BMJ Open

Assessing the acceptability of, adherence to, and preference for a dual prevention pill (DPP) for HIV and pregnancy prevention compared to oral pre-exposure prophylaxis (PrEP) and oral contraception taken separately: protocols for two randomized, controlled, crossover studies in South Africa and Zimbabwe

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075381
Article Type:	Protocol
Date Submitted by the Author:	05-May-2023
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Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Clinical Trial, Decision Making

Protocol for DPP crossover studies in South Africa and Zimbabwe

ABSTRACT

Introduction: Oral pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention method; however, uptake and persistence have been low among southern African women. A dual prevention pill (DPP) that combines PrEP with oral contraception (OC) may increase PrEP use and better meet women's sexual and reproductive health needs. We will gauge the DPP's acceptability in two crossover clinical trials.

Methods and Analysis: PC952 (Zimbabwe) and PC953 (South Africa) will compare acceptability, adherence, and preference for an over-encapsulated DPP versus PrEP and OCs taken separately. HIV-negative, non-pregnant cis-gender females in Johannesburg, South Africa (n~96 16-40-year-olds) and Harare, Zimbabwe (n~30 16-24-year-olds) will be randomized 1:1 to the order of regimens – DPP or 2 separate tablets – each used for 3 28-day cycles, followed by a 6-month Choice period in South Africa. Monthly clinic visits include HIV and pregnancy testing; safety assessments; and risk reduction and adherence counselling. We will assess adherence (monthly) based on tenofovir diphosphate drug levels in dried blood spots and by self-report. We will evaluate acceptability (monthly) and preference (end of crossover) via computer assisted self-interviewing and in-depth interviews with a subset of participants. Data collection started in September 2022 and is projected to end by December 2023.

Ethics and Dissemination: PC952 was approved by the Ministry of Health and Child Care, Medical Research Council, Research Council, and Medicines Control Authority of Zimbabwe; the Chitungwiza City Health Ethics Committee; and the Joint Research Ethics Committee for the University of Zimbabwe Faculty of Medicine and Health Sciences and Parirenyatwa Group of Hospitals. PC953 was approved by the South African Health Products Regulatory Authority and the University of the Witwatersrand's Human Research Ethics Committee. The Population Council IRB approved both studies. We will disseminate results in open access journals, clinical trials registries, and at local and international meetings and conferences.

Protocol for DPP crossover studies in South Africa and Zimbabwe

Trial registration: Both trials were registered on ClinicalTrials.gov on 3 March 2021: Zimbabwe: NCT04778514; South Africa: NCT04778527.

Keywords: HIV, HIV prevention, PrEP, oral contraceptive (OC), pregnancy prevention, dual prevention pill (DPP), multipurpose prevention technologies (MPT), randomized controlled trial, AGYW, South Africa, Zimbabwe.

Strengths and limitations of these studies

- These DPP studies will provide the first empirical evidence of whether women prefer a novel MPT option combining HIV and pregnancy prevention versus HIV prevention and pregnancy prevention separately, as indicated in multiple surveys and placebo studies.
- The two pilot studies enable early assessments of the DPP in two different contexts: South Africa (low COC use/high HIV incidence and prevalence) and Zimbabwe (high COC use/moderate HIV incidence and prevalence), and among AGYW and older women.
- The crossover design is advantageous as women will be able to directly compare taking the DPP (intervention) versus PrEP and COCs separately (standard of care) and enables a smaller sample size with women serving as their own controls.
- The key limitation of the studies is the use of an over-encapsulated DPP as a proxy for the ultimate co-formulated tablet, which may not accurately capture acceptability, preference and adherence for the eventual product which will be smaller and will be a tablet versus a capsule.
- Another limitation is the different study designs and sample sizes for the two studies, primarily related to their respective funding mechanisms, that may limit the ability to directly compare results from the two countries.

INTRODUCTION

Despite substantial advances in HIV treatment and prevention over the last decade, women and girls in eastern and southern Africa continue to be disproportionally affected by HIV/AIDS, accounting for 63% of all new HIV infections in the region in 2021 [1]. In 2021, new HIV infections in South Africa were more than double among women aged 15 and over than among men of the same age (130,000 versus 70,000, respectively) [2]. Similarly in Zimbabwe, nearly twice as many women 15 and older acquired HIV in 2021 compared to their male peers [1].

Oral pre-exposure prophylaxis (PrEP) is more than 90% effective in reducing HIV transmission [3]. However, many oral PrEP clinical trials and demonstration projects in sub-Saharan Africa have been plagued by low adherence, particularly among adolescent girls and young women (AGYW) [4,5]. Stigma and fear of intimate partner violence or relationship dissolution are often cited as reasons for non-use of PrEP [6–9]. Novel strategies to bolster uptake and adherence are needed to increase PrEP use among women and girls at high risk of HIV.

Many women – and AGYW in particular – are more worried about unintended pregnancy than HIV [10,11]. Furthermore, there is a growing body of evidence indicating that many women may be more likely to use an HIV prevention method that also prevents pregnancy [12–19]. Condoms are currently the only multipurpose prevention technologies (MPTs) that prevent both HIV and unintended pregnancy [20]. Male condoms, however, are not under a woman's control; female condoms have had limited uptake due to access and acceptability issues [21,22]; and many women risk gender-based violence by merely suggesting condom use [23]. Several novel MPTs are in the pipeline [24], including a dual prevention pill (DPP) containing the ingredients in PrEP and a combined oral contraceptive (COC). Current DPP development efforts are based on a 28-day COC regimen (150 mcg levonorgestrel [LNG], 30 mcg ethinyl estradiol [EE]) and a generic equivalent of Truvada® (300 mg tenofovir disoproxil fumarate [TDF], 200 mg of emtricitabine

[FTC]) [25] [26]. The DPP is likely to be the fastest route to an approved MPT as it contains two registered products that are safe and effective for their respective indications [27–30] with no evidence of drug-drug interactions [31–34]. In South Africa 25.6% of women report ever having used COCs and 10.5% currently use them [35,36]. In Zimbabwe, COCs are the most common family planning (FP) method, used by 57% of women on contraceptives [37]. Truvada® is approved as PrEP in more than 20 countries globally, including South Africa and Zimbabwe, and is recommended by WHO and CDC for women at risk of HIV using COCs [29,38],

We hypothesize that the DPP could greatly increase PrEP adherence, while also meeting women's unmet FP needs. Our goal is to generate data to inform DPP introduction through two clinical crossover studies comparing acceptability of, adherence to, and preference for the DPP versus two separate tablets. To that end, and in parallel with development of the co-formulated DPP, we have over-encapsulated PrEP and a COC into a single capsule (**Figure 1**) for our studies to provide an early indication of DPP acceptability.

INSERT FIGURE 1 HERE

METHODS AND ANALYSIS

Trial Design

(Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines used.) Population Council Protocols 952 and 953 are randomized, controlled, open-label, parallel group, crossover studies.

Participant and public involvement

Formative research (December 2020-June 2021) with service providers and potential end users in South Africa and Zimbabwe informed the clinical trial design, materials, and recruitment

methods. Established community and/or youth advisory groups at each site reviewed the protocols and provided input into the consent forms, behavioral questionnaires, and translations. The study teams have also benefitted from participation in the DPP consortium, a collaborative group of researchers, donors, and civil society advocates established to inform and accelerate DPP development and introduction [39].

Study settings

Hillbrow (Johannesburg), South Africa

PC953 is being conducted at the Wits RHI Research Centre, a large research clinic situated in Hillbrow, Johannesburg. As of 2020, Johannesburg had 756,751 people living with HIV with an overall HIV prevalence of 13%. HIV prevalence was highest among females across all age groups: 28.3% for 25-49-year-olds, 15% for women 50 and above and 9% for 15-24-year-olds [40]. Wits RHI conducts research on HIV, sexual and reproductive health (SRH) and vaccine preventable diseases.

Chitungwiza (Harare), Zimbabwe

PC952 is being implemented by the University of Zimbabwe Clinical Trials Research Centre (UZ-CTRC) at the Zengeza Clinical Research Site (CRS) in Chitungwiza, Zimbabwe's second largest city approximately 30km south of Harare, with a generalized epidemic and HIV prevalence of 3.8% among 15-19-year-old women and 6.3% among 20-24-year-old women [41]. The Zengeza CRS is located within one of four Chitungwiza City Health Department's Municipal Clinics and conducts research on female-controlled HIV/STI prevention strategies, including microbicides, oral and injectable PrEP and cervical barriers, and integrated strategies for HIV prevention.

Study populations

We are recruiting potential participants (~96 16-40-year-olds, South Africa; 30 16-24-year-olds, Zimbabwe) from FP, PrEP and SRH clinics, and the general population. Although the DPP is likely to appeal to a range of individuals, including those using other contraceptives or with an unmet FP need, we are enrolling participants who are already using COCs in these pilot acceptability studies because they are already accustomed to taking a daily pill with any associated side effects.

Inclusion/Exclusion Criteria

Eligible participants are healthy, HIV-negative, non-pregnant, sexually active, cis-gender females at moderate to high risk of HIV infection. Specific eligibility criteria (**Table 1**) for the two protocols are similar, with several differences (such as age range). Women are screened by nurses/clinicians based on medical history, physical examination, and clinical laboratory tests. HIV risk is assessed by clinicians using local PrEP guidelines and by participants who are offered access to tools, such as BWise [42], to help them make that determination. Key exclusion criteria and prohibited medications relate to contraindications for COCs or PrEP use (such as rifampicin, anticonvulsants), and inability to swallow a large vitamin pill similar in size to the over-encapsulated DPP (**Figure 1**).

Table 1. Inclusion and exclusion criteria for South Africa (SA) and Zimbabwe (Zim)

Criteria	SA	Zim
INCLUSION CRITERIA		
Age 16 through 40 years old (inclusive) at Screening, verified per site-specific SOPs.	X	
Age 16 through 24 years old (inclusive) at Screening, verified per site-specific SOPs.		X
Able and willing to provide informed consent per site SOPs. (If under the legal age of consent [18 years old] be able to provide informed assent and obtain parental or guardian consent, to be screened for and to enroll in the study.)	X	X
Fluent in spoken Zulu and/or English.	X	
Fluent in spoken Shona and/or English.		X
Able and willing to provide adequate locator information, as defined in site SOPs.	X	X
Able and willing to comply with all study procedures, including being comfortable taking the study products as evident by nurse/clinician-observed swallowing at Screening of a large Vitamin capsule that is of similar size to the study products.	X	X
Post-menarche, per participant report at Screening.	X	X
Sexually active, defined as having had penile-vaginal sex with a male within the 3 months before Screening (per self-report).	X	X
At moderate to high risk of HIV infection based on clinician assessment.	X	X
Considers herself to be at moderate to high risk of HIV acquisition based on self-assessment.	X	X
Has been using COCs for contraception for at least 3 months prior to Screening as confirmed by contraceptive card and intends to continue using COCs for at least 12 months.	X	
Currently using COCs for contraception and has been using them for at least 3 months prior to Screening.		X
HIV-negative per rapid test at Screening and Enrolment per site-specific SOP.	X	X
Negative pregnancy test at Screening and Enrolment.	X	X
Negative for chlamydia, gonorrhea, trichomoniasis, and syphilis at Screening; women who test positive at Screening may be treated and enrolled.	X	X
Hepatitis B surface antigen (HBsAG) negative per blood test at Screening.	X	
Hepatitis B surface antigen and Hepatitis C negative per blood test at Screening.		X
Normal estimated creatinine clearance (eCrCl) ≥ 60 ml/min per blood test at Screening.	X	X
EXCLUSION CRITERIA		
Currently using emtricitabine (FTC) or tenofovir (TDF) at Screening (per self-report)		X
Intends to become pregnant within the next 12 months.	X	X
Intolerance, adverse reaction, or laboratory abnormality associated with PrEP use in the past.	X	X
Use of PEP within 3 months of Screening (per self-report).	X	X
Breastfeeding < 6 months postpartum (per self-report).	X	X
Less than 6 weeks (≤42 days) postpartum and not breastfeeding (per self-report).	X	X
For women 35 and older, currently smokes cigarettes (self-report).	X	

EXCLUSION CRITERIA		
History of deep vein thrombosis / pulmonary embolism (self-report) or history of thrombophlebitis or thromboembolic disorders at Screening (per self-report or medical records).	X	X
Prolonged immobilization (self-report).	X	X
Known thrombogenic mutation/complicated valvular disease (per self-report).	X	X
History of cerebro-vascular or coronary artery disease reported at Screening.		X
Ischemic heart disease (per self-report).	X	X
Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies (per self-report).	X	X
Migraines with aura	X	X
For women over 35 years old, migraines without aura (per self-report).	X	
History of undiagnosed abnormal genital bleeding reported at Screening.		X
Current breast cancer or within 5 years of past breast cancer (per self-report) or history of carcinoma of the breast or other estrogen-dependent neoplasia reported at Screening.	X	X
Diabetes with nephropathy, retinopathy, or neuropathy (per self-report).	X	X
Diabetes for > 20 years (per self-report).	X	X
Symptomatic gall bladder disease (per self-report).	X	X
Severe cirrhosis (per self-report).	X	X
Liver tumor (per self-report).	X	X
Any other condition the clinician feels would jeopardize the health and wellbeing of the participant.	X	X

Study Schema

At Enrollment, participants are randomized to the sequence of study regimens (**Figure 2**): Sequence 1 = single DPP capsule once daily for three 28-day cycles (Regimen A) followed by two separate tablets (oral PrEP and COC) once daily for three 28-day cycles (Regimen B); Sequence 2 = Regimen B followed by Regimen A. In South Africa, after the six-month crossover period, participants may choose Regimen A, B or neither for up to six additional 28-day cycles. Study product regimens are described in detail in **Table 2**.

INSERT FIGURE 2 HERE

All participants take Truvada (FTC/TDF 200/300 mg) once daily by mouth, whether in the DPP capsule or as separate tablets, throughout the entire study. Similarly, all participants are following the prescribed 21/7 COC regimen (21 days of active tablets followed by seven days of placebo tablets), regardless of regimen. The selection and timing of the doses correspond to the labels for Truvada for PrEP (Gilead Sciences, Inc; Foster City, CA, USA) and for Zinnia F COCs (Mylan Laboratories Limited**,** Hyderabad, India). During the "placebo" days of Regimen A, participants take one capsule containing Truvada only, whereas the placebo days of Regimen B consist of two separate tablets: one containing Truvada and one placebo COC tablet. The DPP capsules were manufactured and packaged by PCI Pharma Services (Rockford, IL, USA) from the same batches of Truvada and Zinnia F as the separate pills procured from Gilead and Mylan, respectively.

Table 2. Study products

Regimen	Description	Dose, Route and Frequency
A – Dual Prevention Pill (DPP)	Each DPP kit contains 28 capsules divided into 4 pouches, 1 per cycle week. Each pouch contains a blister strip of 7 capsules (plus desiccant). 3 pouches contain 21 pink and white capsules which each have 1 Truvada tablet (FTC 200mg/TDF 300 mg) and one Zinnia F tablet. (EE/LNG 30/150 mcg) • 1 pouch contains 7 white capsules containing 1 Truvada tablet.	• Participants will take 1 DPP capsule orally, once daily at approximately the same time each day for 12 weeks (Crossover period), taking the next consecutively numbered capsule from each pouch, in order (Week 1, Week 2, Week 3, Week 4). In South Africa, the DPP may be taken for ≤6 additional months (Choice period). • If they miss 1 DPP capsule, participants will be instructed to take it as soon as they remember, up to the time of their next dose, but no more than 2 doses in a 24-hour period. • Participants will be counseled to use back-up contraception (e.g. condoms or abstinence) for 7 days if they miss 2 or more consecutive doses.
B – 2 Separate Tablets	Bottle of 30* Truvada (FTC/TDF 200/300 mg) tablets (PrEP) Blister card of Zinnia F COCs: 21 white active EE/LNG 30/150 mcg pills and 7 brown placebo pills (no hormone) *At the end of the 28-day period, participants should have 2 Truvada tablets remaining in the bottle and will be instructed to return those tablets to the study clinic.	• Participants will take 1 Zinnia F tablet and 1 Truvada tablet once daily. Tablets may be taken together or separately, but each tablet (Zinnia F, Truvada) should be taken at the same time each day. • Zinnia F tablets are to be taken in the order indicated on the pack, including the 7 placebo tablets. If a participant misses a COC dose, she will be instructed to take it as soon as she remembers. If a full day has passed, she should take 2 tablets the next day, per the label. Participants will be counseled to use back-up protection for 7 days if they miss ≥2 consecutive doses. • If a participant misses 1 Truvada dose, she will be counseled to take 1 tablet the next day, per the label, but not to take more than 1 dose in 24 hours. • Participants will be counseled that the effectiveness of PrEP may be reduced if doses are missed.

Study objectives

Objectives and outcomes are similar in both trials (**Table 3**).

Table 3. Objectives and Endpoints for PC952 (Zimbabwe) and PC953 (South Africa)

Objective	Endpoint	Type of endpoint (Country)
PREFERENCE		
To determine preference for taking a single DPP capsule once daily versus 2 separate tablets (PrEP and COC) once daily among women after using each regimen for three 28-day cycles.	Proportion of women who prefer the DPP (Regimen A) vs 2 separate tablets (Regimen B) after using each regimen for 3 28-day cycles.	Primary
To determine if more women choose Regimen A versus Regimen B for the Choice period.	Proportion of women who choose Regimen A vs B for the Choice period.	Primary (South Africa only)
ADHERENCE		
To compare adherence to the DPP (Regimen A) versus 2 separate tablets (Regimen B) among women using each regimen daily for 3 28-day menstrual cycles during the Crossover period.	TFV-DP levels in dried blood spots (DBS) by regimen, and overall, at follow up visits every 4 weeks visits during Crossover period.	Primary (South Africa) Secondary (Zimbabwe)
To compare adherence among women who choose the DPP (Regimen A) versus adherence among women who choose 2 separate tablets (Regimen B) during the Choice period.	TFV-DP levels in DBS by regimen, and overall, at follow up visits every 4 weeks during Choice period.	Primary (South Africa only)
To assess and compare self-reported adherence to Regimen A vs Regimen B during the Crossover period, and to the chosen method during the Choice period.	Self-assessment of ability to adhere to instructions for product use in audio computer-assisted self-interviewing (CASI) interviews and proportion of doses taken by pill count (DPP capsule, FTC/TDF and COCs as applicable) at follow up visits every 4 weeks during the Crossover and Choice periods.	Primary (South Africa)
To compare daily adherence to PrEP for six 28-day cycles among women when taken in the DPP capsule (Regimen A) versus as a separate tablet (Regimen B)	Difference in measurable TFV-DP drug levels in DBS between the 2 regimens; difference in adherence between the 2 regimens based on doses taken compared to total number of doses expected per self-report and pill count.	Secondary (Zimbabwe)

Objective	Endpoint	Type of endpoint (Country)
To explore if socio-ecological factors, product characteristics and product use experiences are associated with adherence to PrEP whether taken as part of the DPP capsule or as a separate tablet.	Results of multivariate modeling indicating which, if any, factors are associated with adherence.	Secondary (Zimbabwe)
To explore facilitators and barriers to use, as well as socioecological factors that may be associated with acceptability, preferences and adherence.	Results of multivariate modeling indicating which, if any, factors are associated with adherence.	Secondary (South Africa)
ACCEPTABILITY		
To assess the acceptability of taking the DPP capsule versus two separate tablets once daily to prevent HIV and unintended pregnancy among women who use each regimen for three 28-day cycles	Acceptability scores by regimen and overall, per a quantitative acceptability questionnaire.	Primary (Zimbabwe)
To assess the acceptability of taking the DPP (Regimen A) vs 2 separate tablets (Regimen B) once daily to prevent HIV and unintended pregnancy among women who use each regimen for 3 28-day cycles during the Crossover period	Scores by regimen and overall, as measured in a quantitative acceptability measurement tool via CASI at the Crossover visit, the start of the Choice period, and the end of the study.	Secondary (South Africa)
To assess if pre-use opinions are associated with actual experiences and preferences after using each regimen	Proportion of women whose pre-use preference matches post-use experience based on an CASI questionnaire at baseline and at the end of the Crossover period.	Secondary (South Africa)
To understand barriers and facilitators to product use and adherence.	Results of thematic qualitative data analysis from in-depth interviews with participants at study exit focusing on facilitators and barriers of product use and adherence.	Secondary

Objective	Endpoint	Type of endpoint (Country)
To explore if socio-ecological factors, product characteristics and product use experiences are associated with acceptability of the DPP and of 2 separate tablets.	Results of multivariate modeling indicating which, if any, factors are associated with acceptability.	Secondary
SAFETY		
To compare the safety of Regimen A versus Regimen B among women using each regimen for 3 28-day cycles during the Crossover period, and the safety of Regimen A versus Regimen B among women choosing each regimen during the Choice period.	Number of AEs by regimen (including social harms, drug side effects) during the Crossover and Choice periods.	Secondary (South Africa)

Study procedures

Informed consent

Before undergoing screening procedures, a counselor/designee leads an informed consent discussion with potential participants in their preferred language (English or isiZulu, South Africa; English or Shona, Zimbabwe). The same study staff member implements a comprehension assessment to check participants' understanding of key study aspects before they both sign the consent form. For unemancipated minors (16-17-year-olds), informed consent from the parent/legal guardian consent is obtained before assent from the minor. Key elements of the informed consent are reviewed on an ongoing basis and willingness to continue study participation is ascertained.

