Healthcare Clinical Data Inc. The Research Coordinator(s) and site PIs will supervise each study site's research personnel (ie, research coordinators, nurses and nurse practitioners) who will screen, enrol and follow all participants. The Tulane site will serve as the Data Management Centre. Dr Kissinger has managed three prior large NIH trials[23 31 39] and numerous other cohort studies[6 39–41] and is well equipped to manage the large amount of data that will be generated from this trial.[42–44] The study protocol and manual of operations will be posted on a password-protected study BOX folder, accessible to all research personnel involved with the study. Site study staff and co-investigators will prepare monthly recruitment and follow-up statistics that will be reviewed during monthly Zoom conference calls with the entire research team for the duration of the trial.

Patient and public involvement

Before the trial started, we conducted formative qualitative work to inform clinical trial recruitment approaches and study procedures (UAB IRB Protocol #: IRB-300012965 and Tulane IRB-2024-906). This work was essential in ensuring that the perspectives and experiences of the intended participant populations were incorporated into all aspects of the study. In October 2024, our research team, which has experience conducting sexual health qualitative research,[8 45–47] led five focus groups (two groups with women only and three groups with people of all genders), including a total of 18 participants. Ages of participants ranged from 19 to 47 years old and they were from New Orleans, LA (n=5), Birmingham, AL (n=12), or other locations (n=1). During the focus groups, participants were shown prototypical study flyers and asked to provide feedback and share their preferences for which would be most effective. They were also asked about their experiences and comfort levels with self-collecting urine and vaginal specimens at home as well as their input on feasibility and acceptability of telehealth for the TOC visit. All recruitment flyers and study procedures that were adopted for this clinical trial were informed by this work.

ETHICS AND DISSEMINATION

This protocol is approved through a single Institutional Review Board (IRB) mechanism by the Tulane Human Research Protection Programme (Protocol # 2024–101 SPHTM). External relying sites are the UAB IRB

(including both the UAB Sexual Health Research Clinic and Gynaecology Clinics; Protocol ID IRB-300012617), the LSUHSC-NO IRB (LSU-CrescentCare Sexual Health Centre; Protocol ID 6979) and the Advarra IRB (Healthcare Clinical Data Inc; Protocol ID Pro00085531). This study is also approved for referral purposes only by the Research Review Committee at the Jefferson County Department of Health (JCDH) Sexual Health Clinic in Birmingham, AL (JCDH Research Number 2024–03). Study findings will be presented in scientific conferences and peer-reviewed journals, shared with treatment advisory boards, as well as disseminated to providers and patients in communities of interest. The study Data Safety and Monitoring Board (DSMB) will meet twice a year to review patient safety data including symptoms and side effect monitoring, and study progress and provide recommendations on the study's continuation or modification. Protocol changes are communicated to all sites at monthly supervisory meetings and are approved by the Tulane IRB. The most recent protocol, ICF and HIPAA form are available for all sites on REDCap and in box.

DISCUSSION

The main strength of this study is that it is the first head-to-head comparison of multi-dose oral MTZ and single-dose oral SEC for both women and men infected with *T. vaginalis*. The use of a multi-centred randomised trial design with objective measurement of the outcome of interest will improve generalisability and validity. If it is found that single dose oral SEC is superior to multi-dose oral MTZ for the treatment of *T. vaginalis*; this could have far-reaching implications in future national and international STI treatment guidelines by modifying the currently recommended treatment regimens for women and men with *T. vaginalis* infection. Currently, treatment recommendations for *T. vaginalis* in the U.S. differ by sex.[9] Results from this clinical trial may help to harmonise treatment recommendations moving forward, particularly as most patients and providers prefer a single dose approach.[48] If oral SEC is found to be superior to multi-dose oral MTZ, there will be the benefit of having a highly efficacious single dose for treatment of *T. vaginalis*.

Despite this major strength of this study, there are limitations. It may be difficult to enrol a sufficient number of men in the study to examine the main analysis by sex, as men are not routinely tested for *T. vaginalis*. We will attempt to increase the number of men enrolled by asking female participants to refer their male sex partner(s). Additionally, single dose oral SEC is substantially more expensive than multi-dose oral MTZ and will not be available in generic format until 2035. Should single-dose oral SEC prove to be superior, the next step will be to initiate negotiations with the manufacturer of oral SEC to reduce costs.

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Contributors PJK and CAM conceived and designed the study. SS and PJK contributed to the data analysis plan. JA, RL, SC, CAM, ARK, MS and OTVG were involved in the implementation and management of the study. ARK, MS and PJK are managing the data acquisition. PJK and CAM drafted and revised the manuscript. All the authors read, revised and approved the final version of the manuscript. Dr Kissinger is the guarantor.

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Competing interests CAM has received research grant support to her institution from NIH/NIAID, Gilead, Abbott Molecular, Aim Max Therapeutics and BioNTech. CAM also reports honourarium and/or consulting fees from Abbott, bioMérieux, BioNTech, Cepheid and Elsevier. She is a member of the editorial board of the Merck Manuals and receives royalties from UpToDate. PJK has received research grant support to her institution from NIH/NIAID. She also received consulting funds from Abbott. RAL has received research grant support to her institution from NIH/NIAID, conducted clinical trials at her institution for Abbott, Becton Dickinson, bioMérieux, Cepheid, Chembio, Cue, Gilead, GSK, Hologic, LabCorp/Sequenom, Merck, Nanopath, QuidelOrtho, Roche, Sherlock and Visby; has served on an advisory board for Abbott, GSK and Roche; has served as a clinical advisor for Nanopath; and has received personal fees for educational events from bioMérieux, Cepheid, QuidelOrtho and Roche. OTVG has received research funding to her institution from Gilead Sciences, NIH/NIAID and BioNTech; consulting fees/honoraria paid to her from GSK, Abbott, ThermoFisher, bioMérieux and the American STD Association. JLA has received research grant support to her institution from Abbott, Abbvie, Bayer, Organon and PinkDx. She has also served as a consultant to Abbott. SEC has received research funding to his institution from Astellas, Cue, Signos Inc., Visby, Bayer and Cook MyoSite.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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