Thetha Nami ngithethe nawe
(Let's Talk)

A stepped-wedge cluster randomised trial of social mobilisation by peer navigators into community-based sexual health and HIV care, including pre-exposure prophylaxis (PrEP), to reduce sexually transmissible HIV amongst young people in rural KwaZulu-Natal, South Africa

Statistical Analysis Plan

Version 1.0

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1 Introduction

We describe the statistical analysis plan (SAP) of the *Thetha nami ngithethe nawe* (Let's Talk) trial. *Thetha nami* is a stepped-wedge cluster randomised trial of a peer navigator-led mobilisation into decentralised sexual and reproductive health (SRH) services and tailored HIV prevention. In the second period (step), a trial of long-acting injectable PrEP (the LAPIS trial) will be nested within the *Thetha nami* trial. This SAP describes the procedures to be applied to the primary and secondary analyses for the main *Thetha nami* trial, once the trial has been completed. A separate SAP will be prepared for the LAPIS trial.

This analysis plan was finalised during the *Thetha nami* trial implementation, and all analyses were prospectively defined. Any deviations from the SAP will be described and justified in the final report of the trial. The analysis plan will be posted alongside the full protocol on ClinicalTrials.gov. Suggestions for additional analyses from journal editors or referees will be thoughtfully considered and carried out to the best of our ability, while adhering to the principles outlined in the analysis plan. If any suggestions are incorporated and reported, proper acknowledgement will be provided to acknowledge the source of the suggestion.

1.1 Rationale

Antiretroviral therapy (ART) through universal test and treat (UTT) and HIV pre-exposure prophylaxis (PrEP) substantially reduces HIV-related mortality and incidence. Moreover, HIV prevention has advanced in recent years because of new developments in biomedical HIV prevention tools, including HIV point-of-care tests (POCT) and self-tests; the use of daily oral tenofovir/emtricitabine and most recently long-acting cabotegravir for PrEP, which reduce HIV acquisition by up to 90%; and HIV treatment with antiretroviral therapy (ART) that eliminates onward transmission. However, effective ART-based prevention has not translated into population-level impact in southern Africa due to sub-optimal coverage among adolescents and young people, as our studies have shown a high unmet sexual health need in this age group and low engagement with existing HIV prevention and care services.

1.2 Objectives of the trial

Main objective

To identify scalable and sustainable ways to stem the HIV epidemic and its negative impact on young people aged 15-30 in rural Kwa-Zulu Natal (KZN), South Africa through effective implementation of biosocial HIV prevention.

Specific objectives

1. To measure the effectiveness of social mobilisation by peer navigators combined with decentralised sexual and reproductive health (SRH) services and tailored HIV prevention in
    a. creating demand for differentiated HIV prevention and care, and
    b. reducing the prevalence of transmissible HIV
2. To understand real-world implementation of social mobilisation by peer navigators and decentralised SRH to deliver tailored, differentiated biosocial HIV prevention, by evaluating its acceptability, feasibility, reach, scalability and cost-effectiveness.

1.3 Trial design, relation to the nested LAPIS trial

This effectiveness-implementation hybrid trial design includes a cluster randomised stepped-wedge design which will sequentially deliver the study intervention to all trial clusters over two periods ('steps') (**Figure 1**). This trial is being conducted in 40 clusters. The cluster refers to the unit of randomisation, which is an administrative area/community in rural KZN. Clusters are randomly allocated to receive the intervention in period 1 (early intervention roll-out) or period 2 (delayed intervention roll-out). The trial will include three cross-sectional surveys: the first conducted at baseline, the second conducted at the end of period 1 (midline) and the third at the end of period 2 (endline). Data collection from the surveys is supplemented with data from clinics for some outcomes.