Eligibility screening

After consenting, potential participants are assigned a unique Participant Identification number and undergo screening procedures. All screening test results and, if enrolled, study information (data, specimens) is recorded with IDs and no other identifying information to preserve participant confidentiality. Locator information is collected at screening and reviewed at each study visit to

ensure participants are contactable for retention purposes. The screening process typically takes more than one day because several lab tests are outsourced. At screening (Visit 0), a nurse/clinician takes a complete medical history, including gynecologic and obstetric history. A clinical exam is performed to assess overall health (including complete blood count [CBC] in Zimbabwe). Urine is tested for pregnancy (human chorionic gonadotrophin [hCG]), and *Neisseria gonorrhoeae/Chlamydia trachomatis* (nucleic acid amplification test [NAAT]). Blood is tested for HIV, syphilis, and hepatitis B virus (and Hepatitis C in Zimbabwe), and to measure creatinine clearance. Screening also includes direct observation of participants swallowing a large vitamin capsule, similar in size to the 000 DPP capsule (**Figure 1**).

Enrollment and randomization

Enrollment (Visit 1) is scheduled when participants are starting their next COC pack (+/- 5 days). At Enrollment, participants are tested for HIV (rapid antigen blood test) and pregnancy (urine hCG) to confirm eligibility. Those eligible are enrolled and randomized (1:1) to the sequence of regimens, are given a supply of their first study product with detailed dosing instructions and take their first dose directly observed in the clinic. Participants are counseled on management of anticipated side effects and missed pills based on recommendations developed by a sub-group of the DPP Consortium incorporating differing guidelines for COCs and oral PrEP [43]. Participants also receive counselling on HIV/STI risk reduction, contraception, and protocol compliance – including the importance of coming for clinic visits and taking the study products – at every visit starting at Enrollment.

Follow-up visits

Table 4 contains the detailed schedule of visits and procedures. At all visits, blood is collected for dried blood spots (DBS) to assess tenofovir-diphosphate (TFV-DP) levels as a measure of PrEP adherence [44] and for rapid HIV testing. Urine is collected for pregnancy testing. After the first

three cycles, participants "crossover" to their second regimen at Month 3/Visit 4 and return unused study product from their first regimen. They then receive their first supply of the second regimen, with detailed instructions, and take their first dose directly observed in the clinic. Participants attend monthly follow up visits during the second regimen (Month 4/Visit 5; Month 5/Visit 6). At Month 6/Visit 7, all Zimbabwean participants exit the study while South African participants may continue using either regimen (or neither) for up to another six months during a "Choice" period, with similar monthly visits.

Laboratory procedures

Laboratory assessments are listed in **Table 4**. Blood specimens for hepatitis, creatinine, HIV confirmation testing (and CBC in Zimbabwe) are processed off-site by BARC (South Africa) and UZ-CTRC (Zimbabwe). DBS specimens are analyzed at the University of Cape Town by a liquid chromatography-tandem mass spectrometry assay [44].

Table 4. Schedule of Visits and Procedures for PC952 (Zimbabwe) and PC953 (South Africa)

PROCEDURES	VISIT Day/Week													
	V0	V1	V2	V3	V4	V5	V6	V7[3]	V8[2]	V9[2]	V10[2]	V11[2]	V12[2]	V13[1]/Early Termination
	Day ≤-45	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
Visit Type	SCR	ENR	FU	FU	CO	FU	FU	CH	FU	FU	FU	FU	FU	CLO
ADMINISTRATIVE														
Informed consent	X													
Assign participant ID number	X													
Assess eligibility	X	X												
Demographics	X													
Randomization		X												
COUNSELING														
HIV pre and post-test counseling and testing, risk reduction counseling	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
STI/HIV risk reduction counseling	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Contraceptive counseling	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Protocol adherence counseling		X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	
CLINICAL														
Administer HIV risk assessments (clinician-based and self-assessment)	X													
Medical history	X													
Record medication history/ concomitant medications	X	*	*	*	*	*	*	*	*	*	*	*	*	*
Vital signs	X♦§	X	X♦	X	X	X♦	X	X	X♦[2]	X[2]	X[2]	X[2]	X[2]	X♦[2]
Complete physical exam	X	*	*	*	*	*	*	X[1]	*	*	*	*	*	X
Targeted physical exam		X	*	*	*	*	*	*	*	*	*	*	*	
Pelvic exam	*[2] X	*	*	*	*	*	*	*	*	*	*	*	*	*
Record adverse events/social harms		*	*	*	*	*	*	*	*	*	*	*	*	*
LABORATORY ASSESSMENTS														
Urine														
Urine pregnancy test	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
GeneXpert (urine) for chlamydia and gonorrhea (NAAT)	X	*	*	*	*	*	*	*	*	*	*	*	*	*
Urinalysis	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Blood														
Rapid HIV-1 blood tests	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
HIV confirmation blood test	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Syphilis serology	X	*	*	*	*	*	*	*	*	*	*	*	*	*
Hepatitis B antigen test	X													
Hepatitis C test	X[3]													
Creatinine blood test	X	*	X	*	*	X	*	X[1]	X[2]	*	*	*	*	X[2]

PROCEDURES	VISIT Day/Week													
	V0	V1	V2	V3	V4	V5	V6	V7[3]	V8[2]	V9[2]	V10[2]	V11[2]	V12[2]	V13[1]/Early Termination
	Day ≤-45	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
Collect blood for DBS to assess adherence			X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Blood draw for Complete Blood Count	X[1]	*	*	*	*	*	*	X[1]						
Pelvic														
Rapid trichomonas (TV)	X[3]													
Wet mount (TV, BV, candida)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Study product														
DOD first dose of regimen		X			X									
Distribute product supply		X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	
Collect used and unused product supplies			X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Behavioral														
CASI baseline questionnaire		X												
CASI monthly questionnaire			X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X2	X2
In-depth exit interview								X[1]						(X)[2]

[1]Zimbabwe only; [2]South Africa only; [3]Visit 7 is the Closing Visit in Zimbabwe

V = Visit; Wk = week; SCR = Screening; ENR = Enrolment; FU = follow up; CO = crossover; CH = Choice; CLO = Closing Visit; *If indicated; (X) sub-set of participants

♦Weight only at specified visits (when creatinine/creatinine clearance assessed); §Height only at Screening

Safety monitoring and adverse event (AE) reporting

Clinical assessments at each visit post-enrollment are done to monitor potential AEs and social harms. In general, individual participants who develop a Grade 1 AE based on the Division of AIDS Grading system [45] regardless of relatedness, or an unrelated Grade 2 AE may continue using their assigned study product(s) per protocol, at the site PI's/designee's discretion. Individuals who develop a related Grade 2 AE, or who develop a Grade 3 AE, regardless of relatedness, will be evaluated by the site PI/designee and Medical Monitor for possible discontinuation from the study. Individuals who develop a Grade 4 AE, regardless of relatedness, will be evaluated by the site PI/designee and Population Council Medical Monitor and discontinued from the study. No dose modifications will be undertaken nor are there any *a priori* stopping rules because both study products (PrEP and COCs) are marketed drugs.

Seroconversion or pregnancy

HIV testing occurs at each visit and any participant who seroconverts will be terminated from the study. At their closing visit, study staff will collect unused pills, conduct resistance and viral load testing, and link the participant to HIV/FP care per local guidelines. Similarly, participants who become pregnant will be terminated and referred to services for pregnant individuals, including PrEP provision, if desired. The sites will make every effort to follow-up on all pregnancy outcomes. The sites may continue to counsel participants as they transition to services to preserve their confidentiality when they discontinue.

Creatinine

Creatinine levels are monitored in accordance with PrEP guidelines in each country, approximately quarterly [46,47]. Participants with abnormal creatinine levels may be put on a temporary product hold, pending the PI/designee's decision, until a repeat test can be done. Participants who have two tests outside the normal range will be permanently discontinued to reduce their risk if the DPP or PrEP is contraindicated.

Data and safety monitoring

The Population Council monitor conducted site qualification and initiation visits at both sites before data collection began and periodic monitoring visits ensure the protocol and good clinical practice (GCP) are being followed. The monitor reviews source documents to confirm that the data recorded on case report forms (CRFs) is accurate, and reviews relevant documents to verify protocol compliance. A data safety and monitoring board (DSMB) has been established for both studies, consisting of three individuals with clinical expertise in HIV and contraception, epidemiology, biostatistics, and clinical trials. The DSMB (charter available upon request) will review data after all participants have been enrolled (both countries), and after all participants complete the Crossover period (South Africa). All serious AEs (SAEs) and AEs leading to

discontinuation will be reported to the relevant IRBs/ethics committees, drug regulatory authorities, sponsor, DSMB, and funders. Unanticipated AEs that are potentially related to the study product(s) will be reported as Suspected Unexpected Serious Adverse Reaction to the manufacturers (Gilead or Mylan).

Clinical staff are trained to identify, probe for, manage, and report AEs and social harms, documented at every visit. Study clinicians review abnormal test results, liaise with local clinic doctors, and have the authority to terminate participants based on clinical opinion. Upon completion of the study, participants are referred to local clinics for PrEP and COC services, if they want to continue the methods. Any breaches in confidentiality, study protocol or AEs attributable to this study will be reported to the relevant IRBs/ethics committees and regulatory authorities.

Data collection and management

Clinical case report forms (CRFs)

CRFs were developed by the Population Council and the trial sites to capture demographics, medical history, clinical exam results, laboratory test results, product supply/pill counts, AEs, randomization, and termination data. Data are collected and managed using REDCap (Research Electronic Data Capture) hosted at the Population Council [48,49]. Data are entered into REDCap within five days of each participant's visit. Queries are triggered during data entry or by the Population Council data manager during weekly data reviews.

Quantitative behavioral surveys

Starting at Enrollment/Visit 1, participants complete a behavioral questionnaire via computer-assisted self-interview (CASI) in their choice of English or the local language (isiZulu in South Africa, Shona in Zimbabwe). Surveys last 30 to 60 minutes, depending on the visit, and include

questions about product acceptability, adherence, and overall trial experiences. Participants complete their interviews privately on tablet computers, with study staff nearby to address potential technical challenges.

Qualitative exit interviews

After exiting the study, a subset of participants will take part in in-depth interview (IDIs) lasting 40-60 minutes. In South Africa, we will interview up to 30 participants representing those exiting early during the Crossover period, those exiting after the Crossover period, and those who complete the Choice period (with a purposively selected mixture of women who preferred the DPP or two separate tablets). In Zimbabwe, we will interview all willing participants. Interviews will explore reasons for continuation/discontinuation; influence of partners, family, and support structures; side effects; provider interactions; and other factors on DPP acceptability and adherence. IDIs may be conducted at or after the Closing Visit, depending on participant availability and visit length, in the participant's choice of language; will be audio recorded and transcribed; and translated into English (as necessary) for analysis.

STATISTICAL CONSIDERATIONS

Sample size and power calculations

South Africa

The sample size calculation was based on comparing ***adherence*** between the two regimens. A sample size of 86 has 80% power to detect a difference between the proportion of women who are adherent to each regimen assuming 25% of women are adherent to PrEP alone, 40% are adherent to the DPP, with a correlation between regimens of 50%, and no period effect. We increased the sample to 96 in case 10% of participants discontinue early while still having 86 participants complete the Crossover period.

Zimbabwe

The sample size was calculated based on detecting a difference in ***preference*** for the DPP versus two separate pills. A sample size of 30 has 94% power to detect a preference for one regimen over the other when the true preference for one regimen is at least 80% based on the exact binomial test (alpha = 0.04). If only 27 AGYW complete the study (10% loss to follow up), we have 84% power to detect a preference for one regimen over the other when the true preference for one regimen is at least 80%, based on the exact binomial test (alpha = 0.02).

Randomization

Independent randomization schemes for each study were developed by the Population Council Biostatistician using Statistical Analysis Software (SAS/STAT) version 9.4 (SAS Institute Inc., Cary, North Carolina) with a 1:1 allocation using permutated block sizes. In South Africa, randomization is in blocks of 12, six participants per sequence in each of eight blocks. In Zimbabwe, randomization is in blocks of ten, five participants per sequence in each of three blocks. The randomization schemes are embedded within the REDCap systems for each study.

At enrollment, the clinician consults REDCap to assign the treatment sequence for each sequentially enrolled participant.

Data Analysis

The "all participants" population includes all enrolled participants; the "safety population" includes all participants who have used at least one dose of either regimen; and the "per protocol" population includes all participants who complete both regimens. In general, descriptive statistics (frequencies, mean, standard deviation, range) will be used to summarize data and to characterize data collated on differences in participants assigned to each Sequence. Point estimates and corresponding 2-sided 95% confidence intervals will be presented for endpoints, where appropriate. Missing data will not be imputed.

Preference for the DPP will be measured as the proportion of women (per protocol population) reporting at the end of the Crossover period that they prefer the DPP capsule versus two separate tablets (or vice versa) by testing whether this proportion is greater than 0.5 using a z-test statistic under the exact binomial test in Zimbabwe (n=30), and normal approximation of the binomial distribution in South Africa (n=96). However, if the number of women completing each sequence is unbalanced, the comparison will be done using a random effects mixed model adjusting for effects treatment sequence may have on preference. In South Africa, we will similarly analyze the proportion of women who choose the DPP versus two separate tablets for the Choice period.

Adherence (overall) will be measured (safety population) by the total number of doses taken versus expected as measured by self-report, pill count and tenofovir-diphosphate (TFV-DP) levels in DBS measured at each follow-up visit (approximately every 28 days) and will be compared by regimen. Adherence DBS will be done by comparing the proportion of women with TFV-DP levels consistently greater than the threshold known to provide efficacy, using McNemar's test for paired

proportions. Adherence by pill count will be measured as the proportion of the total number of doses taken out of the number of expected doses, as measured at each follow up visit. If all women do not complete the Crossover period, analyses will be conducted with those who completed all six visits (24 weeks). Adherence during the Choice period (South Africa) will be analyzed similarly.

Acceptability of using the DPP capsule versus two separate pills will be measured in the safety population using a quantitative acceptability questionnaire. The primary outcome of acceptability will be measured as a scaled response to questions in the following acceptability domains: use attributes, product attributes, side-effects, sexual activity. Acceptability scores will be summarized overall and by regimen and timepoint and compared by regimen at each visit. Scores will be compared using a random effects mixed model to evaluate the effects of regimen and timepoint.

Safety data include findings from physical (and pelvic, when indicated) exams, laboratory tests, and AEs. AEs will be coded in accordance with the Medical Dictionary for Regulatory Activities [50]. A summary of AEs will be based on treatment-emergent AEs (TEAEs), which include all events that occur on or after the first dose. The number and percent of participants for each AE and SAE will be summarized by system organ class and preferred term, overall and by regimen.

Effects of socio-cultural and demographic characteristics (e.g., age, education, income, employment, relationship status, HIV risk perception, self-efficacy for HIV prevention) on preference, acceptability and adherence will be explored using random effects mixed models. Socio-cultural and demographic data will be collected at screening and enrollment (Visit 1/Day 1).

A thematic analysis approach will be employed to analyze the IDIs, which entails careful reading of the data to identify themes that will serve as the analysis categories. Inductive (data-driven)

and deductive (*a priori*) codes will be developed and applied to the data. Coded data will be synthesized to generate descriptions of behaviors, attitudes and beliefs about the acceptability of the DPP capsule, preference for the DPP or two separate pills, trial experiences, and other emergent themes [51–53].

ETHICS AND DISSEMINATION

Ethics

Both protocols and amendments, informed consent forms, and recruitment materials have been approved by the Institutional Review Board of the Population Council (NY, NY, USA). The South Africa protocol and amendments (PC 953, Version 3.0, 08th June 2022), consent forms, recruitment materials and data collection instruments in both English and isiZulu were reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee and South African Health Products Regulatory Authority. The Zimbabwe protocol and amendments (PC952, Version 3.0, 17 June 2022), consent forms, recruitment materials and data collection instruments in English and Shona were also approved by the Medical Research Council of Zimbabwe, the Medicines Control Authority of Zimbabwe, the Joint Research Ethics Committee of the University of Zimbabwe, the Ministry of Health and Child Care of Zimbabwe, the Chitungwiza City Health Ethics Committee, and the Research Council of Zimbabwe. Both studies are being conducted in accordance with the United States Code of Federal Regulations, the International Conference for Harmonization of Technical requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice E6 (R2), and local standard operating procedures at each site. Participants receive compensation for each visit to cover their time, transportation costs, and inconvenience of the study visits, commensurate with the norms and standards in each country. Both trials are registered on clinicaltrials.gov (NCT04778514 and NCT04778527). Screening began in August 2022 and data collection is projected to end by December 2023.

Dissemination

The study teams provide periodic updates to their communities and Community Advisory Boards during trial implementation. On completion, results will be presented locally at each site during

in-person/virtual meetings with study participants, community advisory boards, and other local stakeholders; at national and international conferences; through the DPP consortium; and posted on PrEP Watch. Manuscripts will be submitted to peer-reviewed journals and will be made available via open-access whenever feasible. Data will be uploaded on the ClinicalTrials.gov site, the U.S. Agency for International Development's (USAID) Data Development Library (South Africa only) and in country registries, as applicable. Datasets and protocols will be available from the sponsor upon request.

AUTHOR CONTRIBUTIONS

BAF wrote both study protocols and the final version of the manuscript; SM conceptualized and wrote the behavioral data collection aspects of the protocol and manuscript; MP wrote the data management and statistical analysis sections of the protocol and manuscript; NM, AD, CM, PM, SM, TP-P, KR, NN, SK, LS, BZ and LH participated in protocol development and contributed to the manuscript. ML wrote an earlier draft of the paper; IB oversees study implementation, assisted in writing and editing the paper, and prepared the manuscript for publication. All authors reviewed and approved the final version of the manuscript.

FUNDING

PC953 is made possible by the generous support of the American people through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and U.S. Agency for International Development (USAID) via cooperative agreement #No. AID-OAA-A-13-00088. The contents are the responsibility of the authors and do not necessarily reflect the views of PEPFAR, USAID, or the U.S. Government.

PC952 research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under Award Number R34MH119982. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The Children's Investment Fund Foundation (CIFF) Award Number 2106-06589 supported the manufacturing of the study product, as well as supplementing funding the US government funding for both studies. The content is solely the responsibility of the authors and does not necessarily reflect the views of CIFF.

ACKNOWLEDGMENTS

We would like to acknowledge George Creasy, who spearheaded work to develop a DPP; Bruce Variano for overseeing the development and testing of the over-encapsulated DPP; Dan Loeven for overseeing regulatory aspects of manufacturing the DPP; Susanna Grecky and Rebecca Brodsky for liaising with suppliers and manufacturers; Sherry Hutchinson for creating the educational materials for the trial and graphics appearing in the paper; and Heather Sussman for study oversight as clinical trial monitor.

COMPETING INTERESTS

None declared

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Figure 1. Over-encapsulated dual prevention pill (DPP) *Note: The hand shown is of one of the co-authors and is not a patient.

436x261mm (300 x 300 DPI)

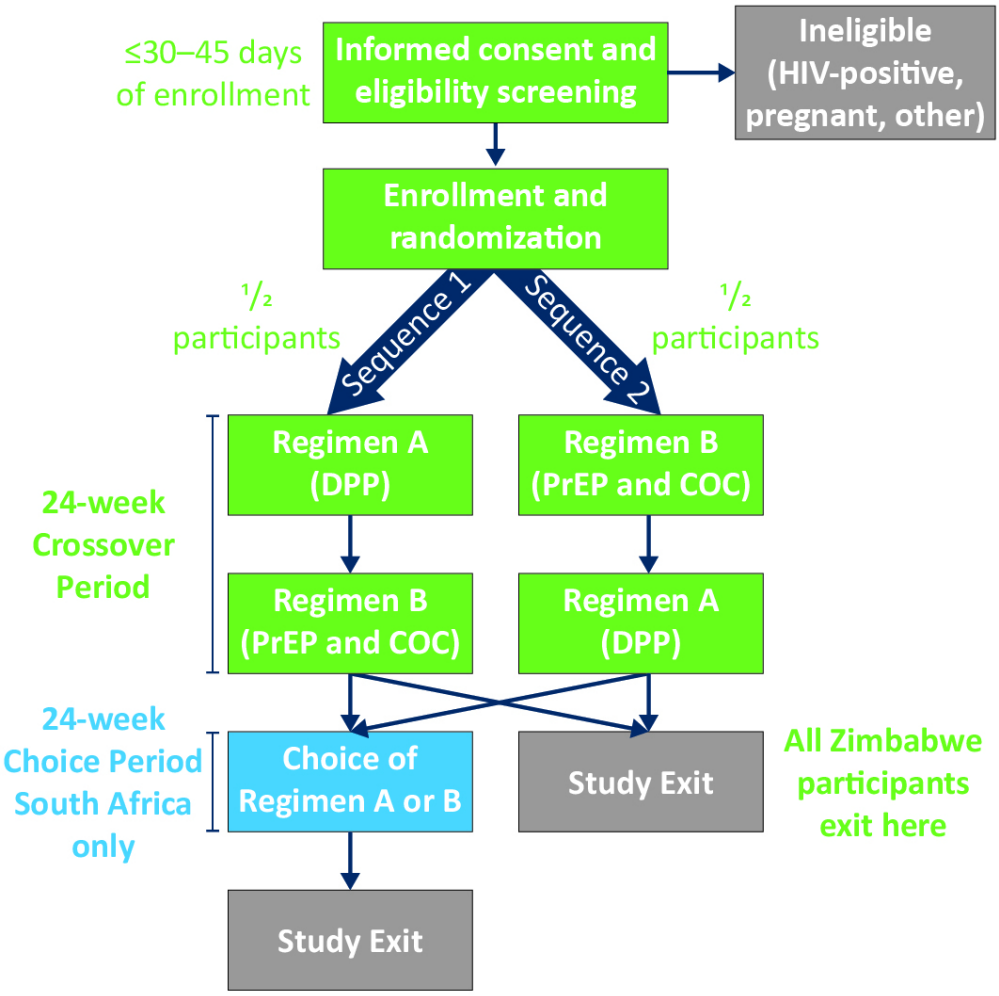

Figure 2. Study Schema

90x90mm (300 x 300 DPI)

PARTICIPANT INFORMATION SHEET (PIS) AND INFORMED ASSENT FOR YOUNG WOMEN AGED 16-17 YEARS

*Each participant must receive, read and understand this document **before** any study-related procedure*

SHEET 1: Screening and Enrolment

STUDY TITLE: A randomized, crossover study to compare adherence, preference and acceptability of an over-encapsulated dual prevention pill (DPP) containing oral pre-exposure prophylaxis (PrEP) and a combined oral contraceptive (COC) versus two separate tablets (PrEP and COC) among women at risk of HIV and unintended pregnancy in Johannesburg, South Africa

SHORT TITLE FOR THE STUDY: DPP Capsule Study

FUNDER: WCG Cares, San Diego, California (CA), United States of America (USA)

SPONSOR: Population Council, New York (NY) USA

PRINCIPAL INVESTIGATORS: Prof Thesla Palanee-Phillips and Dr Nkosiphile Ndlovu

INSTITUTION: Wits Reproductive Health and HIV Institute (Wits RHI), University of the Witwatersrand

DAY TIME AND AFTER-HOURS TELEPHONE NUMBERS: Day Tel: 011 358 5424

A/H Tel: 083 783 3574

To the potential Participant: *This assent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home **an unsigned copy of this assent** form to think about or discuss with family or friends **before making your decision.***

DATE AND START TIME OF INFORMED ASSENT DISCUSSION:

DD	**MMM**	**YYYY**

:
Time *(24hr clock)*

Participant Initials: ____ ____ ____

INTRODUCTION

Hello my name is _____ and I work at the Wits Reproductive Health and HIV Institute (Wits RHI) as a _____. The Wits RHI does research in reproductive health, including HIV. We have projects in many areas including Esselen Street in Hillbrow (Esselen Street Clinic and Research Centre) and Yeoville. The Wits RHI is a part of the University of Witwatersrand, Johannesburg.