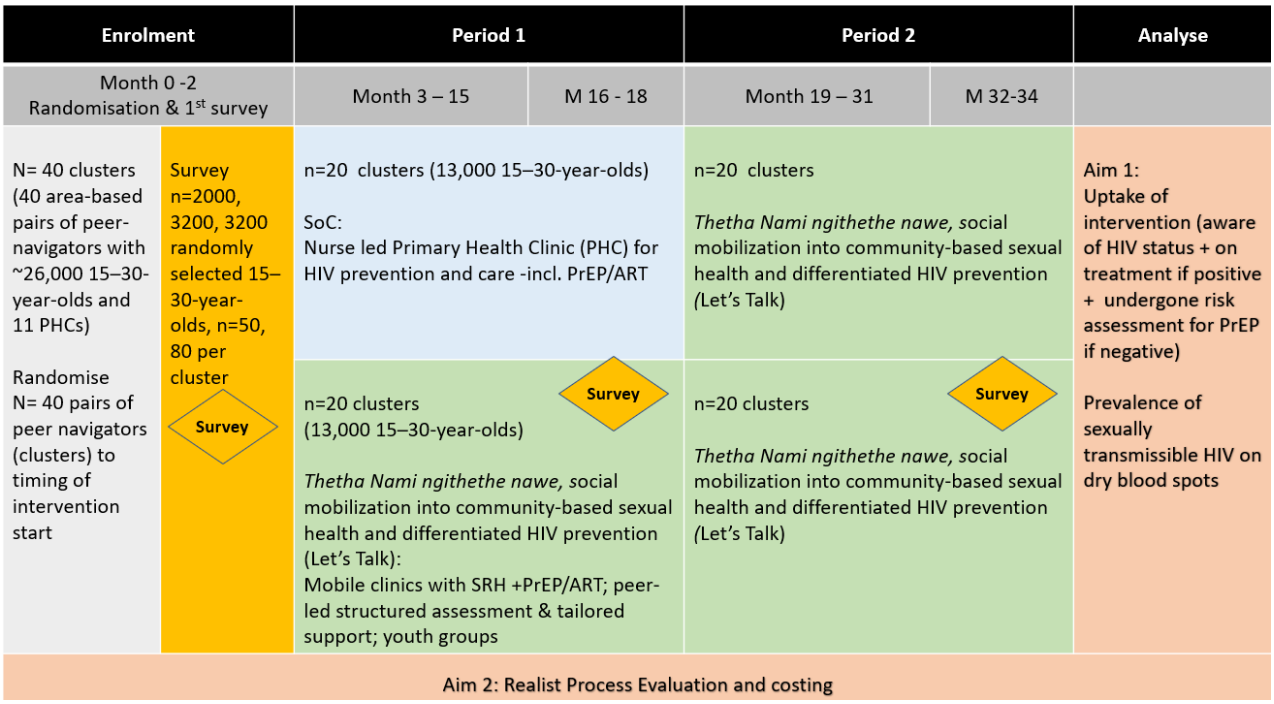

Figure 1 Schematic diagram of the *Thetha nami ngithethe nawe* (Let's talk) intervention. A minimum of 2000 participants were enrolled at the baseline survey. The sample size was increased to 3,200 participants for both the midline and endline surveys.

The Long-Acting HIV Pre-Exposure Prophylaxis Integrated with Sexual and Reproductive Health (LAPIS) trial (NCT06250504) is a parallel group 1:1 cluster randomised trial nested within the same trial clusters as the *Thetha nami ngithethe nawe* (Let's Talk) trial (**Figure 2**). Specifically, during period two, clusters are randomised to LAPIS intervention or control, with randomisation stratified by sequence in Let's Talk. Clusters randomised to the LAPIS intervention are offered a choice of long-acting injectable PrEP [Cabotegravir (CAB-LA)] or oral PrEP while the control clusters will only receive all the components of Let's talk intervention as enhanced standard of care (ESoC). This is not expected to influence the outcomes of Let's Talk; we will account for LAPIS randomisation through adjustment, treating this as a design factor and considering an appreciable interaction between the interventions in the two trials to be unlikely.

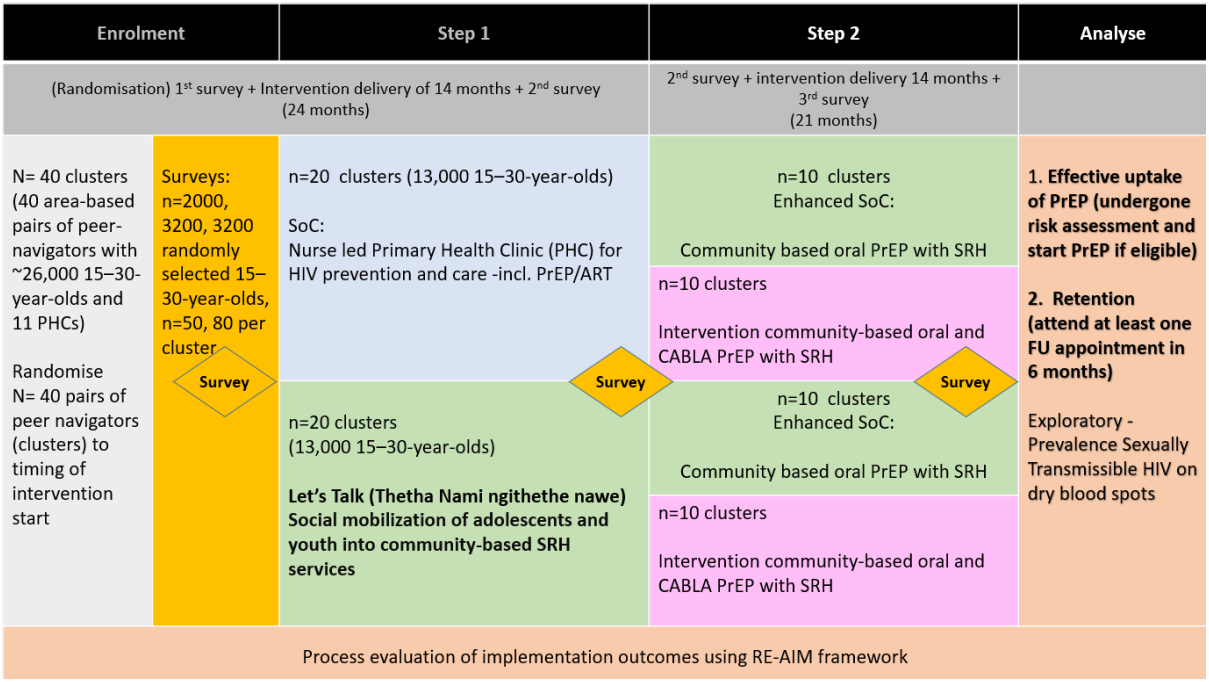

Figure 2 Schematic diagram of the nested LAPIS intervention

1.4 Eligibility

The population eligible to receive the Let's Talk intervention

All young people aged 15-30 years residing in the 40 clusters are eligible to receive the Let's Talk intervention. We estimate that 20% are at risk of HIV acquisition (based on our pilot work using a screening tool based on the South African national guidelines) and would benefit from PrEP.

The eligible population for the evaluation

The primary outcome of the prevalence of transmissible HIV is collected through three population-based surveys among a random sample of 16–30-year-olds who are resident in the 40 clusters: at baseline, at the end of period 1 (midline) and at the end of period 2 (endline). All individuals in this age range who are resident in one of the trial clusters are eligible for the surveys. Additional data are collected from clinic records (see later).

1.5 Intervention

1.5.1 Standard of Care (SOC)

All young people in the standard of care (SOC) clusters are able to access the nurse-led HIV prevention and treatment services at primary health care clinics (PHCs) in the surveillance area. Standard services include HIV counselling and POCT, with immediate initiation of ART if positive, or PrEP if negative and eligible according to South African National PrEP guidelines(1) and family planning support and syndromic management for STIs as per South African National Department of Health Guidelines. Individuals who are initiated on PrEP are seen again at 1 month, and then every 3 months, for repeat HIV testing, counselling and adherence support, and prescription refills. Individuals who initiate ART are seen every 3 months for prescription refills, adherence counselling, and have viral load measurements at 6 and 12 months, then annually thereafter if suppressed.

1.5.2 *Thetha nami ngithethe nawe* intervention

The intervention is a tailored psychosocial support and social mobilisation into community-based SRH and differentiated HIV prevention, including PrEP and UTT. The intervention is provided by 90 (17 men, 73 women aged 18-30) area-based peer navigators and adolescent- and youth-friendly nurse-led SRH mobile clinics that regularly visit fixed sites across the clusters.

Peer navigators deliver the following services to 15-30-year-olds in their area: providing safe spaces and community advocacy to create an enabling environment; youth groups to mobilize young people; structured psychosocial and health needs assessment using a secure electronic clinical management tool programmed into a tablet or mobile phone using REDCap software(2) to tailor support. Based on the needs assessment, peer navigators grade the needs as high (in need of immediate escalation to the committee for nurse or social worker assistance); medium (referral to clinical, educational, legal, advocacy, or social services and follow-up within a week); and low need (health promotion, provision of contact details of peer navigator and clinic hotline and re-assess in 3 months).