The Wits RHI would like to invite you to participate in a study called The DPP Capsule Study. The DPP Capsule Study is being done to see how adolescent girls and women in Johannesburg and surrounding areas feel about using a single capsule containing an oral PrEP tablet (a tablet to prevent HIV) and an oral contraceptive (OC) tablet – the Dual Prevention Pill (DPP) capsule – compared to taking PrEP and OC tablets separately. The persons in charge of the study at this site are Prof Thesla Palanee-Phillips and Dr Nkosiphile Ndlovu. The study is funded by WCG Cares, a non-profit organization based in San Diego, California (CA), United States of America (USA) and sponsored by the Population Council, a not-for-profit research organization based in New York, NY (USA). This study has been reviewed and approved by the University of the Witwatersrand (Wits) Human Research Ethics Committee (HREC) in Johannesburg, South Africa and the Institutional Review Board (IRB) of the Population Council in New York, USA.

Before you decide if you want to join the DPP Capsule study, we want you to know about it. This form gives you information about this study. The study staff will talk with you and your parent/guardian about the study and answer your questions. If you or your parent/guardian would like to speak with a medical doctor or if you have medical questions, please let me know so that this can be arranged. You may choose to stop being in the study at any time. Once you read this form (or have read to you), discuss and understand the study, and if you and your parent/guardian agree to study participation, we will ask you to sign or mark this form. We will offer you a copy of this form to keep.

Your parent/guardian will be asked to sign a separate consent form granting you permission to join the study. If you reach the age of 18 years old during the study, you will go through the informed consent process again as an adult and will be asked to sign a new informed consent form.

If you have a personal doctor, you are welcome to discuss with or inform him/her of your possible participation in this study. If you wish, I can also tell your personal doctor about the study.

YOUR PARTICIPATION IS VOLUNTARY

If you decide not to take part in the study, you may still have the opportunity to join other studies in the future, if one is available and you qualify. However, you cannot join the DPP Capsule Study if you are taking part in another study of medicines, medical devices or vaccines. You are asked to tell the study staff if you are taking part in or thinking of taking part in any other studies.

We check for your co-enrolment in other studies by capturing your fingerprints on an electronic system called the Biometric Co-Enrolment Prevention System (BCEPS). You will need to place your fingers onto a mini screen which will enter your fingerprints on to BCEPS. This system will then check if your fingerprints are stored on the system for any other studies. Only a few members of the study team can see the information in BCEPS using a secure password. This is done at the beginning of your visit and is covered on a separate informed consent form.

PURPOSE OF THE STUDY

This research study is known as the DPP Capsule Study. The main aim of the study is to find out if adolescent girls and women who already use OCs for family planning and who want to protect themselves from getting HIV would prefer taking a single DPP capsule containing both PrEP and a OC compared to 2 separate tablets. A second aim is to understand how adolescent girls and women use these products when in the study. Finally, researchers would like to know what adolescent girls and women think about the introduction of a DPP in their communities.

STUDY PRODUCTS

Study participants will take OCs and PrEP either as 2 separate tablets or together in the DPP capsule for the duration of the study.

Oral contraceptive (OC): Zinnia F is the OC regimen that will be used in this study. Zinnia F is similar to the OC pill you have been using to prevent unintended pregnancy. Zinnia F contains small amounts of two hormones: ethinyl estradiol (EE) and levonorgestrel (LNG) that work to prevent pregnancy. The OC pack contains 28 tablets; 21 white tablets are "active" and contain the hormones that prevent unintended pregnancy; 7 brown tablets are "placebos" which do not contain any medicine and are "inactive". Most women get their menstrual period on the days while taking the placebos.
All 28 tablets in the pack are numbered in the order you will need to take them.

PrEP: PrEP is a method to prevent HIV which is approved for adults and adolescents who weigh at least 35 kgs. It is a tablet that contains 2 drugs known as emitricitabine and tenofovir disoproxil fumarate, which are also used to treat people living with HIV when combined with other drugs. PrEP works by stopping HIV from making copies of itself. PrEP comes in a bottle of 30 tablets and is very effective for preventing HIV when taken daily. However, studies have shown that PrEP does not work if it is not taken every day.

DPP capsule: In this study, OC tablets and PrEP tablets will be put together in a single capsule. The DPP capsule regimen will consist of 21 pink and white capsules containing one PrEP tablet and one OC tablet, and 7 white capsules containing a PrEP tablet only. This study is the first time that PrEP and an OC are being combined in a single capsule.

WHO WILL BE IN THIS RESEARCH STUDY?

Approximately 96 healthy adolescent girls and women from Johannesburg and surrounding areas who are 16 to 40 years old, are sexually active and consider themselves to be at risk for HIV and are already using OCs for family planning will be in the study.

WHAT DO YOU HAVE TO DO IF YOU DECIDE TO TAKE PART IN THIS STUDY?

As shown in the picture below, the study has 3 periods. In the first 2 periods, you will use the DPP capsule for 3 28-day menstrual cycles (12 weeks) and you will use two separate tablets (OCs and PrEP) for 3 28-day menstrual cycles (12 weeks). You will be randomly assigned to the order of the sequences like tossing a coin or playing dice. Neither you nor the study staff can choose the sequence that you will use the products. Half of the participants will use the DPP capsule for 3 cycles first and will then switch to using 2 separate tablets. The other half of the participants will take 2 separate tablets first and switch to the DPP Capsule after 3 cycles.

After you have used the DPP capsule and 2 separate tablets for 12 weeks each, you will have the opportunity to continue in the Choice Period. In the Choice Period you will be able to choose to use either the DPP capsule or 2 separate tablets for up to 24 more weeks. If you do not wish to use either regimen (DPP Capsule or 2 separate tablets), you will exit the study at this point.

If your participation in the study is stopped for any reason, it is important that you contact your healthcare provider to make sure you continue taking your usual supply of OCs or other family planning

method. If you would like to continue taking PrEP after the study, we will refer you to PrEP services in the community.

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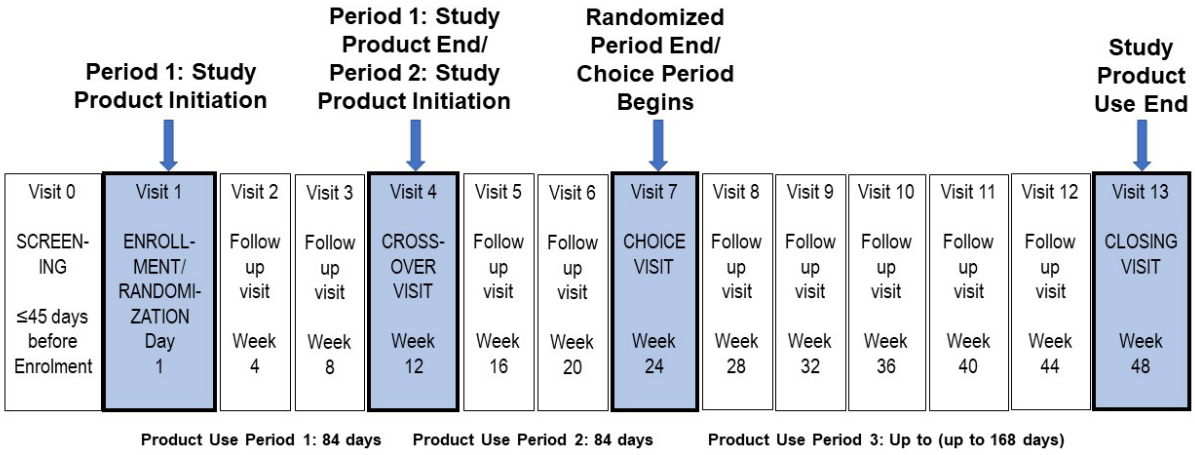

If it seems like you can join, you will be asked to come back for an Enrolment visit (Visit 1) no later than 45 days from today. At Enrolment, you will find out which regimen you will start with (DPP capsule or 2 separate tablets). After Enrolment, you will have 12 visits, approximately every 4 weeks, as shown in the picture above. You will have a total of up to 14 visits, including the Screening Visit and will be in the study for up to one year.

DO YOU HAVE TO BE IN THIS STUDY?

You do *not* have to be in this study. You can still get the care you need from your local/public clinic even if you do not join the study. If you join today, you can change your mind later.

WHAT PROCEDURES WILL BE DONE FOR THIS STUDY?

Your first visit will happen today after you read (or have read to you), discuss, understand and sign this informed consent form. The procedures done at this visit will let us know if you can join this study. Today's visit will last about 4 hours.

SCREENING PROCESS

It is expected that all screening procedures will be done today. However, you may need to come back to complete the screening process. Some tests may need to be repeated.

The following will happen during your screening visit today:

- You will be asked to confirm where you live and how to contact you.
- We will ask you questions about your health and any medicines which you might be taking. We will also ask you questions about your living situation to see if it might interfere with your use of the study products. We will also ask you about your reasons for wanting to join this study and how you see your risk of getting HIV.
- We will draw blood from your arm to test for the following diseases or conditions:
  - About 1 teaspoon/5ml to test for HIV
  - About 1 teaspoon/5ml to test the health of your kidneys
  - About 1 teaspoon/5ml to test for syphilis and Hepatitis B infection
- You will be asked to give a urine sample to check if you are pregnant, and to test for Gonorrhea and Chlamydia which are sexually transmitted infections (STIs). If you have symptoms, you may also be tested for a urinary tract infection (UTI).

- A nurse/doctor will examine you to make sure you are in good health. If you have symptoms, a pelvic exam may be done to check for reproductive tract infections (RTIs) or other STIs. If a pelvic exam is done, the nurse or doctor will use a speculum – a metal or plastic device to help open the vagina -- to examine your vagina and your cervix. If a pelvic exam is done, the nurse or doctor will use a swab to take fluids for a wet mount test to check for RTIS or STIs like *Trichomonas vaginalis (TV*), bacterial vaginosis (BV) and candida.
- A study staff member will talk to you about what you will need to do if you join the study, how to protect yourself from infections, including HIV, and how to prevent pregnancy. You must have been using OCs for at least 3 months before joining the study. You will also need to swallow a large Vitamin C capsule in front of a study nurse or doctor to make sure you will be comfortable taking the DPP, which is also a large capsule.

Results of some tests like, HIV, pregnancy, UTI, *Trichomonas vaginalis* and wet mount test will be available on the same day and treatment provided, if applicable. You will be contacted about results from other tests when available. If you have an STI other than HIV, study staff from our clinic will contact you to come to the clinic where a study staff member will give you the results that showed you have an STI(s) and will give you treatment. You will be asked to tell your sex partner(s) and to bring him/them to the clinic for treatment if they are agreeable. If your sex partner/s cannot come to the clinic for treatment, they will be referred for/offered treatment. If you do not have Hepatitis B infection, you may be offered the Hepatitis B vaccine.

No samples collected at the Screening visit will be kept or used for any other tests other than those listed above.

ENROLMENT

<u>About 4 weeks after your Screening Visit, we will confirm your eligibility when the results from screening are known.</u>

- If you are pregnant, you will not be able to join the study and your participation will end. We will refer you to healthcare services in the community.
- If the tests show that you have HIV, you cannot participate in the study. If you agree, you will be referred immediately for HIV treatment.
- If it is not clear if you have HIV (indeterminate result) you will not be eligible for the study. If you agree, you will be told where to go for further testing and to get appropriate medical help.
- If the results of your HIV test show that you have no HIV infection, you will be eligible to participate in the study, as long as there are no other reasons that you cannot enrol.
- You may not be eligible for the study because of information you give during the Screening process or because of other laboratory test results. If this is the case, you will be informed that you are not eligible for the study.
- You will be referred to other health services if you need them.

At your Enrolment visit, if your test results show you can participate in the study, a study staff member will explain the study to you again and answer any questions you may have.

At the beginning of each visit, we will go over the procedures to happen on that day. Each visit will last about 4 to 5 hours. After the Enrolment visit, you will be asked to come to the clinic for 12 more visits. The study staff will also contact you between visits. Your visits will be about 4 weeks apart.

<u>ALL VISITS</u>

<u>The following procedures will happen at all visits:</u>

- **Confirm contact details:** We will confirm where you live and how to contact you.

- **Pregnancy test:** You will be asked to give a urine sample to test for pregnancy.
- **HIV test:** We will draw about 5 ml/1 tsp blood from your arm for an HIV test.
- **Counseling:** We will talk to you about what you are expected to do during the study and will counsel you about how to use the study products, how to protect yourself from infection, including HIV, and how to prevent pregnancy. We will counsel you about how condoms can protect you from getting HIV and other STIs and we will offer you condoms.
- **Meeting with a nurse or doctor:** You will meet with a nurse or doctor who will conduct a brief physical exam to make sure you are in good health. This will include checking your vital signs (temperature, pulse, blood pressure, respiration rate) and asking you if you are having any symptoms and about any medications you may be taking. If you have signs or symptoms of an STI, RTI or UTI at any visit, the nurse or doctor may perform a pelvic exam or collect specimens. At some visits you will have blood drawn, as explained below.
- **Interview on a computer:** You will be asked to answer some questions in private, using a computer. The study staff will show you how to use the computer to answer the questions. The questions will ask you what you think about the study products, about your behaviours, including having sex, if you are having sex. Some questions might be sensitive. If you ever feel uncomfortable, you can choose not to answer the questions at any time. When you finish answering the questions, the computer locks in your information. No one at the clinic can see your answers.
- **Scheduling your next visit:** At the end of each visit, we will schedule your next visit before you leave the clinic.

<u>PROCEDURES TO BE DONE AT SOME VISITS</u>

Blood tests:

- At all visits starting at Visit 2/Week 4, we will draw 5 ml/1 tsp of blood to check the amount of PrEP drugs in your blood. You will not get these results, which will not have any impact on your participation in the study.
- At Visits 2, 5, 8 and 13, we will draw an additional 5 mL/1 tsp of blood from your arm to check the health of your kidneys (4 visits).

Study products:

- At each visit starting at Enrolment through Visit 7, you will be given a supply of your study product, based on the group you are assigned to A study staff member will give you detailed instructions about how to use the product and you will have a chance to ask any questions you may have.
- At the first visit that you start each Regimen, a study staff member will watch you take the study product(s) to make sure you do not have a problem swallowing the pills.
- From Visit 8 through Visit 13, you will be given a supply of the study product you have chosen to use for the CHOICE period..
- At all visits after Enrolment, you will be asked to return all study products, including bottles, pill packages and DPP kits, regardless of whether they are used or unused, at each clinic visit.
- Between every visit, we will send you text messages or call you to help you remember to use the study products. To maintain privacy and confidentiality, our text messages will not refer to your participation in the study or study product use.

Test results: We will give you results of any tests of blood, urine or vaginal specimens when available.
Treatment: We will give you treatment for curable RTIS, UTIs or STIs. If you need, we may also provide you with treatment for other illnesses if we are able or refer you to other services.
Pelvic exam: If you have any symptoms, the study doctor or nurse will conduct a pelvic exam using a speculum.
Physical exam: At any visit, the nurse or doctor may conduct a longer physical exam to make sure you are in good health.

It is important for you to come to every study visit. If you cannot come to the visit, please tell the study staff as soon as possible so that the visit can be rescheduled.

IN-DEPTH INTERVIEW

You may be asked to take part in a one-on-one in-depth interview after you complete the study. You may choose not to be interviewed. If you agree to be interviewed, you may be interviewed at your Closing Visit or we may schedule your interview at another time.

INTERIM/UNSCHEDULED VISITS

Study staff will discuss with you the importance of contacting the clinic as soon as you notice changes in your physical condition or if you experience health related issues. Also, it is possible that you may be asked to come to the clinic for an unscheduled visit in the event of an abnormal test result; difficulties in sample shipping, processing, or testing or to have study procedures repeated; or for other reasons. We will do this if you experience any changes in your physical condition, including symptoms of a UTI, RTI or STI. If you lose study product (DPP capsule, PrEP or OCs), or if you need more supplies, or if you have any problems with the study products at any time, you should return to the clinic and we will help you.

IF YOU BECOME INFECTED WITH HIV

Being in this study will not cause HIV infection. But there is always a chance that you can get HIV through sex or other activities. If you become HIV-positive, you will stop using the study products immediately, be discontinued from the study and referred immediately to HIV treatment and care services in the community. If you get HIV, it is possible that the virus will be resistant to some drugs. This means that some drugs may not work well to treat your HIV. We will do a blood test to find out if you have drug resistance. These results can help us know which drugs would be best to treat your HIV. If you are interested, study staff will inform you of other research studies you may be eligible for. You may be referred to other research studies. If you choose, study staff may contact your partner to come to the clinic and be tested for HIV.

PREGNANCY AND BREASTFEEDING

If you become pregnant during the study, you will stop using the study products and will be discontinued from the study. The study staff will refer you to available medical care and other services for pregnant women. The study does not pay for this care, but these services are generally free in the community. We will contact you to find out about the outcome of your pregnancy and the health of your baby.

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, small clot, or in rare cases, an infection where the needle goes into your hand or arm.

Risks of Pelvic Exams

If you require a pelvic exam, you may feel discomfort, pain or pressure during the exam and when specimens are collected. You may have a small amount of vaginal bleeding or spotting which should stop shortly after the exam.

Risks from taking the study products

The table below lists the most common side effects of OCs, PrEP and the DPP.

Expected Side Effects	OC	PrEP	DPP
Headache	X	X	X

Abdominal Pain	X	X	X
Weight Decreased	X	X	X
Nausea	X	X	X
Vomiting	X	X	X
Diarrhea	X	X	X
Rash	X	X	X
Depression	X	X	X

Risks of taking OCs

The type of OC that will be used in the study is called Zinnia F and is very similar to the OC tablet that you have been taking already. Both OCs contain the same hormones – ethinyl estradiol and levonorgestrel.

Mild side effects: Some women who take OCs experience changes in menstrual bleeding. Most of the time, women may have lighter bleeding during their menses. In some cases, women may have bleeding or spotting on days when they are not having their menses. This occurs more often when pills are missed. Other possible side effects including headache, nausea, abdominal discomfort, increased blood pressure, dark spots on the skin and changes in mood. Because you have been taking a similar OC prior to starting this study, it is unlikely that you will have different side effects during the study from the OCs than you had before the study.

Serious, uncommon side-effects: There is an increased risk of a venous thromboembolic event (VTE), which is a blood clot in a vein, which has been associated with using OCs containing estrogen. The risk of VTE is higher for women who are 35 years of age and older, or women with certain health conditions. We will check to make sure you do not have any of these conditions before you enrol in the study.

Risks of taking PrEP

Most people who take PrEP do not have any side effects. The side effects that some people taking PrEP may have are well known because PrEP has been used by many people.

Mild side effects: One out of 10 people taking PrEP may have mild side effects. Many of these side effects only last for the first month of taking the tablets and get better with time or go away completely. These side effects include mild kidney problems that are only detected by laboratory tests; inability to sleep, lack of energy or tiredness; upset stomach, stomach pain, passing gas, vomiting, soft or liquid stools, headache and dizziness.

Serious, uncommon side-effects: Other side effects are more serious, but less than 1 person in 100 people taking PrEP may have them. These rare side effects include rash, liver problems, serious kidney damage, and allergic reaction. People taking PrEP may also have small changes in the thickness of their bones and bone pain, but these changes have not caused problems for the people who had them. However, more studies are needed to understand if adolescents have long-term changes in bone after taking PrEP.