Peer navigators generate action plans based on the need assessment, which is electronically shared with supervisors. The action plan describes the peer-led health promotion provided and planned; referral to mobile SRH and/or other services; peer-mentorship plans with individualized (risk-informed) psychosocial support and community lay-counselling; provision of condoms, HIV self-tests and/or POCT, pregnancy tests;

ART/PrEP pick-up through serostatus neutral adherence clubs with or without HIV self-test (or peer-led HIV POCT) to support decentralised PrEP. Where relevant the action plans are shared with the SRH mobile clinic via the supervisors and committee.

The SRH mobile clinics visit the intervention clusters regularly. The clinics deliver nurse-led HIV testing, prevention and care including adolescent- and youth-friendly, gender neutral, HIV status neutral, individualized risk assessments for HIV care and PrEP, integrated with SRH services (one stop shops). All clinic attendees receive counselling around sexual health, fertility intentions, contraception, and HIV. They are also offered pregnancy testing (if female), family planning support, choice of contraception, and syndromic management for STIs, and, if male, referral to voluntary medical male circumcision. All those who are HIV negative undergo screening for PrEP eligibility according to South African National guidelines. Those who are sexually active are also offered testing for STIs, including POCT for syphilis and hepatitis B (and vaccine if negative), self-taken vaginal swabs or urine tests for gonorrhoea and chlamydia, and treatment and partner notification if positive.

1.6 Definition of primary and secondary outcomes

1.6.1 Primary outcomes

a) The prevalence of sexually transmissible HIV; defined as the proportion of all participants aged 16-30 years providing a dry blood sample in the population surveys who are living with HIV and have a detectable HIV viral load of ≥ 400 copies/mL.
b) Uptake of universal risk-informed HIV prevention intervention; defined as the proportion of survey participants who are aware of their HIV status and are either on treatment if living with HIV or have taken up PrEP if HIV negative and eligible.
c) The cost per transmissible HIV case averted and the cost per case linked to risk differentiated biosocial HIV prevention; measured as the cost to the provider or healthcare system for each participant screened and enrolled on PrEP/ART (outcome 1) in each arm and the cost to the provider or healthcare system for each case of transmissible HIV averted (calculated as the proportion of 16-30 year olds who are HIV negative or PLHIV who are virologically suppressed in each arm multiplied by the number of 16-30 year olds in that arm) .

1.6.2 Secondary outcomes (see Table 1 for definitions):

a) Access to sexual and reproductive health services (STI prevalence, uptake of contraception, teenage pregnancy, voluntary male medical circumcision (VMMC))

b) Risk of HIV acquisition or transmission
c) Uptake of PrEP
d) Retention in PrEP
e) Recent HIV infection using recency assays
f) Common mental health disorder as measured by PHQ9

1.6.3 Implementation (process) outcomes:

a) Acceptability and reach of peer support
b) Acceptability and reach of mobile SRH services
c) Fidelity

This SAP describes the analysis of the above outcomes except for primary outcome (c): cost per transmissible HIV case averted and the cost per case linked to risk differentiated biosocial HIV prevention. A separate SAP for this outcome will be developed.

In **Table 1** we define the secondary outcomes in more detail and provide details of summary measures and effect measures for all outcomes. Outcomes are described in more detail in Section 3.

Table 1 Summary of the Primary, Secondary and implementation outcomes (detailed definitions in Section 3)