There are studies being done now to learn more about the side effects of PrEP when used by women for HIV prevention. Therefore, a small number of participants in this study may have these side effects or other side effects that we do not know about. Participants will be closely monitored or any side effects. We will screen your kidneys and overall health before you join the study and during the study. This will lower your chances of having any side-effects.

You should call or come to the clinic if you have unexplained changes in urination, weight loss, cramps, muscle pain, dizziness, tiredness, stomach discomfort, nausea, vomiting, or shortness of breath. If you have these symptoms or any other symptoms that bother you the study staff will check you and see if you should stop taking PrEP.

Risks of taking the DPP

The risks of taking the DPP capsule are the same as the risks listed above when taking OCs or PrEP separately. There are no added risks of taking OCs and PrEP together. Studies have shown that there are no interactions between OCs and PrEP that would make either product less safe or effective. International and national guidelines recommend that women at risk for HIV and unintended pregnancy can safely take OCs and PrEP together. However, because the DPP capsule is large, it may be difficult to swallow, increasing the chances of missing a dose, which could increase your risk for HIV and unintended pregnancy.

Risks of HIV and STI Testing

HIV and STI testing may make you feel anxious regardless of the test results. Counseling and testing for HIV and other STIs may cause worry and discomfort by learning more about risk for those conditions. Finding out that you have HIV or an STI may cause worry, sadness or depression. Finding out your HIV status could also cause problems between you and your partner, your family, or your friends. Trained counselors will be available to help you deal with these feelings.

Other Possible Risks

The personal nature of questions may make you feel embarrassed and/or worried when talking about sexual activities (if you are currently sexually active), your living situation, ways to protect against HIV and STIs, and your test results. You may be worried while waiting for your test results. You can choose not to answer questions at any time. Trained study counsellors/clinical staff will help you with any feelings or questions.

PrEP and OCs are very effective for preventing HIV and avoiding pregnancy, but only if they are used consistently and correctly. Being in this study will not prevent you from getting HIV or falling pregnant if you do not use the products consistently and correctly. An unintended/unplanned pregnancy may cause worry, sadness, or depression.

If you become infected with HIV and continue to use the study products it is possible that you may develop HIV drug resistance. This means that any virus that is drug resistant will survive and continue to reproduce (make copies of new HIV) in the presence of the drug that normally weakens or kills it. HIV drug resistance could make it difficult to use the study products or drugs like them to treat the HIV. Drug resistance only occurs if you were to become infected with HIV and continue to use the study product.

Participation in clinical research includes the risk of loss of confidentiality. We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. If you have any problems, study staff will talk with you and if you choose, your partner, to try to help resolve them.

BENEFITS

You will have access to OCs and PrEP, products that are known to be effective in preventing HIV infection and avoiding pregnancy when used correctly and consistently. You will receive medical exams and counselling and testing for HIV, pregnancy, and STIs. You will also receive tests to check your overall health. Regular testing and treatment may help you to stay healthy. You may be offered the

Hepatitis B vaccine if you do not have Hepatitis B infection. Information learned from this study may help us learn how to prevent women from getting HIV and avoiding pregnancy.

This study cannot provide you with general medical care, but study staff will refer you to other available sources of care if needed. You will be offered free condoms. If you are infected with HIV, you will be referred for medical care, counselling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to receive care for HIV infection from your own health care provider. If you have a treatable STI diagnosed, you will receive medicine or a referral, if needed.

NEW INFORMATION

You will be told any new information learned during this study that may affect your willingness to stay in the study. For example, we will let you know if we learn that the study products may be causing bad side effects. We will tell you any new information about preventing HIV, regardless of the product, if we learn that it works in women. We will also tell you when study results may be available, and how to learn about them.

A description of this clinical trial is available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE ASKED TO LEAVE THE STUDY

You may need to leave the study early without your permission if:

- The study is cancelled by the sponsors, funders, the local government or regulatory agency, or the Institutional Review Board (IRB)/Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of study participants.
- You are not able to keep appointments.
- Other reasons that may prevent you from completing the study successfully.

You will be asked to stop using the study products immediately and may be discontinued from the study early if you:

- Use any other drugs for HIV prevention other than what we give you.
- Have a bad reaction to the study products or a study doctor decides that using study products would be bad for you.
- Are unable or unwilling to follow the study rules.

You will be asked to stop using the study products immediately and will be discontinued from the study if you:

- Have a positive test for HIV.
- Become pregnant.

If you are removed from the study or choose to leave, we will ask you to return the study product and to come back for one final clinic visit. If you do not have the study product with you when you come to the clinic, staff members will make every effort where possible to assist you in returning it.

ALTERNATIVES TO BEING IN THE STUDY

You may be able to join other studies here or in the community. There may be other places where you can go for HIV counselling and testing and family planning. We will tell you about those studies and those places if you wish.

EMERGENCY CARE AND HOSPITALISATION

If you have a medical emergency during the time you are enrolled in the study, please seek emergency care at the nearest hospital and inform the doctor treating you that you are participating in the study. That doctor is welcome to call the study staff for information. This includes the time of up to 1 month after you have completed your time in the study. Please inform the study staff of your time in the hospital as soon as possible.

COSTS TO YOU

There is no cost to you for study visits, study products, physical exams, laboratory tests or other procedures. We can give you treatments for STIs other than HIV free of charge while you are in the study, or we can refer you for available treatment.

REIMBURSEMENT

You will receive R 300 for your time, inconvenience and expense to and from the clinic at each scheduled visit according to South African Health Products Regulatory Authority requirements. You may receive up to R 150 for any study related visits which occur in between your normally scheduled visits, depending on your travel and procedures to be completed. You may receive R 20 – R 25 or an SMS/data bundle for responding to text messages.

CONFIDENTIALITY

We will make every effort to keep your information private and confidential.

Study visits will take place in private. To keep your information confidential, your test results will be written down with a unique study identification number and not your name, address or any other information that could identify you. Only this number will be on your results and only clinic staff will be able to link this number to your name. We will keep the information about your study visits in a secure place that only certain people can access for the purposes of this study. We will only enter your information into computers protected by passwords and will not include information that could identify you. If you are selected to participate in an in-depth interview, you can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews confidential and will only use study numbers or fake names. We store the recordings for 2 years after publication of the study results or 6 years if there is no publication.

Data collected from you will not be shared with your parent/guardian without your permission. Only in cases of pending harm such as suicidal ideation or drug abuse, the study staff will consult with your and bring the parent/guardian to discuss the situation, if relevant.

Your personal information may be disclosed if required by law. For example, if we learn something that would immediately put you or others in danger, the study staff must take steps to keep you and others safe. This means that we must share any information with the authorities (hospital, police, or social services) that tells us you may be in danger. For example, if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you.

It may be necessary, depending upon local and national health requirements, for study staff to report diseases, including HIV, identified among DPP Capsule Study participants. The reportable diseases at this site are communicable diseases. If you are suspected of having a communicable disease other than HIV based on clinical examination, you may be treated on site or be referred to a local clinic for further assessment.

The study staff will only use your fingerprints and personal information to verify that you are not taking part in any other research studies on BCEPS. This study will not use your name or identify you personally in any publication.

Your records may be reviewed by:

- Study sponsors and funders
- WCG Cares
- Representatives of Population Council and its monitors
- Representatives of the United States Government including:
  - Representatives of the US Federal Government, including the US Agency for International Development (USAID),
  - The US National Institutes of Health (NIH)
  - The US Department of Health and Human Services (DHHS),
  - Office of Human Research Protection (OHRP)
- Other US, local and international regulatory entities
- Authorized representatives of Gilead and Mylan, the companies that make PrEP and OCs and/or their contractors
- Members of the study protocol team and external advisors
- South African Health Products Regulatory Authority
- Human Research Ethics Committee, University of the Witwatersrand, an Ethics Committee is a committee that watches over the safety and rights of research participants
- National Health Research Ethics Committee (NHREC)
- Members of an Independent Data Safety Monitoring Board who review this clinical trial
- Study monitors
- Study staff

The study staff will do everything they can to protect your privacy.

RESEARCH-RELATED INJURY

Wits RHI has obtained insurance for you in the event of study related injury or illness. A study-related injury or illness is one that occurs as a direct result of the administration of the study medicine or of study specific procedures. It is unlikely that you will be injured as a result of participating in this study. If you are injured as a result of study procedures, the Wits RHI will give you immediate necessary treatment for your injuries. You will not have to pay for this treatment. You will be told where you can get additional treatment for your injuries.

HIV infection is not a study related injury as it could occur at any time when a person has been exposed to the virus. As a study participant the study team will in fact try to offer you the best counselling and prevention options to prevent HIV infection. The research site or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:

- Any injury that happens because you used other medicine during the study that you did not tell us about.
- Any injury that happens because you did not follow instructions given by the study doctor or nurse.
- Any injury that happens because of negligence on your part.

If a research related injury occurs, you have not waived any of the legal rights by signing this form.

INSURANCE AND ABPI STATEMENT

The Wits RHI through trial insurance will provide compensation for reasonable medical expenses incurred as a result of study-related injury or illness, determined according to the guidelines laid down

by the **Association of the British Pharmaceutical Industry (ABPI Guidelines, Version 2014),** and **Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa (version 2006).**

Please notify the study staff immediately of any complications, side effects and/or injuries during the study and the nature of the expenses to be covered. Further detailed information on the payment of medical treatment and compensation due to injury can be obtained from me or other study staff. We have a copy of the ABPI Guidelines (version 2014) and the Insurance Certificate, should you wish to review them.

The insurance does not cover, and the sponsor will not pay for:

- Medical treatment of ***other*** injuries or illnesses
- Injury caused by non-observance of the protocol

The staff working on this study is covered by the insurance if they:

- Comply with the applicable requirements of the study protocol
- Comply with the regulations of the South African Health Products Regulatory Authority and the University of the Witwatersrand, Human Research Ethics Committee (HREC)
- Ensure that the handling and administration of the study medication is in accordance with instructions and guidelines provided in the protocol, subsequent amendments and related documents.

This insurance is not intended to be and is not a substitute for the study staff's personal malpractice insurance.

Please note that if you have a life insurance policy you should enquire whether your insurance company requires notification of your intention to participate in a clinical study. Information to date is that it should not affect any life insurance policy taken out. Nevertheless, you are strongly advised to clarify it with the company concerned.

YOUR RIGHTS AS A RESEARCH PARTICIPANT

- Voluntary: Your participation in this study is entirely voluntary and you can refuse to participate or stop at any time without stating any reason. If you choose not to join or to leave the study, you can still join other studies you are eligible for at this clinic. If you decide to withdraw from the study, the study staff will encourage you to come to the clinic for one final visit to check on your health. Your withdrawal will not affect your access to other medical care at your local clinic. If you want the results of the study after the study is over, let the study staff members know.
- Discontinuation of study products: You must inform the study team if you wish to stop the study products as soon as possible.
- New findings: The study clinic staff will provide you with any additional information that becomes available during the study, which may affect your willingness to continue in the study.

ETHICAL APPROVAL OF THIS STUDY

The DPP Capsule Study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC) and written approval has been granted by the committee. The study has been structured in accordance with the Declaration of Helsinki (last update October 2013), which deals with the recommendations guiding doctors in biomedical research involving human subjects. A copy can be obtained from me if you wish to review it.

PROBLEMS OR QUESTIONS

If you have any questions about the study, who to contact at the study site, or if you have a research related injury or any other problems related to the study, please feel free to contact the clinic staff by visiting the clinic between 08:00 to 16:30 or phoning on 011 358 5424 or after hours on 083 783 3574. If you feel that you require more information than the clinic staff can provide you, please contact one of the people listed below:

Prof Thesla Palanee – Phillips Co-Principal Investigator Wits RHI, Research Centre No. 7 Esselen Street, Hillbrow Tel: 011 358 5471 Emergency Number: 083 783 3574	Dr Nkosiphile Ndlovu Co-Principal Investigator Wits RHI, Research Centre No. 7 Esselen Street, Hillbrow Tel: 011 358 5424

If you want any information regarding your rights as a research participant, or if you have complaints regarding this study, you may contact Prof. Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at 011 717 2301.

Prof. Clement Penny Chairperson for the University of the Witwatersrand, Human Research Ethics Committee University of the Witwatersrand Tel: 011 717 2301

If you have questions about this study, you should first discuss them with your personal/study doctor or the ethics committee (contact details as provided on this form). After you have consulted your personal/study doctor or the ethics committee and if they have not provided you with the answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Chief Executive Officer South African Health Products Regulatory Authority Department of Health Private Bag X828 Pretoria 0001 E-mail: Boitumelo.Semete@sahpra.org.za Tel: Tel: 012 501 0410

DATE AND TIME OF COMPLETION OF INFORMED ASSENT DISCUSSION:

				:
DD	**MMM**	**YYYY**		**Time** *(24 hour clock)*

NOTIFICATION OF PERSONAL DOCTOR:

Please indicate if you would like us to inform your personal doctor about your participation in this study.

Please sign or place your mark/thumbprint next to the option you choose

_____ Participant's signature/mark or	Yes, I want you to inform my personal doctor (Staff to obtain personal doctor contact details)

thumbprint	
_____ Participant's signature/mark or thumbprint	No, I do not want you to inform my personal doctor
_____ Participant's signature/mark or thumbprint	I do not have a personal doctor.

INFORMED ASSENT:

- I hereby confirm that I have been informed by the study staff member_____*(Print full name)*, about the nature, conduct, benefits and risks of the DPP Capsule Study
- I have also received, read (or had read to me) and understood the above written information (Participant Information Sheet and Informed Assent for Screening and Enrolment) regarding the clinical study.
- I am aware that the results of the study, including personal details regarding my ethnicity, race, sex, age, medical conditions, date of birth, initials and diagnosis will be anonymously processed into a study report.
- I may, at any stage, without prejudice, withdraw my assent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

Signature of participant:

Signature/mark or thumbprint		Date of signature			
			DD	MMM	YYYY
Print name		Time of signature	: *(24 hour clock)*		

Signature of witness (if applicable):

Signature		Date of signature			
			DD	MMM	YYYY
Print name		Time of signature	: *(24 hour clock)*		

Signature of study staff taking assent:

Signature		Date of signature			
			DD	MMM	YYYY
Print name		Time of signature	: *(24 hour clock)*		

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-JeriĆ K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Supplied earlier in submission process
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2 (Both trials were registered on ClinicalTrials.gov on 3 March 2021: Zimbabwe: NCT04778514; South Africa: NCT04778527.)
Protocol version	#3	Date and version identifier	24
Funding	#4	Sources and types of financial, material, and other support	26
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	Roles are on page 26. Names/affiliations Entered in BMJ Open Database

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Supplied earlier in submission process
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See funding support statements
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a (not an efficacy trial)
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital)	5

		and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See Figure 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20-21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	21
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	21
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	21
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-20
Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including	13-14

retention		list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20-23
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	22-23
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21-22
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a

Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	24-25
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	24
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24-25
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	18
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24-25
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary information in submitted protocols.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Assessing the acceptability of, adherence to, and preference for a dual prevention pill (DPP) for HIV and pregnancy prevention compared to oral pre-exposure prophylaxis (PrEP) and oral contraception taken separately: protocols for two randomized, controlled, crossover studies in South Africa and Zimbabwe

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075381.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Jan-2024
Complete List of Authors:	Friedland, Barbara; Population Council, Center for Biomedical Research Mgodi, Nyaradzo; University of Zimbabwe - Clinical Trials Research Centre Palanee-Phillips, Thesla; Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Faculty of Health Sciences, School of Public Health; University of Washington, Epidemiology Mathur, Sanyukta; Population Council, Plagianos, Marlena; Population Council Center for Biomedical Research Bruce, Irene; Population Council Center for Biomedical Research Lansiaux, Maud; Population Council Center for Biomedical Research Murombedzi, Caroline; University of Zimbabwe - Clinical Trials Research Centre Musara, Petina; University of Zimbabwe - Clinical Trials Research Centre Dandadzi, Adlight; University of Zimbabwe - Clinical Trials Research Centre Reddy, Krishnaveni ; Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Faculty of Health Sciences, School of Public Health Ndlovu, Nkosiphile; Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Faculty of Health Sciences, School of Public Health Zulu, Sihle; Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Faculty of Health Sciences, School of Public Health Shale, Lerato; Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Faculty of Health Sciences, School of Public Health Zieman, Brady; Population Council Haddad, Lisa; Population Council Center for Biomedical Research
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Sexual health
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Clinical Trial, Decision Making

Protocol for DPP crossover studies in South Africa and Zimbabwe

ABSTRACT

Introduction: Oral pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention method; however, uptake and persistence have been low among southern African women. A dual prevention pill (DPP) that combines PrEP with oral contraception (OC) may increase PrEP use and better meet women's sexual and reproductive health needs. We will gauge the DPP's acceptability in two crossover clinical trials.

Methods and Analysis: PC952 (Zimbabwe) and PC953 (South Africa) will compare acceptability, adherence, and preference for an over-encapsulated DPP versus PrEP and OCs taken separately. HIV-negative, non-pregnant cis-gender females in Johannesburg, South Africa (n~96 16-40-year-olds) and Harare, Zimbabwe (n~30 16-24-year-olds) will be randomized 1:1 to the order of regimens – DPP or 2 separate tablets – each used for 3 28-day cycles, followed by a 6-month Choice period in South Africa. Monthly clinic visits include HIV and pregnancy testing; safety assessments; and risk reduction and adherence counselling. We will assess adherence (monthly) based on tenofovir diphosphate drug levels in dried blood spots and by self-report. We will evaluate acceptability (monthly) and preference (end of crossover) via computer assisted self-interviewing and in-depth interviews with a subset of participants. Data collection started in September 2022 and is projected to end by December 2023.

Ethics and Dissemination: PC952 was approved by the Ministry of Health and Child Care, Medical Research Council, Research Council, and Medicines Control Authority of Zimbabwe; the Chitungwiza City Health Ethics Committee; and the Joint Research Ethics Committee for the University of Zimbabwe Faculty of Medicine and Health Sciences and Parirenyatwa Group of Hospitals. PC953 was approved by the South African Health Products Regulatory Authority and the University of the Witwatersrand's Human Research Ethics Committee. The Population Council IRB approved both studies. We will disseminate results in open access journals, clinical trials registries, and at local and international meetings and conferences.

Trial registration: Both trials were registered on ClinicalTrials.gov on 3 March 2021: Zimbabwe: NCT04778514; South Africa: NCT04778527.

Keywords: HIV, HIV prevention, PrEP, oral contraceptive (OC), pregnancy prevention, dual prevention pill (DPP), multipurpose prevention technologies (MPT), randomized controlled trial, AGYW, South Africa, Zimbabwe.

Strengths and limitations of these studies

- The crossover design enables a direct comparison between the intervention (DPP) and standard of care or control (PrEP and COCs separately) regimens that enables a smaller sample size with women serving as their own controls.
- Participants will be followed monthly, which will enable frequent assessments of PrEP drug levels in blood, however, it will not be feasible to measure contraceptive drug levels in blood due to the short half-life of COCs.
- The two pilot studies enable early assessments of the DPP in two different contexts: South Africa (low COC use/high HIV incidence and prevalence) and Zimbabwe (high COC use/moderate HIV incidence and prevalence), and among AGYW and older women.
- The key limitation of the studies is the use of an over-encapsulated DPP as a proxy for the ultimate co-formulated tablet, which may not accurately capture acceptability, preference and adherence for the ultimate DPP, which will be a smaller tablet versus a capsule.
- Another limitation is the different study designs and sample sizes for the two studies, primarily related to their respective funding mechanisms, that may limit the ability to directly compare results from the two countries.

INTRODUCTION

Despite substantial advances in HIV treatment and prevention over the last decade, women and girls in eastern and southern Africa continue to be disproportionally affected by HIV/AIDS, accounting for 63% of all new HIV infections in the region in 2021 [1]. In 2021, new HIV infections in South Africa were more than double among women aged 15 and over than among men of the same age (130,000 versus 70,000, respectively) [2]. Similarly in Zimbabwe, nearly twice as many women 15 and older acquired HIV in 2021 compared to their male peers [1].

Oral pre-exposure prophylaxis (PrEP) is more than 90% effective in reducing HIV transmission [3]. However, many oral PrEP trials and demonstration projects in sub-Saharan Africa have been plagued by low adherence, particularly among adolescent girls and young women (AGYW) [4,5]. Stigma and fear of intimate partner violence or relationship dissolution are often cited as reasons for non-use of PrEP [6–9]. Novel strategies to bolster uptake and adherence are needed to increase PrEP use among women and girls at high risk of HIV.

Many women – and AGYW in particular – are more worried about unintended pregnancy than HIV [10,11]. Furthermore, there is a growing body of evidence indicating that many women may be more likely to use an HIV prevention method that also prevents pregnancy [12–19]. Condoms are currently the only multipurpose prevention technologies (MPTs) that prevent both HIV and unintended pregnancy [20]. Male condoms, however, are not under a woman's control; female condoms have had limited uptake due to access and acceptability issues [21,22]; and many women risk gender-based violence by merely suggesting condom use [23]. Several novel MPTs are in the pipeline [24], including a dual prevention pill (DPP) containing the ingredients in PrEP and oral contraception. The first DPP being developed is based on the commonly-used 28-day combined oral contraceptive (COC) regimen (150 mcg levonorgestrel [LNG], 30 mcg ethinyl estradiol [EE]) and a generic equivalent of Truvada® (300 mg tenofovir disoproxil fumarate [TDF],

200 mg of emtricitabine [FTC]) [25] [26]. The DPP is likely to be the fastest route to an approved MPT as it contains two registered products that are safe and effective for their respective indications [27–30] with no evidence of drug-drug interactions [31–34]. In South Africa 25.6% of women report ever having used COCs and 10.5% currently use them [35,36]. In Zimbabwe, COCs are the most common family planning (FP) method among those using a modern method [37]. Data on oral contraceptive use among adolescents in sub-Saharan Africa is limited, however, an analysis from 33 sub-Saharan African countries indicated that COC use ranged from approximately 15% to 20% among 15-24 year olds [38]. Truvada® is approved as PrEP in more than 20 countries globally, including South Africa and Zimbabwe, and is recommended by WHO and CDC for women at risk of HIV using COCs [29,39].