Domain	Measure	Metric	Method of aggregation	Timepoint	Source for outcome ascertainment
Primary outcomes					
Sexually transmissible HIV	HIV viral load of ≥ 400 copies/mL (yes/no)	Odds ratio	Frequency and percentage	Baseline, midline, endline	Surveys
Intervention uptake	HIV positive on ART or HIV negative on PrEP (yes/no)	Odds ratio	Frequency and percentage	Baseline, midline, endline	Surveys + Clincs
Secondary outcomes					
Prevalence of sexually transmitted infection	Positive test for chlamydia and/or gonorrhoea	Odds ratio	Frequency and percentage	Baseline, midline, endline	Surveys
Reproductive health	Self-reported current contraception use among females; based on answer to the question, "are you currently using any contraceptive methods to prevent pregnancy?"	Odds ratio	Frequency and percentage		
	Self-reported current pregnancy among females younger than 20; based on answer to the question, "are you currently pregnant?"	Odds ratio	Frequency and percentage		
	VMMC – self reported VMMC in adolescent boys and young men (yes/no)	Odds ratio	Frequency and percentage		
HIV acquisition or transmission	A composite outcome representing the risk of acquisition or transmission, defined as reporting having engaged in condomless sex (regardless of partner type) and meeting one of the following criteria: (1) HIV-negative with no record of receiving PrEP, or (2) living with HIV and not virologically suppressed (VL > 400 copies/mL).	Odds ratio	Frequency and percentage	Baseline, midline, endline	Surveys + Clincs
Uptake of PrEP	Taking PrEP in the last 12 months among HIV-negative AYA at the time of the survey (based on clinic records)	Odds ratio	Frequency and percentage	Baseline, midline, endline	Surveys + Clincs
PrEP retention	Receiving at least two PrEP prescriptions among those who reported PrEP use in the past 12 months.	Odds ratio	Frequency and percentage		Clinics
Recent HIV infection	Prevalence of recent HIV-infection using recency assay	Odds ratio	Frequency and percentage	Baseline, midline, endline	Surveys
	Patient Health Questionnaire-9, total score	Mean difference	Mean and SD		Surveys

Common mental health disorder (depression screening)	Patient Health Questionnaire-9, total score ≥10	Odds ratio	Frequency and percentage	Baseline, midline, endline	
Implementation (process) outcomes					
Acceptability and reach of peer support	Receiving at least peer-led one needs assessment	Odds ratio	Frequency and percentage	Baseline, midline, endline – linked to process data	Process data
Acceptability and reach of mobile SRH clinics	Attending at least one clinic appointment	Odds ratio	Frequency and percentage	Baseline, midline, endline – linked to process data	Process data
Fidelity	Engagement of eligible participants in at least 60% of interventions offered	Odds ratio	Frequency and percentage		Process data

1.7 Sample size & power

Data from our previous studies and the demographic surveillance suggested 8% of young people aged 15–30 have a transmissible HIV viral load (primary outcome 1), and around 35% of all 15–30-year-olds are aware of their HIV status and either on PrEP or on ART with undetectable viral load (primary outcome 2). Our original design specified 2000 young people aged 15-30 (50 per cluster) interviewed in each of the three cross-sectional survey waves. Assuming an intracluster correlation coefficient (ICC) within wave of 0.1 for transmissible HIV and 0.4 for intervention uptake, and a decay (autocorrelation) between waves of 0.9 for both outcomes, this design provided 90% power to detect an increase from 35% to 47% in primary outcome 2 and 80% power to show a reduction in primary outcome 1 from 8% to 4% when comparing the intervention to standard of care(3). The estimates of ICC are based on the coefficient of variation (k) between clusters estimated in the range 0.7-1.0 for intervention uptake seen in a trial of peer navigators in the same area(4). However, in the trial baseline survey data, approximately 6% of young people aged 15–30 had a transmissible HIV viral load. To try to maintain power for the same relative reduction in primary outcome 1, we increased the size of the midline and endline surveys to 3200 (80 per cluster) young people aged 16-30. We note that a design of 3200 young people in each survey would provide 80% power to show a reduction in primary outcome 1 from 6% to 3% when comparing the intervention to standard of care.

1.8 Intervention allocation

The 40 administrative areas were randomly allocated in a 1:1 ratio to early or delayed roll-out of the intervention. Randomisation was restricted to ensure that the trial sequences were reasonably balanced with respect to several key covariates that were thought to be associated with the outcome: the population size of young people aged 15-30 years, location in the northern or southern part of the study area, and proximity to a major road. We restricted to allocation options that had absolute differences in the mean cluster size between the two sequences of ≤100, the proportion of northern clusters in each sequence was 40.5–64.5%, and the proportion along the main road was 12.4–32.6% (mean ± 1.5 standard deviations). These thresholds were defined through an iterative process in which different values were tried and the number and the validity of the acceptable allocations examined. A list of 10,000 acceptable allocations was generated, from which one was randomly selected at a public randomisation ceremony.

1.9 Data collection schedule

Data for outcome ascertainment are/will be collected from four sources outlined in **Table 2**: i) three cross-sectional surveys of random samples of 15–30-year-olds who are resident in the 40 clusters; ii) programme, process, and clinical data; iii) qualitative data collected during the process evaluation; iv) records of resource utilisation (such as consumables, medicines, diagnostics) and cost data including financial reports for staff and overhead costs.

1.10 Trial reporting

The trial will be reported according to the principles of the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines for reporting randomised controlled trials and the CONSORT extension for stepped-wedge cluster randomized trials (SW-CRT) (5–7). The final analysis for the main results will be conducted once the endline survey has been completed. There is no planned interim analysis.

2 Analysis populations

2.1 Post randomisation exclusions

The numbers (with percentages) of post-randomisation exclusions will be reported by trial observation period, and the reasons summarised. The following survey participants will be excluded from the baseline table and the analysis of all outcomes:

- Participants for whom a consent form was not received.
- Participants for whom consent to use any of their data was withdrawn.

2.2 Population definitions

2.2.1 Descriptive and comparative analysis

Demographic and clinical characteristics, and all the outcomes will be reported for all survey participants randomised minus post-randomisation exclusions, and for outcomes minus individuals who are not eligible due to the outcome definition. All analyses will be by intention to treat.

Table 2 Schedule of enrolment, interventions, and assessments for *Thetha nami ngithethe nawe* stepped-wedge cluster randomised trial, including data obtained from primary healthcare clinics

	STUDY PERIOD					
	Allocation (clusters)	**Baseline survey**	**Intervention period 1 (Early)**	**Mid-line survey**	**Intervention period 2 (Delayed)**	**Endline survey**
TIMEPOINT	***Month 0***	***Month 0-5***	***Month 6-19***	***Month 20-25***	***Month 26-39***	***Month 40-45***
ENROLMENT:						
Eligibility screen		X		X		X
Informed consent		X		X		X
Restricted randomisation of N=40 clusters	X					
Allocation	X					
INTERVENTIONS:						
Peer-led mobilisation into community based integrated HIV (PrEP/ ART) and SRH services			20 clusters	20 clusters	40 clusters	40 clusters
Standard of care (primary health care delivery of PrEP, ART and SRH)			20 clusters	20 clusters	0 clusters	0 clusters
ASSESSMENTS:						
Blood sample for HIV testing & viral load if positive		X		X		X
Urine and self-taken vaginal swabs for STI testing		X		X		X
20-30 minute interview-administered questionnaire (uptake of HIV & SRH services, sexual risk, reproductive health, mental health etc.)		X		X		X
Programme data from peer navigators' support management tools			←	—	—	→
Clinical data from clinical management tools and AHRI Clinic-Link			←	—	—	→
Costing Data			←	—	—	→
In-depth interviews with peer navigators, clinic staff and young people			x		X	

3 Detailed definition of outcomes

3.1 Primary outcomes

3.1.1 Sexually transmissible HIV

We will measure sexually transmissible HIV as the proportion of participants aged 16-30 years providing a dried blood spot (DBS) in the population surveys who are living with HIV and have a detectable HIV viral load of ≥ 400 copies/mL. This composite outcome captures the effect of the intervention on both incident HIV and untreated HIV. Success of our intervention implies that there will be fewer cases of young people who acquire HIV, and those who do acquire HIV will be identified and started on treatment, both of which will reduce the number of individuals with unsuppressed (transmissible) HIV.

3.1.2 Uptake of universal risk informed HIV prevention intervention

We will measure the uptake of universal risk informed HIV prevention intervention as a composite outcome defined as the proportion of participants who are aware of their HIV status and are either on ART if living with HIV or have ever taken up PrEP following a risk assessment if HIV negative. This outcome will be defined based on laboratory data and linkage to clinical data (AHRI Link and mobile clinical data through HDSS number). This will be measured among participants enrolled in the population surveys.

- **PrEP uptake** will be measured using clinical data from any linkage to mobile clinics and primary care in those who consent to linking of their data.
- **ART uptake** will be assessed using clinical data from mobile clinics and primary care in those who consent to data linkage and the blood sample result (as with PrEP, an individual is considered on treatment if this is indicated from any available data source) and relates to the previous 12 months.