We hypothesize that the DPP could greatly increase PrEP adherence, while also meeting women's unmet FP needs. Our goal is to generate data to inform DPP introduction through two clinical crossover studies comparing acceptability of, adherence to, and preference for the DPP versus two separate tablets. To that end, and in parallel with development of the co-formulated DPP, we have over-encapsulated PrEP (Truvada®) and a COC (Zinnia F [150 LNG/30 EE]), into a single capsule (**Figure 1**) for our studies to provide an early indication of DPP acceptability.

INSERT FIGURE 1 HERE

METHODS AND ANALYSIS

Trial Design

(Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines used.) Population Council Protocols 952 and 953 are randomized, controlled, open-label, parallel group, crossover studies.

Participant and public involvement

Formative research (December 2020-June 2021) with service providers and potential end users in South Africa and Zimbabwe informed the clinical trial design, materials, and recruitment methods. Established community and/or youth advisory groups at each site reviewed the protocols and provided input into the consent forms, behavioral questionnaires, and translations. The study teams have also benefitted from participation in the DPP consortium, a collaborative group of researchers, donors, and civil society advocates established to inform and accelerate DPP development and introduction [40].

Study settings

Hillbrow (Johannesburg), South Africa

PC953 is being conducted at the Wits RHI Research Centre, a large research clinic situated in Hillbrow, Johannesburg. As of 2020, Johannesburg had 756,751 people living with HIV with an overall HIV prevalence of 13%. HIV prevalence was highest among females across all age groups: 28.3% for 25-49-year-olds, 15% for women 50 and above and 9% for 15-24-year-olds [41]. Wits RHI conducts research on HIV, sexual and reproductive health (SRH) and vaccine preventable diseases.

Chitungwiza (Harare), Zimbabwe

PC952 is being implemented by the University of Zimbabwe Clinical Trials Research Centre (UZ-CTRC) at the Zengeza Clinical Research Site (CRS) in Chitungwiza, Zimbabwe's second largest city approximately 30km south of Harare, with a generalized epidemic and HIV prevalence of 3.8% among 15-19-year-old women and 6.3% among 20-24-year-old women [42]. The Zengeza CRS is located within a Chitungwiza City Health Department Municipal Clinic and conducts research on female-controlled HIV/STI (sexually transmitted infection) prevention strategies, including microbicides, oral and injectable PrEP and cervical barriers, and integrated HIV prevention strategies.

Study populations

We are recruiting participants (~96 16-40-year-olds, South Africa; 30 16-24-year-olds, Zimbabwe) from FP, PrEP and SRH clinics, and the general population. Although the DPP may ultimately appeal to individuals using other contraceptives or with an unmet FP need, we are enrolling participants who are already using COCs and are accustomed to daily pill-taking and the associated side effects of COCs (though they will not be used to the large DPP capsule). In addition, a recent study in Cape Town found that only 52% of 15-19 year olds (n=50/96) randomly assigned to use COCs (versus intravaginal rings or injectables) reported being fully adherent over an 8-week period [43], highlighting the importance of enrolling participants who have already been using COCs for at least three months.

Inclusion/Exclusion Criteria

Eligible participants are healthy, HIV-negative, non-pregnant, sexually active, cis-gender females at moderate to high risk of HIV infection. Specific eligibility criteria (**Table 1**) for the two protocols are similar, with several differences based on routine national protocols for PrEP provision and age range. Screened by nurses/clinicians includes medical history, physical examination, and

clinical laboratory tests. HIV risk is assessed by clinicians using local PrEP guidelines and by participants who are offered access to tools, such as BWise [44], to help them make that determination. Key exclusion criteria and prohibited medications relate to contraindications for COCs or PrEP use. We are also excluding those unable to swallow a large vitamin pill similar in size to the over-encapsulated DPP (**Figure 1**).

Table 1. Inclusion and exclusion criteria for South Africa (SA) and Zimbabwe (Zim)

Criteria	SA	Zim
INCLUSION CRITERIA		
Age 16 through 40 years old (inclusive) at Screening, verified per site-specific SOPs.	X	
Age 16 through 24 years old (inclusive) at Screening, verified per site-specific SOPs.		X
Able and willing to provide informed consent per site SOPs. (If under the legal age of consent [18 years old] be able to provide informed assent and obtain parental or guardian consent, to be screened for and to enroll in the study.)	X	X
Fluent in spoken Zulu and/or English.	X	
Fluent in spoken Shona and/or English.		X
Able and willing to provide adequate locator information, as defined in site SOPs.	X	X
Able and willing to comply with all study procedures, including being comfortable taking the study products as evident by nurse/clinician-observed swallowing at Screening of a large Vitamin capsule that is of similar size to the study products.	X	X
Post-menarche, per participant report at Screening.	X	X
Sexually active, defined as having had penile-vaginal sex with a male within the 3 months before Screening (per self-report).	X	X
At moderate to high risk of HIV infection based on clinician assessment.	X	X
Considers herself to be at moderate to high risk of HIV acquisition based on self-assessment.	X	X
Has been using COCs for contraception for at least 3 months prior to Screening as confirmed by contraceptive card and intends to continue using COCs for at least 12 months.	X	
Currently using COCs for contraception and has been using them for at least 3 months prior to Screening.		X
HIV-negative per rapid test at Screening and Enrolment per site-specific SOP.	X	X
Negative pregnancy test at Screening and Enrolment.	X	X
Negative for chlamydia, gonorrhea, trichomoniasis, and syphilis at Screening; women who test positive at Screening may be treated and enrolled.	X	X
Hepatitis B surface antigen (HBsAG) negative per blood test at Screening.	X	
Hepatitis B surface antigen and Hepatitis C negative per blood test at Screening.		X
Normal estimated creatinine clearance (eCrCl) ≥ 60 ml/min per blood test at Screening.	X	X
EXCLUSION CRITERIA		
Currently using emtricitabine (FTC) or tenofovir (TDF) at Screening (per self-report)		X
Intends to become pregnant within the next 12 months.	X	X
Intolerance, adverse reaction, or laboratory abnormality associated with PrEP use in the past.	X	X
Use of PEP within 3 months of Screening (per self-report).	X	X
Breastfeeding < 6 months postpartum (per self-report).	X	X
Less than 6 weeks (≤42 days) postpartum and not breastfeeding (per self-report).	X	X
For women 35 and older, currently smokes cigarettes (self-report).	X	

EXCLUSION CRITERIA		
History of deep vein thrombosis / pulmonary embolism (self-report) or history of thrombophlebitis or thromboembolic disorders at Screening (per self-report or medical records).	X	X
Prolonged immobilization (self-report).	X	X
Known thrombogenic mutation/complicated valvular disease (per self-report).	X	X
History of cerebro-vascular or coronary artery disease reported at Screening.		X
Ischemic heart disease (per self-report).	X	X
Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies (per self-report).	X	X
Migraines with aura	X	X
For women over 35 years old, migraines without aura (per self-report).	X	
History of undiagnosed abnormal genital bleeding reported at Screening.		X
Current breast cancer or within 5 years of past breast cancer (per self-report) or history of carcinoma of the breast or other estrogen-dependent neoplasia reported at Screening.	X	X
Diabetes with nephropathy, retinopathy, or neuropathy (per self-report).	X	X
Diabetes for > 20 years (per self-report).	X	X
Symptomatic gall bladder disease (per self-report).	X	X
Severe cirrhosis (per self-report).	X	X
Liver tumor (per self-report).	X	X
Any other condition the clinician feels would jeopardize the health and wellbeing of the participant.	X	X

Study Schema

At Enrollment, participants are randomized to the sequence of study regimens (**Figure 2**): Sequence 1 = single DPP capsule once daily for three 28-day cycles (Regimen A) followed by two separate tablets (oral PrEP and COC) once daily for three 28-day cycles (Regimen B); Sequence 2 = Regimen B followed by Regimen A. In South Africa, after the six-month crossover period, participants may choose Regimen A, B or neither for up to six additional 28-day cycles. Study product regimens are described in detail in **Table 2**.

INSERT FIGURE 2 HERE

All participants take PrEP (FTC/TDF 200/300 mg) once daily by mouth throughout the entire study and 21 days of active COCs followed by 7 days of placebo tablets, regardless of regimen. The selection and timing of doses correspond to the labels for Truvada (Gilead Sciences, Inc; Foster City, CA, USA) and Zinnia F COCs (Mylan Laboratories Limited**,** Hyderabad, India). Zinnia F was selected because it is the same formulation as Control L, the COC purchased for public family planning programs in Zimbabwe. During the "placebo" days of Regimen A, participants take one capsule containing Truvada only, whereas the placebo days of Regimen B consist of two separate tablets: Truvada and a placebo COC tablet. The DPP capsules were manufactured and packaged by PCI Pharma Services (Rockford, IL, USA) from the same batches of Truvada and Zinnia F as the separate pills procured from Gilead and Mylan, respectively.

Table 2. Study products

Regimen	Description	Dose, Route and Frequency
A – Dual Prevention Pill (DPP)	Each DPP kit contains 28 capsules divided into 4 pouches, 1 per cycle week. Each pouch contains a blister strip of 7 capsules (plus desiccant). • 3 pouches contain 21 pink and white capsules which each have 1 Truvada tablet (FTC 200mg/TDF 300 mg) and one Zinnia F tablet. (EE/LNG 30/150 mcg) • 1 pouch contains 7 white capsules containing 1 Truvada tablet.	• Participants will take 1 DPP capsule orally, once daily at approximately the same time each day for 12 weeks (Crossover period), taking the next consecutively numbered capsule from each pouch, in order (Week 1, Week 2, Week 3, Week 4). In South Africa, the DPP may be taken for ≤6 additional months (Choice period). • If they miss 1 DPP capsule, participants will be instructed to take it as soon as they remember, up to the time of their next dose, but no more than 2 doses in a 24-hour period. • Participants will be counseled to use back-up contraception (e.g., condoms or abstinence) for 7 days if they miss 2 or more consecutive doses.
B – 2 Separate Tablets	Bottle of 30* Truvada (FTC/TDF 200/300 mg) tablets (PrEP) Blister card of Zinnia F COCs: 21 white active EE/LNG 30/150 mcg pills and 7 brown placebo pills (no hormone) *At the end of the 28-day period, participants should have 2 Truvada tablets remaining in the bottle and will be instructed to return those tablets to the study clinic.	• Participants will take 1 Zinnia F tablet and 1 Truvada tablet once daily. Tablets may be taken together or separately, but each tablet (Zinnia F, Truvada) should be taken at the same time each day. • Zinnia F tablets are to be taken in the order indicated on the pack, including the 7 placebo tablets. If a participant misses a COC dose, she will be instructed to take it as soon as she remembers. If a full day has passed, she should take 2 tablets the next day, per the label. Participants will be counseled to use back-up protection for 7 days if they miss ≥2 consecutive doses. • If a participant misses 1 Truvada dose, she will be counseled to take 1 tablet the next day, per the label, but not to take more than 1 dose in 24 hours. • Participants will be counseled that the effectiveness of PrEP may be reduced if doses are missed.

Study objectives

Objectives and outcomes are similar in both trials (**Table 3**).

180 **Table 3. Objectives and Endpoints for PC952 (Zimbabwe) and PC953 (South Africa)**

Objective	Endpoint	Type of endpoint (Country)
PREFERENCE		
To determine preference for taking a single DPP capsule once daily versus 2 separate tablets (PrEP and COC) once daily among women after using each regimen for three 28-day cycles.	Proportion of women who prefer the DPP (Regimen A) vs 2 separate tablets (Regimen B) after using each regimen for 3 28-day cycles, per self-report on computer-assisted self-interviewing (CASI). .	Primary (South Africa and Zimbabwe)
To determine if more women choose Regimen A versus Regimen B for the Choice period.	Proportion of women who choose Regimen A vs B for the Choice period.	Primary (South Africa only)
ADHERENCE		
To compare adherence to the DPP (Regimen A) versus 2 separate tablets (Regimen B) among women using each regimen daily for 3 28-day menstrual cycles during the Crossover period.	TFV-DP levels in dried blood spots (DBS) by regimen, and overall, at follow up visits every 4 weeks visits during Crossover period.	Primary (South Africa) Secondary (Zimbabwe)
To compare adherence among women who choose the DPP (Regimen A) versus adherence among women who choose 2 separate tablets (Regimen B) during the Choice period.	TFV-DP levels in DBS by regimen, and overall, at follow up visits every 4 weeks during Choice period.	Primary (South Africa only)
To assess and compare self-reported adherence to Regimen A vs Regimen B during the Crossover period, and to the chosen method during the Choice period.	Self-assessment of ability to adhere to instructions for product use in CASI interviews and proportion of doses taken by pill count (DPP capsule, FTC/TDF and COCs as applicable) at follow up visits every 4 weeks during the Crossover and Choice periods.	Primary (South Africa)
To compare daily adherence to PrEP for six 28-day cycles among women when taken in the DPP capsule (Regimen A) versus as a separate tablet (Regimen B).	Difference in measurable TFV-DP drug levels in DBS between the 2 regimens; difference in adherence between the 2 regimens based on doses taken compared to total number of doses expected per self-report and pill count.	Secondary (Zimbabwe)
To explore if socio-ecological factors, product characteristics and product use experiences are associated with adherence to PrEP whether taken as part of the DPP capsule or as a separate tablet.	Results of multivariate modeling indicating which, if any, factors are associated with adherence.	Secondary (Zimbabwe)
To explore facilitators and barriers to use, as well as socioecological factors that may be associated with acceptability, preferences and adherence.	Results of multivariate modeling indicating which, if any, factors are associated with adherence.	Secondary (South Africa)

Objective	Endpoint	Type of endpoint (Country)
ACCEPTABILITY		
To assess the acceptability of taking the DPP capsule versus two separate tablets once daily to prevent HIV and unintended pregnancy among women who use each regimen for three 28-day cycles.	Acceptability scores by regimen and overall, per a quantitative acceptability questionnaire via CASI.	Primary (Zimbabwe)
To assess the acceptability of taking the DPP (Regimen A) vs 2 separate tablets (Regimen B) once daily to prevent HIV and unintended pregnancy among women who use each regimen for 3 28-day cycles during the Crossover period.	Scores by regimen and overall, as measured in a quantitative acceptability questionnaire via CASI at the Crossover visit, the start of the Choice period, and the end of the study.	Secondary (South Africa)
To assess if pre-use opinions are associated with actual experiences and preferences after using each regimen.	Proportion of women whose pre-use preference matches post-use experience based on a CASI questionnaire at baseline and at the end of the Crossover period.	Secondary (South Africa)
To qualitatively understand barriers and facilitators to product use and adherence.	Results of thematic qualitative data analysis from in-depth interviews with participants at study exit focusing on facilitators and barriers of product use and adherence.	Secondary
To explore if socio-ecological factors, product characteristics and product use experiences are associated with acceptability of the DPP and of 2 separate tablets.	Results of multivariate modeling indicating which, if any, factors are associated with acceptability.	Secondary
SAFETY		
To compare the safety of Regimen A versus Regimen B among women using each regimen for 3 28-day cycles during the Crossover period, and the safety of Regimen A versus Regimen B among women choosing each regimen during the Choice period.	Number of AEs by regimen (including social harms, drug side effects) during the Crossover and Choice periods.	Secondary (South Africa)

Study procedures

Informed consent

Before undergoing screening procedures, a counselor/designee leads a discussion to review the informed consent form in detail with potential participants in their preferred language (English or isiZulu, South Africa; English or Shona, Zimbabwe). The same study staff member implements a comprehension assessment to check participants' understanding of key study aspects, including the potential increased risk of HIV or unintended pregnancy if difficulty swallowing the large DPP

capsule leads to more missed doses, before they both sign the consent form. For unemancipated minors (16-17-year-olds), informed consent from the parent/legal guardian consent is obtained before assent from the minor. Key elements of the informed consent are reviewed on an ongoing basis and willingness to continue study participation is ascertained.

Eligibility screening

After consenting, potential participants are assigned a unique Participant Identification number and undergo screening procedures. All screening test results and, if enrolled, study information (data, specimens) are recorded with IDs and no other identifying information to preserve participant confidentiality. Locator information is collected at screening and reviewed at each study visit to ensure participants are contactable for retention purposes. The screening process typically takes more than one day because several lab tests are outsourced. At screening (Visit 0), a nurse/clinician takes a complete medical history, including gynecologic and obstetric history. A clinical exam is performed to assess overall health (including complete blood count [CBC] in Zimbabwe). Urine is tested for pregnancy (human chorionic gonadotrophin [hCG]), and *Neisseria gonorrhoeae/Chlamydia trachomatis* (nucleic acid amplification test [NAAT]). Blood is tested for HIV, syphilis, and hepatitis B virus (and Hepatitis C in Zimbabwe), and to measure creatinine clearance. Screening also includes direct observation of participants swallowing a large vitamin capsule, similar in size to the 000 DPP capsule (**Figure 1**).

Enrollment and randomization

Enrollment (Visit 1) is scheduled when participants are starting their next COC pack (+/- 5 days). At Enrollment, participants are tested for HIV (rapid antigen blood test) and pregnancy (urine hCG) to confirm eligibility. Those eligible are enrolled and randomized (1:1) to the sequence of regimens, are given a supply of their first study product with detailed dosing instructions and take their first dose directly observed in the clinic. Participants are counseled on management of

anticipated side effects and missed pills based on recommendations that incorporate differing guidelines for COCs and oral PrEP [45]. Participants also receive counselling on HIV/STI risk reduction, contraception, and protocol compliance – including the importance of attending clinic visits and taking the study products – at every visit.

Follow-up visits

Supplemental Table 1 contains the detailed schedule of visits and procedures. At all visits, blood is collected for dried blood spots (DBS) to assess tenofovir-diphosphate (TFV-DP) levels as a measure of PrEP adherence [46] and for rapid HIV testing. Urine is collected for pregnancy testing. After the first three cycles, participants "crossover" to their second regimen at Month 3/Visit 4 and return unused study product from their first regimen. They then receive their first supply of the second regimen, with detailed instructions, and take their first dose directly observed in the clinic. Participants attend monthly follow up visits during the second regimen (Month 4/Visit 5; Month 5/Visit 6). At Month 6/Visit 7, all participants exit in Zimbabwe. In South Africa, participants may continue using either regimen (or neither) for up to another six months during a "Choice" period, with similar monthly visits.

Laboratory procedures

Laboratory assessments are listed in **Supplemental Table 1**. Blood specimens for hepatitis, creatinine, HIV confirmation testing (and CBC in Zimbabwe) are processed off-site by BARC (South Africa) and UZ-CTRC (Zimbabwe). DBS specimens are analyzed at the University of Cape Town by liquid chromatography-tandem mass spectrometry [46].

Safety monitoring and adverse event (AE) reporting

Clinical assessments at each visit post-enrollment are done to monitor potential AEs and social harms. Individual participants who develop Grade 1 or unrelated Grade 2 AEs, based on the

Division of AIDS Grading system [47], may continue using their assigned study product(s) per protocol, at the site PI's/designee's discretion. Individuals who develop a related Grade 2 AE, or any Grade 3 AE, regardless of relatedness, will be evaluated by the site PI/designee and Medical Monitor for possible discontinuation from the study. Grade 4 AEs, regardless of relatedness, will be evaluated by the site PI/designee and Population Council Medical Monitor and those participants will be discontinued from the study. No dose modifications will be undertaken nor are there any *a priori* stopping rules because both study products (PrEP and COCs) are marketed drugs.

Seroconversion or pregnancy

Participants who seroconvert are terminated from the study. At their closing visit, study staff will collect unused pills, conduct resistance and viral load testing, and link the participant to HIV/FP care per local guidelines. Similarly, participants who become pregnant will be terminated and referred to services for pregnant individuals, including PrEP provision, if desired. The sites will make every effort to follow-up on all pregnancy outcomes. The sites may continue counselling participants as they transition to services to preserve their confidentiality after discontinuation.

Creatinine

Creatinine levels are monitored according to PrEP guidelines in each country, approximately quarterly [48,49]. Participants with abnormal creatinine levels may be put on a temporary product hold, pending the PI/designee's decision, until a repeat test can be done. Participants who have two tests outside the normal range will be permanently discontinued to reduce their risk if the DPP or PrEP is contraindicated.

Data and safety monitoring

The Population Council monitor conducted site qualification and initiation visits at both sites before data collection began. Periodic monitoring visits ensure the protocol and good clinical practice

are being followed. The monitor reviews source documents to confirm that the data recorded on case report forms (CRFs) is accurate, and reviews relevant documents to verify protocol compliance. A data safety and monitoring board (DSMB) was established, consisting of three experts with clinical expertise in HIV and contraception, epidemiology, biostatistics, and clinical trials. The DSMB (charter available upon request) will review data after all participants are enrolled (both countries), and after all participants complete the crossover visit (South Africa). All serious AEs (SAEs) and AEs leading to discontinuation will be reported to the relevant IRBs/ethics committees, drug regulatory authorities, sponsor, DSMB, and funders. Unanticipated AEs that are potentially related to the study product(s) will be reported as Suspected Unexpected Serious Adverse Reaction to the manufacturers (Gilead or Mylan).

Clinical staff are trained to identify, probe for, manage, and report AEs and social harms at every visit. Study clinicians review abnormal test results, liaise with local clinic doctors, and have the authority to terminate participants based on clinical opinion. Upon completion of the study, participants are referred to local clinics for PrEP and COC services, if they want to continue the methods. Any breaches in confidentiality, study protocol or AEs attributable to this study will be reported to the relevant IRBs/ethics committees and regulatory authorities.

Data collection and management

Clinical case report forms (CRFs)

CRFs were developed by the Population Council and the trial sites to capture demographics, medical history, clinical exam results, laboratory test results, product supply/pill counts, AEs, randomization, and termination data. Data are collected and managed using REDCap (Research Electronic Data Capture) hosted at the Population Council [50,51]. Data are entered into REDCap within five days of each participant's visit. Queries are triggered during data entry or by the Population Council data manager during weekly data reviews.

Quantitative behavioral surveys

At each visit, participants complete a behavioral questionnaire via computer-assisted self-interview (CASI) in their choice of English or the local language (isiZulu in South Africa, Shona in Zimbabwe) CASI questionnaires take approximately 30 minutes to complete and include questions about product acceptability, adherence, and overall trial experiences. Participants complete their interviews privately on tablet computers, with study staff nearby to address potential technical challenges.

Qualitative exit interviews

A subset of participants will take part in an in-depth interview (IDIs) after exiting the study. In South Africa, we will interview up to 30 participants representing those exiting early (during the Crossover period), those exiting after the Crossover period, and those completing the Choice period (half who chose the DPP and half who chose two separate tablets). In Zimbabwe, we will interview all willing participants. IDIs will be conducted by female research assistants using a semi-structured guide to explore preference for the DPP or two separate tablets; reasons for continuation/discontinuation; influence of partners, family, and support structures; side effects; provider interactions; and other factors affecting DPP acceptability and adherence. IDIs will last 40-60 minutes and will be scheduled at the Closing Visit or on a separate date, depending on participant availability. IDIs will be conducted in the participant's choice of language; will be audio recorded and transcribed; and translated into English (if necessary) for analysis.

STATISTICAL CONSIDERATIONS

Sample size and power calculations

South Africa

The sample size calculation was based on comparing ***adherence*** between the two regimens. A sample size of 86 has 80% power to detect a difference between the proportion of women who

are adherent to each regimen assuming 25% of women are adherent to PrEP alone, 40% are adherent to the DPP, with a correlation between regimens of 50%, and no period effect. We estimated 25% of participants would be adherent to the 2-pill regimen based on findings from other PrEP studies among young women in sub-Saharan Africa [5,52]. We increased the sample to 96 in case 10% of participants discontinued early while still having 86 participants complete the Crossover period.

Zimbabwe

The sample size was calculated based on detecting a difference in ***preference*** for the DPP versus two separate pills. A sample size of 30 has 94% power to detect a preference for one regimen over the other when the true preference for one regimen is at least 80% based on the exact binomial test (alpha = 0.04). If only 27 AGYW complete the study (10% loss to follow up), we have 84% power to detect a preference for one regimen over the other when the true preference for one regimen is at least 80%, based on the exact binomial test (alpha = 0.02).

Randomization

Randomization schemes for each study were developed by the Population Council biostatistician using Statistical Analysis Software (SAS/STAT) version 9.4 (SAS Institute Inc., Cary, North Carolina) with a 1:1 allocation using permutated block sizes. In South Africa, randomization is in blocks of 12, six participants per sequence in each of eight blocks. In Zimbabwe, randomization is in blocks of ten, five participants per sequence in each of three blocks. The randomization schemes are embedded within the REDCap systems for each study. At enrollment, the clinician consults REDCap to assign the treatment sequence for each sequentially enrolled participant.

Data Analysis

The “all participants” population includes all enrolled participants, the “safety population” includes

all participants who have used at least one dose of either regimen, and the "per protocol" population includes all participants who complete both regimens. In general, descriptive statistics (frequencies, mean, standard deviation, range) will be used to summarize and characterize data collated on differences in participants assigned to each sequence. Point estimates and corresponding 2-sided 95% confidence intervals will be presented for endpoints, where appropriate. Missing data will not be imputed.

Preference for the DPP will be measured as the proportion of women (per protocol population) reporting at the end of the Crossover period that they prefer the DPP capsule versus two separate tablets (or vice versa) by testing whether this proportion is greater than 0.5 using a z-test statistic under the exact binomial test in Zimbabwe (n=30), and normal approximation of the binomial distribution in South Africa (n=96). However, if the number of women completing each sequence is unbalanced, the comparison will be done using a random effects mixed model adjusting for effects treatment sequence may have on preference. In South Africa, we will similarly analyze the proportion of women who choose the DPP versus two separate tablets for the Choice period.

Adherence (overall) will be measured (safety population) by self-report, pill count and TFV-DP levels in DBS measured at each visit, and will be compared by regimen. Adherence in DBS will be assessed by comparing the proportion of women with TFV-DP levels consistently greater than the threshold known to provide efficacy, using McNemar's test for paired proportions. Adherence by pill count and self-report will be measured as the proportion of the total number of doses taken of the number of expected doses. If all women do not complete the Crossover period, analyses will be conducted with those who completed all six visits (24 weeks). Adherence during the Choice period (South Africa) will be analyzed similarly.

Acceptability of using the DPP capsule versus two separate pills will be measured in the safety

population using a quantitative acceptability questionnaire. The primary outcome of acceptability will be measured based on responses to questions in the following acceptability domains: use attributes, product attributes, side-effects, and effect on sexual activity. Acceptability scores will be summarized by regimen and timepoint and compared by regimen at each visit. Scores will be compared using a random effects mixed model to evaluate the effects of regimen and timepoint.

Safety data include findings from physical (and pelvic, when indicated) exams, laboratory tests, and AEs. AEs will be coded in accordance with the Medical Dictionary for Regulatory Activities [53]. A summary of AEs will be based on treatment-emergent AEs, which include all AEs occuring on or after the first dose. The number and percent of participants for each AE and SAE will be summarized by system organ class and preferred term, overall and by regimen.

Effects of socio-cultural and demographic characteristics (e.g., age, education, income, employment, relationship status, HIV risk perception, self-efficacy for HIV prevention) on preference, acceptability and adherence will be explored using random effects mixed models. Socio-cultural and demographic data will be collected at screening and enrollment.

Qualitative data will be analyzed thematically by researchers at the study sites and the Population Council. We will apply inductive (data-driven) and deductive (*a priori*) codes to the data using software, such as NVivo. Coded data will be synthesized to generate descriptions of behaviors, attitudes and beliefs about the acceptability of the DPP capsule, preference for the DPP or two separate pills, trial experiences, and other emergent themes [54–56].

ETHICS AND DISSEMINATION

Ethics

Both protocols and amendments, informed consent forms, and recruitment materials were approved by the Institutional Review Board of the Population Council (NY, NY, USA). The South Africa protocol and amendments (PC 953, Version 3.0, 08th June 2022), consent forms, recruitment materials and data collection instruments in both English and isiZulu were reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee and South African Health Products Regulatory Authority. The Zimbabwe protocol and amendments (PC952, Version 3.0, 17 June 2022), consent forms, recruitment materials and data collection instruments in English and Shona were approved by the Medical Research Council of Zimbabwe, the Medicines Control Authority of Zimbabwe, the Joint Research Ethics Committee of the University of Zimbabwe, the Ministry of Health and Child Care of Zimbabwe, the Chitungwiza City Health Ethics Committee, and the Research Council of Zimbabwe. Both studies are being conducted in accordance with the United States Code of Federal Regulations, the International Conference for Harmonization of Technical requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice E6 (R2), and local standard operating procedures at each site. Participants are compensated for each visit commensurate with the norms and standards in each country. Both trials are registered on clinicaltrials.gov (NCT04778514 and NCT04778527). Screening began in August 2022 and data collection ended in January 2024.

Dissemination

The study teams provide periodic updates to their communities and Community Advisory Boards during trial implementation. On completion, results will be presented locally at each site during in-person/virtual meetings with study participants, community advisory boards, and other local stakeholders; at national and international conferences; through the DPP consortium; and posted on PrEP Watch. Manuscripts will be submitted to peer-reviewed journals and will be made

available via open-access whenever feasible. Data will be uploaded on the ClinicalTrials.gov site, the U.S. Agency for International Development's (USAID) Data Development Library (South Africa only) and in country registries, as applicable. Datasets and protocols will be available from the sponsor upon request.

Figure 1. Over-encapsulated dual prevention pill (DPP)

Figure 2. Study Schema

AUTHOR CONTRIBUTIONS

BAF wrote both study protocols and the final version of the manuscript; SM conceptualized and wrote the behavioral data collection aspects of the protocol and manuscript; MP wrote the data management and statistical analysis sections of the protocol and manuscript; NM, AD, CM, PM, SM, TP-P, KR, NN, SK, LS, BZ and LH participated in protocol development and contributed to the manuscript. ML wrote an earlier draft of the paper; IB oversees study implementation, assisted in writing and editing the paper, and prepared the manuscript for publication. All authors reviewed and approved the final version of the manuscript.

FUNDING

PC953 is made possible by the generous support of the American people through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and U.S. Agency for International Development (USAID) via cooperative agreement #No. AID-OAA-A-13-00088. The contents are the responsibility of the authors and do not necessarily reflect the views of PEPFAR, USAID, or the U.S. Government.

PC952 research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under Award Number R34MH119982. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The Children's Investment Fund Foundation (CIFF) Award Number R-1903-03681, 2106-06589 supported the manufacturing of the study product, as well as supplementing the US government funding for both studies. The content is solely the responsibility of the authors and does not necessarily reflect the views of CIFF.

ACKNOWLEDGMENTS

We would like to acknowledge George Creasy, who spearheaded work to develop a DPP; Bruce Variano for overseeing the development and testing of the over-encapsulated DPP; Dan Loeven for overseeing regulatory aspects of manufacturing the DPP; Susanna Grecky and Rebecca Brodsky for liaising with suppliers and manufacturers; Sherry Hutchinson for creating the educational materials for the trial and graphics appearing in the paper; and Heather Sussman for study oversight as clinical trial monitor.

COMPETING INTERESTS

None declared

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Figure 1. Over-encapsulated dual prevention pill (DPP) *Note: The hand shown is of one of the co-authors and is not a patient.

436x261mm (300 x 300 DPI)

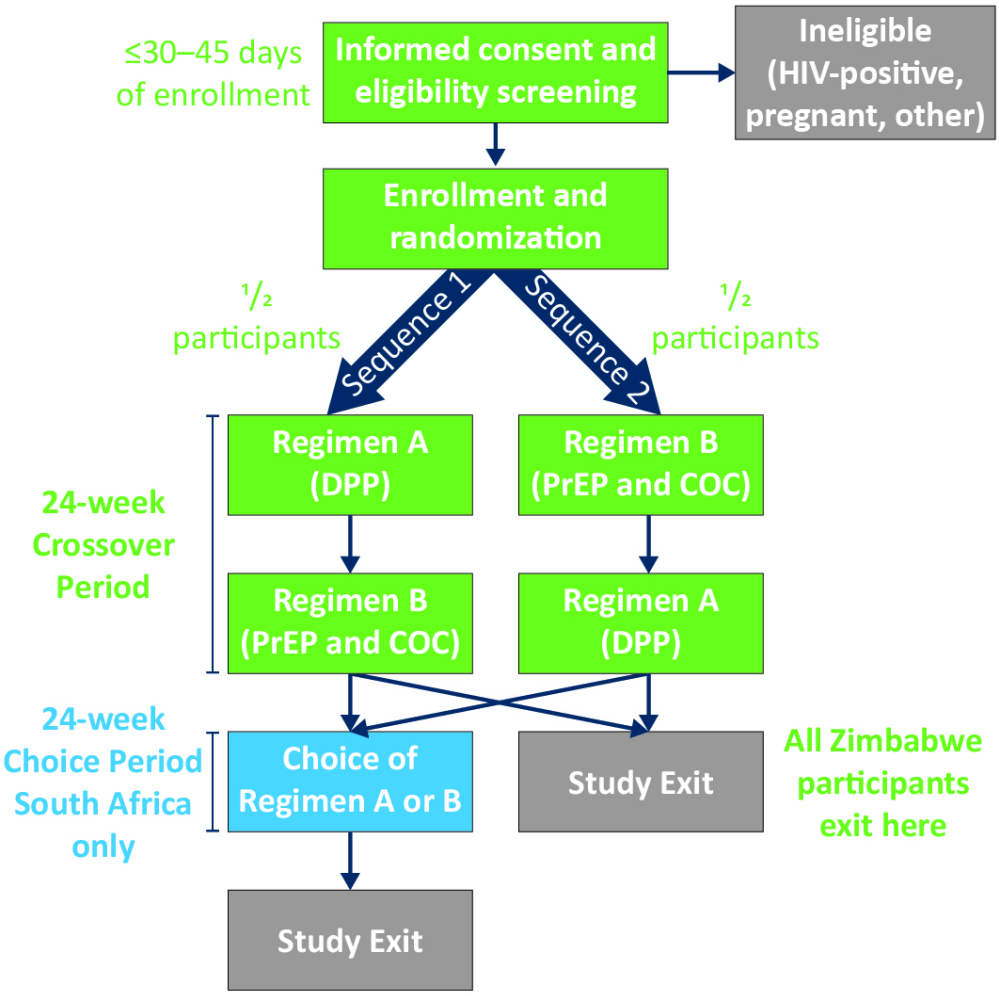

Figure 2. Study Schema

90x90mm (300 x 300 DPI)

Supplemental Table 1. Schedule of Visits and Procedures for PC952 (Zimbabwe) and PC953 (South Africa)

PROCEDURES	VISIT Day/Week													
	V0	V1	V2	V3	V4	V5	V6	V7[3]	V8[2]	V9[2]	V10[2]	V11[2]	V12[2]	V13[1]/Early Termination
	Day ≤-45	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
Visit Type	SCR	ENR	FU	FU	CO	FU	FU	CH	FU	FU	FU	FU	FU	CLO
ADMINISTRATIVE														
Informed consent	X													
Assign participant ID number	X													
Assess eligibility	X	X												
Demographics	X													
Randomization		X												
COUNSELING														
HIV pre and post-test counseling and testing, risk reduction counseling	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
STI/HIV risk reduction counseling	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Contraceptive counseling	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Protocol adherence counseling		X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	
CLINICAL														
Administer HIV risk assessments (clinician-based and self-assessment)	X													
Medical history	X													
Record medication history/ concomitant medications	X	*	*	*	*	*	*	*	*	*	*	*	*	*
Vital signs	X♦§	X	X♦	X	X	X♦	X	X	X♦[2]	X[2]	X[2]	X[2]	X[2]	X♦[2]
Complete physical exam	X	*	*	*	*	*	*	X[1]	*	*	*	*	*	X
Targeted physical exam		X	*	*	*	*	*	*	*	*	*	*	*	
Pelvic exam	*[2] X	*	*	*	*	*	*	*	*	*	*	*	*	*
Record adverse events/social harms		*	*	*	*	*	*	*	*	*	*	*	*	*
LABORATORY ASSESSMENTS														
Urine														
Urine pregnancy test	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
GeneXpert (urine) for chlamydia and gonorrhea (NAAT)	X	*	*	*	*	*	*	*	*	*	*	*	*	*
Urinalysis	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Blood														
Rapid HIV-1 blood tests	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
HIV confirmation blood test	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Syphilis serology	X	*	*	*	*	*	*	*	*	*	*	*	*	*
Hepatitis B antigen test	X													
Hepatitis C test	X[3]													
Creatinine blood test	X	*	X	*	*	X	*	X[1]	X[2]	*	*	*	*	X[2]

PROCEDURES	VISIT Day/Week													
	V0	V1	V2	V3	V4	V5	V6	V7[3]	V8[2]	V9[2]	V10[2]	V11[2]	V12[2]	V13[1]/Early Termination
	Day ≤-45	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
Collect blood for DBS to assess adherence			X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Blood draw for Complete Blood Count	X[1]	*	*	*	*	*	*	X[1]						
Pelvic														
Rapid trichomonas (TV)	X[3]													
Wet mount (TV, BV, candida)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Study product														
DOD first dose of regimen		X			X									
Distribute product supply		X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	
Collect used and unused product supplies			X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Behavioral														
CASI baseline questionnaire		X												
CASI monthly questionnaire			X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X2	X2
In-depth exit interview								X[1]						(X)[2]

[1]Zimbabwe only; [2]South Africa only; [3]Visit 7 is the Closing Visit in Zimbabwe

V = Visit; Wk = week; SCR = Screening; ENR = Enrolment; FU = follow up; CO = crossover; CH = Choice; CLO = Closing Visit; *If indicated; (X) sub-set of participants

♦Weight only at specified visits (when creatinine/creatinine clearance assessed); §Height only at Screening

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-JeriĆ K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Supplied earlier in submission process
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2 (Both trials were registered on ClinicalTrials.gov on 3 March 2021: Zimbabwe: NCT04778514; South Africa: NCT04778527.)
Protocol version	#3	Date and version identifier	24
Funding	#4	Sources and types of financial, material, and other support	26
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	Roles are on page 26. Names/affiliations Entered in BMJ Open Database

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Supplied earlier in submission process
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See funding support statements
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a (not an efficacy trial)
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital)	5

		and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See Figure 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20-21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	21
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	21
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	21
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-20
Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including	13-14

retention		list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20-23
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	22-23
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21-22
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a

Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	24-25
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	24
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24-25
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	18
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24-25
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary information in submitted protocols.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Assessing the acceptability of, adherence to, and preference for a dual prevention pill (DPP) for HIV and pregnancy prevention compared to oral pre-exposure prophylaxis (PrEP) and oral contraception taken separately: protocols for two randomized, controlled, crossover studies in South Africa and Zimbabwe

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075381.R2
Article Type:	Protocol
Date Submitted by the Author:	06-Feb-2024
Complete List of Authors:	Friedland, Barbara; Population Council, Center for Biomedical Research Mgodi, Nyaradzo; University of Zimbabwe - Clinical Trials Research Centre Palanee-Phillips, Thesla; Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Faculty of Health Sciences, School of Public Health; University of Washington, Epidemiology Mathur, Sanyukta; Population Council, Plagianos, Marlena; Population Council Center for Biomedical Research Bruce, Irene; Population Council Center for Biomedical Research Lansiaux, Maud; Population Council Center for Biomedical Research Murombedzi, Caroline; University of Zimbabwe - Clinical Trials Research Centre Musara, Petina; University of Zimbabwe - Clinical Trials Research Centre Dandadzi, Adlight; University of Zimbabwe - Clinical Trials Research Centre Reddy, Krishnaveni ; Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Faculty of Health Sciences, School of Public Health Ndlovu, Nkosiphile; Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Faculty of Health Sciences, School of Public Health Zulu, Sihle; Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Faculty of Health Sciences, School of Public Health Shale, Lerato; Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Faculty of Health Sciences, School of Public Health Zieman, Brady; Population Council Haddad, Lisa; Population Council Center for Biomedical Research
Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Sexual health
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Clinical Trial, Decision Making

Protocol for DPP crossover studies in South Africa and Zimbabwe

ABSTRACT

Introduction: Oral pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention method; however, uptake and persistence have been low among southern African women. A dual prevention pill (DPP) that combines PrEP with oral contraception (OC) may increase PrEP use and better meet women's sexual and reproductive health needs. We will gauge the DPP's acceptability in two crossover clinical trials.

Methods and Analysis: PC952 (Zimbabwe) and PC953 (South Africa) will compare acceptability, adherence, and preference for an over-encapsulated DPP versus PrEP and OCs taken separately. HIV-negative, non-pregnant cis-gender females in Johannesburg, South Africa (n~96 16-40-year-olds) and Harare, Zimbabwe (n~30 16-24-year-olds) will be randomized 1:1 to the order of regimens – DPP or 2 separate tablets – each used for 3 28-day cycles, followed by a 6-month Choice period in South Africa. Monthly clinic visits include HIV and pregnancy testing; safety assessments; and risk reduction and adherence counselling. We will assess adherence (monthly) based on tenofovir diphosphate drug levels in dried blood spots and by self-report. We will evaluate acceptability (monthly) and preference (end of crossover) via computer assisted self-interviewing and in-depth interviews with a subset of participants. Data collection started in September 2022 and is projected to end by December 2023.

Ethics and Dissemination: PC952 was approved by the Ministry of Health and Child Care, Medical Research Council, Research Council, and Medicines Control Authority of Zimbabwe; the Chitungwiza City Health Ethics Committee; and the Joint Research Ethics Committee for the University of Zimbabwe Faculty of Medicine and Health Sciences and Parirenyatwa Group of Hospitals. PC953 was approved by the South African Health Products Regulatory Authority and the University of the Witwatersrand's Human Research Ethics Committee. The Population Council IRB approved both studies. We will disseminate results in open access journals, clinical trials registries, and at local and international meetings and conferences.

Trial registration: Both trials were registered on ClinicalTrials.gov on 3 March 2021: Zimbabwe: NCT04778514; South Africa: NCT04778527.

Keywords: HIV, HIV prevention, PrEP, oral contraceptive (OC), pregnancy prevention, dual prevention pill (DPP), multipurpose prevention technologies (MPT), randomized controlled trial, AGYW, South Africa, Zimbabwe.

Strengths and limitations of these studies

- The crossover design enables a direct comparison between the intervention (DPP) and standard of care or control (PrEP and COCs separately) regimens that enables a smaller sample size with women serving as their own controls.
- Participants will be followed monthly, which will enable frequent assessments of PrEP drug levels in blood, however, it will not be feasible to measure contraceptive drug levels in blood due to the short half-life of COCs.
- The two pilot studies enable early assessments of the DPP in two different contexts: South Africa (low COC use/high HIV incidence and prevalence) and Zimbabwe (high COC use/moderate HIV incidence and prevalence), and among AGYW and older women.
- The key limitation of the studies is the use of an over-encapsulated DPP as a proxy for the ultimate co-formulated tablet, which may not accurately capture acceptability, preference and adherence for the ultimate DPP, which will be a smaller tablet versus a capsule.
- Another limitation is the different study designs and sample sizes for the two studies, primarily related to their respective funding mechanisms, that may limit the ability to directly compare results from the two countries.

INTRODUCTION

Despite substantial advances in HIV treatment and prevention over the last decade, women and girls in eastern and southern Africa continue to be disproportionally affected by HIV/AIDS, accounting for 63% of all new HIV infections in the region in 2021 [1]. In 2021, new HIV infections in South Africa were more than double among women aged 15 and over than among men of the same age (130,000 versus 70,000, respectively) [2]. Similarly in Zimbabwe, nearly twice as many women 15 and older acquired HIV in 2021 compared to their male peers [1].

Oral pre-exposure prophylaxis (PrEP) is more than 90% effective in reducing HIV transmission [3]. However, many oral PrEP trials and demonstration projects in sub-Saharan Africa have been plagued by low adherence, particularly among adolescent girls and young women (AGYW) [4,5]. Stigma and fear of intimate partner violence or relationship dissolution are often cited as reasons for non-use of PrEP [6–9]. Novel strategies to bolster uptake and adherence are needed to increase PrEP use among women and girls at high risk of HIV.

Many women – and AGYW in particular – are more worried about unintended pregnancy than HIV [10,11]. Furthermore, there is a growing body of evidence indicating that many women may be more likely to use an HIV prevention method that also prevents pregnancy [12–19]. Condoms are currently the only multipurpose prevention technologies (MPTs) that prevent both HIV and unintended pregnancy [20]. Male condoms, however, are not under a woman's control; female condoms have had limited uptake due to access and acceptability issues [21,22]; and many women risk gender-based violence by merely suggesting condom use [23]. Several novel MPTs are in the pipeline [24], including a dual prevention pill (DPP) containing the ingredients in PrEP and oral contraception. The first DPP being developed is based on the commonly-used 28-day combined oral contraceptive (COC) regimen (150 mcg levonorgestrel [LNG], 30 mcg ethinyl estradiol [EE]) and a generic equivalent of Truvada® (300 mg tenofovir disoproxil fumarate [TDF],

200 mg of emtricitabine [FTC]) [25] [26]. The DPP is likely to be the fastest route to an approved MPT as it contains two registered products that are safe and effective for their respective indications [27–30] with no evidence of drug-drug interactions [31–34]. In South Africa 25.6% of women report ever having used COCs and 10.5% currently use them [35,36]. In Zimbabwe, COCs are the most common family planning (FP) method among those using a modern method [37]. Data on oral contraceptive use among adolescents in sub-Saharan Africa is limited, however, an analysis from 33 sub-Saharan African countries indicated that COC use ranged from approximately 15% to 20% among 15-24 year olds [38]. Truvada® is approved as PrEP in more than 20 countries globally, including South Africa and Zimbabwe, and is recommended by WHO and CDC for women at risk of HIV using COCs [29,39].

We hypothesize that the DPP could greatly increase PrEP adherence, while also meeting women's unmet FP needs. Our goal is to generate data to inform DPP introduction through two clinical crossover studies comparing acceptability of, adherence to, and preference for the DPP versus two separate tablets. To that end, and in parallel with development of the co-formulated DPP, we have over-encapsulated PrEP (Truvada®) and a COC (Zinnia F [150 LNG/30 EE]), into a single capsule (**Figure 1**) for our studies to provide an early indication of DPP acceptability.

INSERT FIGURE 1 HERE

METHODS AND ANALYSIS

Trial Design

(Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines used.) Population Council Protocols 952 and 953 are randomized, controlled, open-label, parallel group, crossover studies.

Participant and public involvement

Formative research (December 2020-June 2021) with service providers and potential end users in South Africa and Zimbabwe informed the clinical trial design, materials, and recruitment methods. Established community and/or youth advisory groups at each site reviewed the protocols and provided input into the consent forms, behavioral questionnaires, and translations. The study teams have also benefitted from participation in the DPP consortium, a collaborative group of researchers, donors, and civil society advocates established to inform and accelerate DPP development and introduction [40].

Study settings

Hillbrow (Johannesburg), South Africa

PC953 is being conducted at the Wits RHI Research Centre, a large research clinic situated in Hillbrow, Johannesburg. As of 2020, Johannesburg had 756,751 people living with HIV with an overall HIV prevalence of 13%. HIV prevalence was highest among females across all age groups: 28.3% for 25-49-year-olds, 15% for women 50 and above and 9% for 15-24-year-olds [41]. Wits RHI conducts research on HIV, sexual and reproductive health (SRH) and vaccine preventable diseases.

Chitungwiza (Harare), Zimbabwe

PC952 is being implemented by the University of Zimbabwe Clinical Trials Research Centre (UZ-CTRC) at the Zengeza Clinical Research Site (CRS) in Chitungwiza, Zimbabwe's second largest city approximately 30km south of Harare, with a generalized epidemic and HIV prevalence of 3.8% among 15-19-year-old women and 6.3% among 20-24-year-old women [42]. The Zengeza CRS is located within a Chitungwiza City Health Department Municipal Clinic and conducts research on female-controlled HIV/STI (sexually transmitted infection) prevention strategies, including microbicides, oral and injectable PrEP and cervical barriers, and integrated HIV prevention strategies.

Study populations

We are recruiting participants (~96 16-40-year-olds, South Africa; 30 16-24-year-olds, Zimbabwe) from FP, PrEP and SRH clinics, and the general population. Although the DPP may ultimately appeal to individuals using other contraceptives or with an unmet FP need, we are enrolling participants who are already using COCs and are accustomed to daily pill-taking and the associated side effects of COCs (though they will not be used to the large DPP capsule). In addition, a recent study in Cape Town found that only 52% of 15-19 year olds (n=50/96) randomly assigned to use COCs (versus intravaginal rings or injectables) reported being fully adherent over an 8-week period [43], highlighting the importance of enrolling participants who have already been using COCs for at least three months.

Inclusion/Exclusion Criteria

Eligible participants are healthy, HIV-negative, non-pregnant, sexually active, cis-gender females at moderate to high risk of HIV infection. Specific eligibility criteria (**Table 1**) for the two protocols are similar, with several differences based on routine national protocols for PrEP provision and age range. Screened by nurses/clinicians includes medical history, physical examination, and

clinical laboratory tests. HIV risk is assessed by clinicians using local PrEP guidelines and by participants who are offered access to tools, such as BWise [44], to help them make that determination. Key exclusion criteria and prohibited medications relate to contraindications for COCs or PrEP use. We are also excluding those unable to swallow a large vitamin pill similar in size to the over-encapsulated DPP (**Figure 1**).

Table 1. Inclusion and exclusion criteria for South Africa (SA) and Zimbabwe (Zim)

Criteria	SA	Zim
INCLUSION CRITERIA		
Age 16 through 40 years old (inclusive) at Screening, verified per site-specific SOPs.	X	
Age 16 through 24 years old (inclusive) at Screening, verified per site-specific SOPs.		X
Able and willing to provide informed consent per site SOPs. (If under the legal age of consent [18 years old] be able to provide informed assent and obtain parental or guardian consent, to be screened for and to enroll in the study.)	X	X
Fluent in spoken Zulu and/or English.	X	
Fluent in spoken Shona and/or English.		X
Able and willing to provide adequate locator information, as defined in site SOPs.	X	X
Able and willing to comply with all study procedures, including being comfortable taking the study products as evident by nurse/clinician-observed swallowing at Screening of a large Vitamin capsule that is of similar size to the study products.	X	X
Post-menarche, per participant report at Screening.	X	X
Sexually active, defined as having had penile-vaginal sex with a male within the 3 months before Screening (per self-report).	X	X
At moderate to high risk of HIV infection based on clinician assessment.	X	X
Considers herself to be at moderate to high risk of HIV acquisition based on self-assessment.	X	X
Has been using COCs for contraception for at least 3 months prior to Screening as confirmed by contraceptive card and intends to continue using COCs for at least 12 months.	X	
Currently using COCs for contraception and has been using them for at least 3 months prior to Screening.		X
HIV-negative per rapid test at Screening and Enrolment per site-specific SOP.	X	X
Negative pregnancy test at Screening and Enrolment.	X	X
Negative for chlamydia, gonorrhea, trichomoniasis, and syphilis at Screening; women who test positive at Screening may be treated and enrolled.	X	X
Hepatitis B surface antigen (HBsAG) negative per blood test at Screening.	X	
Hepatitis B surface antigen and Hepatitis C negative per blood test at Screening.		X
Normal estimated creatinine clearance (eCrCl) ≥ 60 ml/min per blood test at Screening.	X	X
EXCLUSION CRITERIA		
Currently using emtricitabine (FTC) or tenofovir (TDF) at Screening (per self-report)		X
Intends to become pregnant within the next 12 months.	X	X
Intolerance, adverse reaction, or laboratory abnormality associated with PrEP use in the past.	X	X
Use of PEP within 3 months of Screening (per self-report).	X	X
Breastfeeding < 6 months postpartum (per self-report).	X	X
Less than 6 weeks (≤42 days) postpartum and not breastfeeding (per self-report).	X	X
For women 35 and older, currently smokes cigarettes (self-report).	X	

EXCLUSION CRITERIA		
History of deep vein thrombosis / pulmonary embolism (self-report) or history of thrombophlebitis or thromboembolic disorders at Screening (per self-report or medical records).	X	X
Prolonged immobilization (self-report).	X	X
Known thrombogenic mutation/complicated valvular disease (per self-report).	X	X
History of cerebro-vascular or coronary artery disease reported at Screening.		X
Ischemic heart disease (per self-report).	X	X
Systemic lupus erythematosus with positive or unknown antiphospholipid antibodies (per self-report).	X	X
Migraines with aura	X	X
For women over 35 years old, migraines without aura (per self-report).	X	
History of undiagnosed abnormal genital bleeding reported at Screening.		X
Current breast cancer or within 5 years of past breast cancer (per self-report) or history of carcinoma of the breast or other estrogen-dependent neoplasia reported at Screening.	X	X
Diabetes with nephropathy, retinopathy, or neuropathy (per self-report).	X	X
Diabetes for > 20 years (per self-report).	X	X
Symptomatic gall bladder disease (per self-report).	X	X
Severe cirrhosis (per self-report).	X	X
Liver tumor (per self-report).	X	X
Any other condition the clinician feels would jeopardize the health and wellbeing of the participant.	X	X

Study Schema

At Enrollment, participants are randomized to the sequence of study regimens (**Figure 2**): Sequence 1 = single DPP capsule once daily for three 28-day cycles (Regimen A) followed by two separate tablets (oral PrEP and COC) once daily for three 28-day cycles (Regimen B); Sequence 2 = Regimen B followed by Regimen A. In South Africa, after the six-month crossover period, participants may choose Regimen A, B or neither for up to six additional 28-day cycles. Study product regimens are described in detail in **Table 2**.

INSERT FIGURE 2 HERE

All participants take PrEP (FTC/TDF 200/300 mg) once daily by mouth throughout the entire study and 21 days of active COCs followed by 7 days of placebo tablets, regardless of regimen. The selection and timing of doses correspond to the labels for Truvada (Gilead Sciences, Inc; Foster City, CA, USA) and Zinnia F COCs (Mylan Laboratories Limited**,** Hyderabad, India). Zinnia F was selected because it is the same formulation as Control L, the COC purchased for public family planning programs in Zimbabwe. During the "placebo" days of Regimen A, participants take one capsule containing Truvada only, whereas the placebo days of Regimen B consist of two separate tablets: Truvada and a placebo COC tablet. The DPP capsules were manufactured and packaged by PCI Pharma Services (Rockford, IL, USA) from the same batches of Truvada and Zinnia F as the separate pills procured from Gilead and Mylan, respectively.

Table 2. Study products

Regimen	Description	Dose, Route and Frequency
A – Dual Prevention Pill (DPP)	Each DPP kit contains 28 capsules divided into 4 pouches, 1 per cycle week. Each pouch contains a blister strip of 7 capsules (plus desiccant). • 3 pouches contain 21 pink and white capsules which each have 1 Truvada tablet (FTC 200mg/TDF 300 mg) and one Zinnia F tablet. (EE/LNG 30/150 mcg) • 1 pouch contains 7 white capsules containing 1 Truvada tablet.	• Participants will take 1 DPP capsule orally, once daily at approximately the same time each day for 12 weeks (Crossover period), taking the next consecutively numbered capsule from each pouch, in order (Week 1, Week 2, Week 3, Week 4). In South Africa, the DPP may be taken for ≤6 additional months (Choice period). • If they miss 1 DPP capsule, participants will be instructed to take it as soon as they remember, up to the time of their next dose, but no more than 2 doses in a 24-hour period. • Participants will be counseled to use back-up contraception (e.g., condoms or abstinence) for 7 days if they miss 2 or more consecutive doses.
B – 2 Separate Tablets	Bottle of 30* Truvada (FTC/TDF 200/300 mg) tablets (PrEP) Blister card of Zinnia F COCs: 21 white active EE/LNG 30/150 mcg pills and 7 brown placebo pills (no hormone) *At the end of the 28-day period, participants should have 2 Truvada tablets remaining in the bottle and will be instructed to return those tablets to the study clinic.	• Participants will take 1 Zinnia F tablet and 1 Truvada tablet once daily. Tablets may be taken together or separately, but each tablet (Zinnia F, Truvada) should be taken at the same time each day. • Zinnia F tablets are to be taken in the order indicated on the pack, including the 7 placebo tablets. If a participant misses a COC dose, she will be instructed to take it as soon as she remembers. If a full day has passed, she should take 2 tablets the next day, per the label. Participants will be counseled to use back-up protection for 7 days if they miss ≥2 consecutive doses. • If a participant misses 1 Truvada dose, she will be counseled to take 1 tablet the next day, per the label, but not to take more than 1 dose in 24 hours. • Participants will be counseled that the effectiveness of PrEP may be reduced if doses are missed.

Study objectives

Objectives and outcomes are similar in both trials (**Table 3**).

Table 3. Objectives and Endpoints for PC952 (Zimbabwe) and PC953 (South Africa)

Objective	Endpoint	Type of endpoint (Country)
PREFERENCE		
To determine preference for taking a single DPP capsule versus 2 separate tablets (PrEP and COC) once daily among women after using each regimen for three 28-day cycles.	Proportion of women who prefer the DPP (Regimen A) vs 2 separate tablets (Regimen B) after using each regimen for 3 28-day cycles, per self-report on computer-assisted self-interviewing (CASI).	Primary (South Africa and Zimbabwe)
To determine if more women choose Regimen A versus Regimen B for the Choice period.	Proportion of women who choose Regimen A vs B for the Choice period.	Primary (South Africa)
ADHERENCE		
To compare adherence to the DPP capsule (Regimen A) versus 2 separate tablets (Regimen B) among women using each regimen daily for 3 28-day menstrual cycles during the Crossover period.	TFV-DP levels in dried blood spots (DBS) by regimen, and overall, at follow up visits every 4 weeks during Crossover period.	Primary (South Africa)
To compare adherence among women who choose the DPP capsule (Regimen A) versus adherence among women who choose 2 separate tablets (Regimen B), each taken daily during the Choice period.	TFV-DP levels in DBS by regimen, and overall, at follow up visits every 4 weeks during Choice period.	Primary (South Africa)
To assess and compare self-reported adherence to Regimen A vs Regimen B during the Crossover period, and to the chosen method during the Choice period.	Self-assessment of ability to adhere to instructions for product use (DPP capsule, FTC/TDF and COCs as applicable) in CASI interviews at follow up visits every 4 weeks during the Crossover and Choice periods.	Primary (South Africa)
To assess and compare adherence to Regimen A vs Regimen B during the Crossover period, and to the chosen method during the Choice period based on pill count.	Proportion of doses taken vs expected by pill count (DPP capsule, FTC/TDF and COCs as applicable) at follow up visits every 4 weeks during the Crossover and Choice periods.	Primary (South Africa)
To assess and compare daily adherence to PrEP for six 28-day cycles among AGYW when taken in the DPP capsule (Regimen A) or as a separate tablet (Regimen B) via a biomarker.	TFV-DP drug levels in dried blood spots (DBS).	Secondary (Zimbabwe)
To assess and compare self-reported adherence to PrEP for six 28-day cycles among AGYW when taken in the DPP capsule (Regimen A) or as a separate tablet (Regimen B).	Proportion of PrEP doses taken compared to total number of doses expected per self-report based on a CASI questionnaire.	Secondary (Zimbabwe)
To assess and compare adherence to the DPP (Regimen A) vs PrEP as a separate tablet (Regimen B) each used for 3 28 day cycles by pill count.	Proportion of DPP and PrEP doses taken compared to total number of doses expected per pill count.	Secondary (Zimbabwe)
To explore if socio-ecological factors, product characteristics and product use experiences are associated with adherence to PrEP whether taken as part of the DPP capsule or as a separate tablet.	Results of multivariate modeling indicating which, if any, factors are associated with adherence.	Secondary (Zimbabwe)
To explore facilitators and barriers to use, as well as socio-ecological factors that may be associated with adherence.	Results of multivariate modeling indicating which, if any, factors are associated with adherence.	Secondary (South Africa)

Objective	Endpoint	Type of endpoint (Country)
ACCEPTABILITY		
To assess the acceptability of taking the DPP capsule versus two separate tablets once daily to prevent HIV and unintended pregnancy among women who use each regimen for three 28-day cycles.	Acceptability scores by regimen and overall, per a quantitative acceptability questionnaire via CASI.	Primary (Zimbabwe)
To assess the acceptability of the DPP vs 2 separate tablets taken daily to prevent HIV and unintended pregnancy among women using each regimen for 3 28-day cycles during the Crossover period, and for up to 6 28-day cycles during the Choice period.	Scores by regimen and overall, as measured in a quantitative acceptability questionnaire via CASI at the Crossover visit, the start of the Choice period, and the end of the study.	Secondary (South Africa)
To assess if pre-use opinions are associated with actual experiences and preferences after using each regimen.	Proportion of women whose pre-use preference matches post-use experience based on a CASI questionnaire at baseline and at the end of the Crossover period.	Secondary (South Africa)
To qualitatively understand barriers and facilitators to product use and adherence.	Results of thematic qualitative data analysis from in-depth interviews with participants at study exit focusing on facilitators and barriers of product use and adherence.	Secondary (South Africa and Zimbabwe)
To explore if socio-ecological factors, product characteristics and product use experiences are associated with acceptability of the DPP and of 2 separate tablets.	Results of multivariate modeling indicating which, if any, factors are associated with acceptability.	Secondary (South Africa and Zimbabwe)
SAFETY		
To compare the safety of Regimen A versus Regimen B among women using each regimen for 3 28-day cycles during the Crossover period, and the safety of Regimen A versus Regimen B among women choosing each regimen during the Choice period.	Number of AEs by regimen (including social harms, drug side effects) during the Crossover and Choice periods.	Secondary (South Africa)

Study procedures

Informed consent

Before undergoing screening procedures, a counselor/designee leads a discussion to review the informed consent form in detail with potential participants in their preferred language (English or isiZulu, South Africa; English or Shona, Zimbabwe). The same study staff member implements a comprehension assessment to check participants' understanding of key study aspects, including the potential increased risk of HIV or unintended pregnancy if difficulty swallowing the large DPP capsule leads to more missed doses, before they both sign the consent form. For unemancipated minors (16-17-year-olds), informed consent from the parent/legal guardian consent is obtained

before assent from the minor. Key elements of the informed consent are reviewed on an ongoing basis and willingness to continue study participation is ascertained.

Eligibility screening

After consenting, potential participants are assigned a unique Participant Identification number and undergo screening procedures. All screening test results and, if enrolled, study information (data, specimens) are recorded with IDs and no other identifying information to preserve participant confidentiality. Locator information is collected at screening and reviewed at each study visit to ensure participants are contactable for retention purposes. The screening process typically takes more than one day because several lab tests are outsourced. At screening (Visit 0), a nurse/clinician takes a complete medical history, including gynecologic and obstetric history. A clinical exam is performed to assess overall health (including complete blood count [CBC] in Zimbabwe). Urine is tested for pregnancy (human chorionic gonadotrophin [hCG]), and *Neisseria gonorrhoeae/Chlamydia trachomatis* (nucleic acid amplification test [NAAT]). Blood is tested for HIV, syphilis, and hepatitis B virus (and Hepatitis C in Zimbabwe), and to measure creatinine clearance. Screening also includes direct observation of participants swallowing a large vitamin capsule, similar in size to the 000 DPP capsule (**Figure 1**).

Enrollment and randomization

Enrollment (Visit 1) is scheduled when participants are starting their next COC pack (+/- 5 days). At Enrollment, participants are tested for HIV (rapid antigen blood test) and pregnancy (urine hCG) to confirm eligibility. Those eligible are enrolled and randomized (1:1) to the sequence of regimens, are given a supply of their first study product with detailed dosing instructions and take their first dose directly observed in the clinic. Participants are counseled on management of anticipated side effects and missed pills based on recommendations that incorporate differing guidelines for COCs and oral PrEP [45]. Participants also receive counselling on HIV/STI risk

reduction, contraception, and protocol compliance – including the importance of attending clinic visits and taking the study products – at every visit.

Follow-up visits

Supplemental Table 1 contains the detailed schedule of visits and procedures. At all visits, blood is collected for dried blood spots (DBS) to assess tenofovir-diphosphate (TFV-DP) levels as a measure of PrEP adherence [46] and for rapid HIV testing. Urine is collected for pregnancy testing. After the first three cycles, participants "crossover" to their second regimen at Month 3/Visit 4 and return unused study product from their first regimen. They then receive their first supply of the second regimen, with detailed instructions, and take their first dose directly observed in the clinic. Participants attend monthly follow up visits during the second regimen (Month 4/Visit 5; Month 5/Visit 6). At Month 6/Visit 7, all participants exit in Zimbabwe. In South Africa, participants may continue using either regimen (or neither) for up to another six months during a "Choice" period, with similar monthly visits.

Laboratory procedures

Laboratory assessments are listed in **Supplemental Table 1**. Blood specimens for hepatitis, creatinine, HIV confirmation testing (and CBC in Zimbabwe) are processed off-site by BARC (South Africa) and UZ-CTRC (Zimbabwe). DBS specimens are analyzed at the University of Cape Town by liquid chromatography-tandem mass spectrometry [46].

Safety monitoring and adverse event (AE) reporting

Clinical assessments at each visit post-enrollment are done to monitor potential AEs and social harms. Individual participants who develop Grade 1 or unrelated Grade 2 AEs, based on the Division of AIDS Grading system [47], may continue using their assigned study product(s) per protocol, at the site PI's/designee's discretion. Individuals who develop a related Grade 2 AE, or

any Grade 3 AE, regardless of relatedness, will be evaluated by the site PI/designee and Medical Monitor for possible discontinuation from the study. Grade 4 AEs, regardless of relatedness, will be evaluated by the site PI/designee and Population Council Medical Monitor and those participants will be discontinued from the study. No dose modifications will be undertaken nor are there any *a priori* stopping rules because both study products (PrEP and COCs) are marketed drugs.

Seroconversion or pregnancy

Participants who seroconvert are terminated from the study. At their closing visit, study staff will collect unused pills, conduct resistance and viral load testing, and link the participant to HIV/FP care per local guidelines. Similarly, participants who become pregnant will be terminated and referred to services for pregnant individuals, including PrEP provision, if desired. The sites will make every effort to follow-up on all pregnancy outcomes. The sites may continue counselling participants as they transition to services to preserve their confidentiality after discontinuation.

Creatinine

Creatinine levels are monitored according to PrEP guidelines in each country, approximately quarterly [48,49]. Participants with abnormal creatinine levels may be put on a temporary product hold, pending the PI/designee's decision, until a repeat test can be done. Participants who have two tests outside the normal range will be permanently discontinued to reduce their risk if the DPP or PrEP is contraindicated.

Data and safety monitoring

The Population Council monitor conducted site qualification and initiation visits at both sites before data collection began. Periodic monitoring visits ensure the protocol and good clinical practice are being followed. The monitor reviews source documents to confirm that the data recorded on case report forms (CRFs) is accurate, and reviews relevant documents to verify protocol

compliance. A data safety and monitoring board (DSMB) was established, consisting of three experts with clinical expertise in HIV and contraception, epidemiology, biostatistics, and clinical trials. The DSMB (charter available upon request) will review data after all participants are enrolled (both countries), and after all participants complete the crossover visit (South Africa). All serious AEs (SAEs) and AEs leading to discontinuation will be reported to the relevant IRBs/ethics committees, drug regulatory authorities, sponsor, DSMB, and funders. Unanticipated AEs that are potentially related to the study product(s) will be reported as Suspected Unexpected Serious Adverse Reaction to the manufacturers (Gilead or Mylan).

Clinical staff are trained to identify, probe for, manage, and report AEs and social harms at every visit. Study clinicians review abnormal test results, liaise with local clinic doctors, and have the authority to terminate participants based on clinical opinion. Upon completion of the study, participants are referred to local clinics for PrEP and COC services, if they want to continue the methods. Any breaches in confidentiality, study protocol or AEs attributable to this study will be reported to the relevant IRBs/ethics committees and regulatory authorities.

Data collection and management

Clinical case report forms (CRFs)

CRFs were developed by the Population Council and the trial sites to capture demographics, medical history, clinical exam results, laboratory test results, product supply/pill counts, AEs, randomization, and termination data. Data are collected and managed using REDCap (Research Electronic Data Capture) hosted at the Population Council [50,51]. Data are entered into REDCap within five days of each participant's visit. Queries are triggered during data entry or by the Population Council data manager during weekly data reviews.

Quantitative behavioral surveys

At each visit, participants complete a behavioral questionnaire via computer-assisted self-interview (CASI) in their choice of English or the local language (isiZulu in South Africa, Shona in Zimbabwe) CASI questionnaires take approximately 30 minutes to complete and include questions about product acceptability, adherence, and overall trial experiences. Participants complete their interviews privately on tablet computers, with study staff nearby to address potential technical challenges.

Qualitative exit interviews

A subset of participants will take part in an in-depth interview (IDIs) after exiting the study. In South Africa, we will interview up to 30 participants representing those exiting early (during the Crossover period), those exiting after the Crossover period, and those completing the Choice period (half who chose the DPP and half who chose two separate tablets). In Zimbabwe, we will interview all willing participants. IDIs will be conducted by female research assistants using a semi-structured guide to explore preference for the DPP or two separate tablets; reasons for continuation/discontinuation; influence of partners, family, and support structures; side effects; provider interactions; and other factors affecting DPP acceptability and adherence. IDIs will last 40-60 minutes and will be scheduled at the Closing Visit or on a separate date, depending on participant availability. IDIs will be conducted in the participant's choice of language; will be audio recorded and transcribed; and translated into English (if necessary) for analysis.

STATISTICAL CONSIDERATIONS

Sample size and power calculations

South Africa

The sample size calculation was based on comparing ***adherence*** between the two regimens. A sample size of 86 has 80% power to detect a difference between the proportion of women who are adherent to each regimen assuming 25% of women are adherent to PrEP alone, 40% are adherent to the DPP, with a correlation between regimens of 50%, and no period effect. We

estimated 25% of participants would be adherent to the 2-pill regimen based on findings from other PrEP studies among young women in sub-Saharan Africa [5,52]. We increased the sample to 96 in case 10% of participants discontinued early while still having 86 participants complete the Crossover period.

Zimbabwe

The sample size was calculated based on detecting a difference in ***preference*** for the DPP versus two separate pills. A sample size of 30 has 94% power to detect a preference for one regimen over the other when the true preference for one regimen is at least 80% based on the exact binomial test (alpha = 0.04). If only 27 AGYW complete the study (10% loss to follow up), we have 84% power to detect a preference for one regimen over the other when the true preference for one regimen is at least 80%, based on the exact binomial test (alpha = 0.02).

Randomization

Randomization schemes for each study were developed by the Population Council biostatistician using Statistical Analysis Software (SAS/STAT) version 9.4 (SAS Institute Inc., Cary, North Carolina) with a 1:1 allocation using permutated block sizes. In South Africa, randomization is in blocks of 12, six participants per sequence in each of eight blocks. In Zimbabwe, randomization is in blocks of ten, five participants per sequence in each of three blocks. The randomization schemes are embedded within the REDCap systems for each study. At enrollment, the clinician consults REDCap to assign the treatment sequence for each sequentially enrolled participant.

Data Analysis

The “all participants” population includes all enrolled participants, the “safety population” includes all participants who have used at least one dose of either regimen, and the “per protocol” population includes all participants who complete both regimens. In general, descriptive statistics

(frequencies, mean, standard deviation, range) will be used to summarize and characterize data collated on differences in participants assigned to each sequence. Point estimates and corresponding 2-sided 95% confidence intervals will be presented for endpoints, where appropriate. Missing data will not be imputed.

Preference for the DPP will be measured as the proportion of women (per protocol population) reporting at the end of the Crossover period that they prefer the DPP capsule versus two separate tablets (or vice versa) by testing whether this proportion is greater than 0.5 using a z-test statistic under the exact binomial test in Zimbabwe (n=30), and normal approximation of the binomial distribution in South Africa (n=96). However, if the number of women completing each sequence is unbalanced, the comparison will be done using a random effects mixed model adjusting for effects treatment sequence may have on preference. In South Africa, we will similarly analyze the proportion of women who choose the DPP versus two separate tablets for the Choice period.

Adherence (overall) will be measured (safety population) by self-report, pill count and TFV-DP levels in DBS measured at each visit, and will be compared by regimen. Adherence in DBS will be assessed by comparing the proportion of women with TFV-DP levels consistently greater than the threshold known to provide efficacy, using McNemar's test for paired proportions. Adherence by pill count and self-report will be measured as the proportion of the total number of doses taken of the number of expected doses. If all women do not complete the Crossover period, analyses will be conducted with those who completed all six visits (24 weeks). Adherence during the Choice period (South Africa) will be analyzed similarly.

Acceptability of using the DPP capsule versus two separate pills will be measured in the safety population using a quantitative acceptability questionnaire. The primary outcome of acceptability will be measured based on responses to questions in the following acceptability domains: use

attributes, product attributes, side-effects, and effect on sexual activity. Acceptability scores will be summarized by regimen and timepoint and compared by regimen at each visit. Scores will be compared using a random effects mixed model to evaluate the effects of regimen and timepoint.

Safety data include findings from physical (and pelvic, when indicated) exams, laboratory tests, and AEs. AEs will be coded in accordance with the Medical Dictionary for Regulatory Activities [53]. A summary of AEs will be based on treatment-emergent AEs, which include all AEs occuring on or after the first dose. The number and percent of participants for each AE and SAE will be summarized by system organ class and preferred term, overall and by regimen.

Effects of socio-cultural and demographic characteristics (e.g., age, education, income, employment, relationship status, HIV risk perception, self-efficacy for HIV prevention) on preference, acceptability and adherence will be explored using random effects mixed models. Socio-cultural and demographic data will be collected at screening and enrollment.

Qualitative data will be analyzed thematically by researchers at the study sites and the Population Council. We will apply inductive (data-driven) and deductive (*a priori*) codes to the data using software, such as NVivo. Coded data will be synthesized to generate descriptions of behaviors, attitudes and beliefs about the acceptability of the DPP capsule, preference for the DPP or two separate pills, trial experiences, and other emergent themes [54–56].

ETHICS AND DISSEMINATION

Ethics

Both protocols and amendments, informed consent forms, and recruitment materials were approved by the Institutional Review Board of the Population Council (NY, NY, USA). The South Africa protocol and amendments (PC 953, Version 3.0, 08th June 2022), consent forms, recruitment materials and data collection instruments in both English and isiZulu were reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee and South African Health Products Regulatory Authority. The Zimbabwe protocol and amendments (PC952, Version 3.0, 17 June 2022), consent forms, recruitment materials and data collection instruments in English and Shona were approved by the Medical Research Council of Zimbabwe, the Medicines Control Authority of Zimbabwe, the Joint Research Ethics Committee of the University of Zimbabwe, the Ministry of Health and Child Care of Zimbabwe, the Chitungwiza City Health Ethics Committee, and the Research Council of Zimbabwe. Both studies are being conducted in accordance with the United States Code of Federal Regulations, the International Conference for Harmonization of Technical requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice E6 (R2), and local standard operating procedures at each site. Participants are compensated for each visit commensurate with the norms and standards in each country. Both trials are registered on clinicaltrials.gov (NCT04778527 and NCT04778514). Screening began in August 2022 and data collection ended in January 2024.

Dissemination

The study teams provide periodic updates to their communities and Community Advisory Boards during trial implementation. On completion, results will be presented locally at each site during in-person/virtual meetings with study participants, community advisory boards, and other local stakeholders; at national and international conferences; through the DPP consortium; and posted on PrEP Watch. Manuscripts will be submitted to peer-reviewed journals and will be made

available via open-access whenever feasible. Data will be uploaded on the ClinicalTrials.gov site, the U.S. Agency for International Development's (USAID) Data Development Library (South Africa only) and in country registries, as applicable. Datasets and protocols will be available from the sponsor upon request.

Figure 1. Over-encapsulated dual prevention pill (DPP) *Note: The hand shown is of one of the co-authors and is not a patient.

Figure 2. Study Schema

AUTHOR CONTRIBUTIONS

BAF wrote both study protocols and the final version of the manuscript; SM conceptualized and wrote the behavioral data collection aspects of the protocol and manuscript; MP wrote the data management and statistical analysis sections of the protocol and manuscript; NM, AD, CM, PM, SM, TP-P, KR, NN, SK, LS, BZ and LH participated in protocol development and contributed to the manuscript. ML wrote an earlier draft of the paper; IB oversees study implementation, assisted in writing and editing the paper, and prepared the manuscript for publication. All authors reviewed and approved the final version of the manuscript.

FUNDING

PC953 is made possible by the generous support of the American people through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and U.S. Agency for International Development (USAID) via cooperative agreement #No. AID-OAA-A-13-00088. The contents are the responsibility of the authors and do not necessarily reflect the views of PEPFAR, USAID, or the U.S. Government.

PC952 research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under Award Number R34MH119982. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The Children's Investment Fund Foundation (CIFF) Award Number R-1903-03681, 2106-06589 supported the manufacturing of the study product, as well as supplementing the US government funding for both studies. The content is solely the responsibility of the authors and does not necessarily reflect the views of CIFF.

ACKNOWLEDGMENTS

We would like to acknowledge George Creasy, who spearheaded work to develop a DPP; Bruce Variano for overseeing the development and testing of the over-encapsulated DPP; Dan Loeven for overseeing regulatory aspects of manufacturing the DPP; Susanna Grecky and Rebecca Brodsky for liaising with suppliers and manufacturers; Sherry Hutchinson for creating the educational materials for the trial and graphics appearing in the paper; and Heather Sussman for study oversight as clinical trial monitor.

COMPETING INTERESTS

None declared

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Figure 1. Over-encapsulated dual prevention pill (DPP) *Note: The hand shown is of one of the co-authors and is not a patient.

436x261mm (300 x 300 DPI)

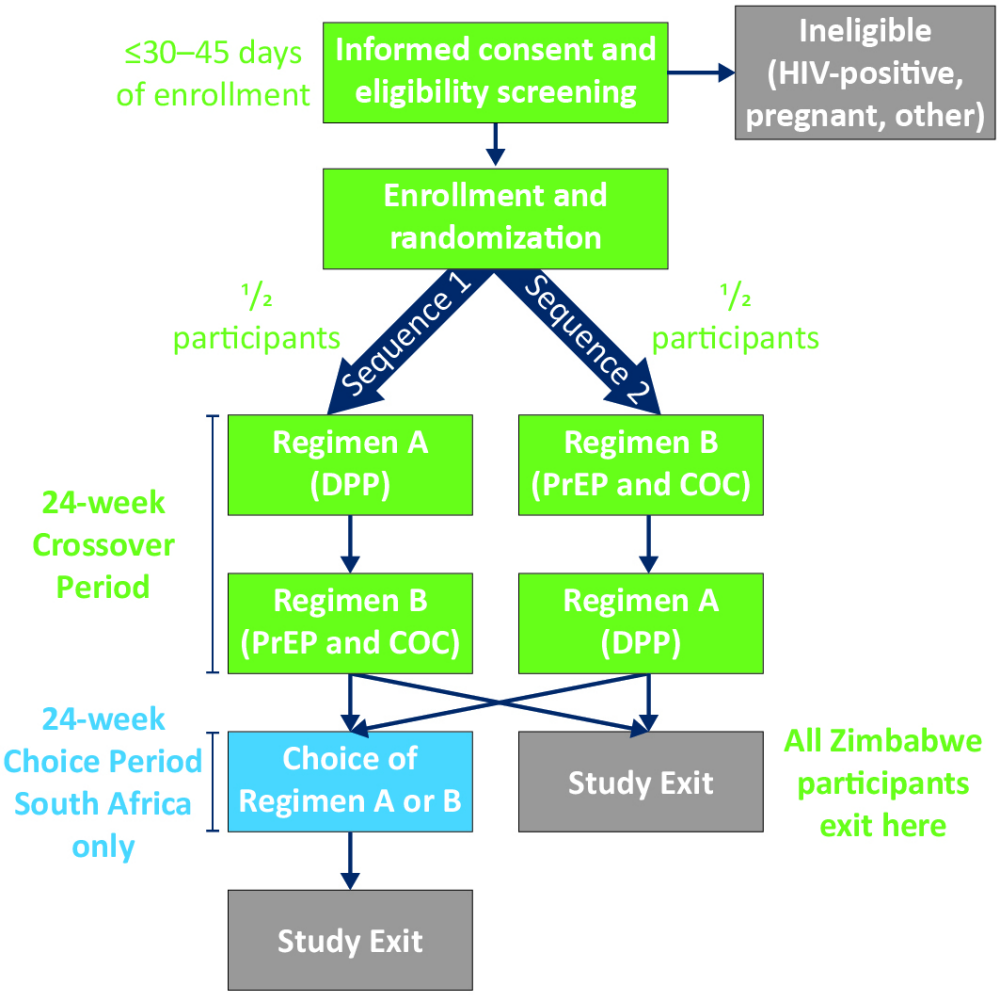

Figure 2. Study Schema

90x90mm (300 x 300 DPI)

Supplemental Table 1. Schedule of Visits and Procedures for PC952 (Zimbabwe) and PC953 (South Africa)

PROCEDURES	VISIT Day/Week													
	V0	V1	V2	V3	V4	V5	V6	V7[3]	V8[2]	V9[2]	V10[2]	V11[2]	V12[2]	V13[1]/Early Termination
	Day ≤-45	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
Visit Type	SCR	ENR	FU	FU	CO	FU	FU	CH	FU	FU	FU	FU	FU	CLO
ADMINISTRATIVE														
Informed consent	X													
Assign participant ID number	X													
Assess eligibility	X	X												
Demographics	X													
Randomization		X												
COUNSELING														
HIV pre and post-test counseling and testing, risk reduction counseling	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
STI/HIV risk reduction counseling	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Contraceptive counseling	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Protocol adherence counseling		X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	
CLINICAL														
Administer HIV risk assessments (clinician-based and self-assessment)	X													
Medical history	X													
Record medication history/ concomitant medications	X	*	*	*	*	*	*	*	*	*	*	*	*	*
Vital signs	X♦§	X	X♦	X	X	X♦	X	X	X♦[2]	X[2]	X[2]	X[2]	X[2]	X♦[2]
Complete physical exam	X	*	*	*	*	*	*	X[1]	*	*	*	*	*	X
Targeted physical exam		X	*	*	*	*	*	*	*	*	*	*	*	
Pelvic exam	*[2] X	*	*	*	*	*	*	*	*	*	*	*	*	*
Record adverse events/social harms		*	*	*	*	*	*	*	*	*	*	*	*	*
LABORATORY ASSESSMENTS														
Urine														
Urine pregnancy test	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
GeneXpert (urine) for chlamydia and gonorrhea (NAAT)	X	*	*	*	*	*	*	*	*	*	*	*	*	*
Urinalysis	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Blood														
Rapid HIV-1 blood tests	X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
HIV confirmation blood test	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Syphilis serology	X	*	*	*	*	*	*	*	*	*	*	*	*	*
Hepatitis B antigen test	X													
Hepatitis C test	X[3]													
Creatinine blood test	X	*	X	*	*	X	*	X[1]	X[2]	*	*	*	*	X[2]

PROCEDURES	VISIT Day/Week													
	V0	V1	V2	V3	V4	V5	V6	V7[3]	V8[2]	V9[2]	V10[2]	V11[2]	V12[2]	V13[1]/Early Termination
	Day ≤-45	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
Collect blood for DBS to assess adherence			X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Blood draw for Complete Blood Count	X[1]	*	*	*	*	*	*	X[1]						
Pelvic														
Rapid trichomonas (TV)	X[3]													
Wet mount (TV, BV, candida)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Study product														
DOD first dose of regimen		X			X									
Distribute product supply		X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	
Collect used and unused product supplies			X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Behavioral														
CASI baseline questionnaire		X												
CASI monthly questionnaire			X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]	X2	X2
In-depth exit interview								X[1]						(X)[2]

[1]Zimbabwe only; [2]South Africa only; [3]Visit 7 is the Closing Visit in Zimbabwe

V = Visit; Wk = week; SCR = Screening; ENR = Enrolment; FU = follow up; CO = crossover; CH = Choice; CLO = Closing Visit; *If indicated; (X) sub-set of participants

♦Weight only at specified visits (when creatinine/creatinine clearance assessed); §Height only at Screening

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Supplied earlier in submission process
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2 (Both trials were registered on ClinicalTrials.gov on 3 March 2021: Zimbabwe: NCT04778514; South Africa: NCT04778527.)
Protocol version	#3	Date and version identifier	24
Funding	#4	Sources and types of financial, material, and other support	26
Roles and responsibilities:	#5a	Names, affiliations, and roles of protocol contributors	Roles are on page 26. Names/affiliations Entered in BMJ Open Database

contributorship			
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Supplied earlier in submission process
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	See funding support statements
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a (not an efficacy trial)
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital)	5

		and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	See Figure 2
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20-21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	21
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	21
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	21
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-20
Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including	13-14

retention		list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20-23
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	22-23
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21-22
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a

Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	24-25
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	24
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24-25
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	18
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24-25
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See supplementary information in submitted protocols.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a