Individuals who are on PrEP will be considered as aware of their status. Individuals whose HIV viral load is <400 copies/mL will be considered to be aware of their status and on treatment. All others will be considered as either not aware of their status or not on treatment/PrEP.

3.2 Secondary Outcomes

3.2.1 Access to SRH services

We will measure access to SRH services with the following outcomes:

3.2.1.1 Curable Sexually Transmissible Infections (STI)

At each population survey, participants provide male urine and female self-taken vaginal swabs or urine specimens for STI testing. We use polymerase chain reaction (PCR) with *Cepheid* Xpert to test for two curable STIs, chlamydia and gonorrhoea. We will present the prevalence of any STI, defined as the proportion of participants tested who received positive test results for at least one of the specified STIs. Additionally, we will report the prevalence of each individual STI.

3.2.1.2 Uptake of contraception, defined as current contraception use

We will measure this outcome as the proportion of women in the population surveys who self-report current contraception use. This outcome will be derived using the following question "Are you currently using any contraceptive methods to prevent pregnancy?"

3.2.1.3 Teenage pregnancy

The teenage pregnancy outcome will be defined as the proportion of adolescent girls younger than 20 years who self-report currently being pregnant in the population surveys.

3.2.1.4 Voluntary male medical circumcision (VMMC)

At each survey, men are asked if they have ever been circumcised. We will measure this outcome as the proportion of men who self-report ever being circumcised, among all males.

3.2.2 Risk of HIV acquisition or transmission

A composite outcome will be derived as the proportion of men and women aged 15–30 who are at risk of either acquiring or transmitting HIV, based on survey and clinic data. The analysis for this outcome will be restricted to individuals who have provided DBS during the survey or at any clinic visit if the participant accepted testing in the clinic and did not provide a DBS sample during the survey.

- **Risk of HIV acquisition**: Defined as participants who are HIV-negative (based on DBS), report any condomless sex (regardless of partner type), and have no record of PrEP use (per clinic records).
- **Risk of HIV transmission**: Defined as participants living with HIV (based on DBS), who report any condomless sex and have a viral load ≥400 copies/mL.

3.2.3. Uptake of PrEP

We will measure this as the proportion of all HIV-negative participants in the population surveys who have taken PrEP during the 12 months prior to the survey. HIV status of the participants will be ascertained based on DBS testing conducted during the surveys, or last HIV test result if the participant accepted testing in the clinic and did not provide a DBS sample during the survey. Uptake of PrEP will be determined using PrEP prescription records from study mobile clinics and primary care clinics.

3.2.4 Retention on PrEP

Using the clinical data, we will measure retention on PrEP as the proportion of the survey participants who have at least two PrEP prescriptions among those who have a record of PrEP use in the past 12 months. As a sensitivity analysis, we will also report the proportion of the participants who have two PrEP prescriptions within 4 months from PrEP initiation.

3.2.5 Recent HIV infection using recency assays

This outcome will be measured as the proportion of participants with recent HIV infections among all living with HIV, determined using recency assays on DBS collected during the cross-sectional surveys. HIV recency assays identify infections within the past 6 months.

3.2.6 Depression screening as measured by Patient Health Questionnaire-9 (PHQ9)

The PHQ-9 is a 9-item multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression. Participants are asked to complete the PHQ9 at each survey. The PHQ-9 total score for the nine items ranges from 0 to 27 and is calculated by assigning scores of 0, 1, 2, and 3, to the response categories [0-not at all, 1-several days, 2-more than half the days, 3-nearly every day]. Missing items for PHQ-9 assessment will be imputed if ≤2 items are missing, using the median score of completed scale items for that participant. Higher scores represent increased depression: 1-4 none/minimal; 5-9 mild; 10-14 moderate; 15-19 moderately severe; 20-27 severe; and will be summarised descriptively using numbers and

percentages in each category. The internal consistency of the scales will be assessed using Cronbach's Alpha. Mean (SD) scores will be presented for each exposure condition but inferential statistics for depression will be based on the binary outcome using a threshold score of ≥10.

3.3 Implementation (process) Outcomes

3.3.1 Acceptability and reach of peer support

We will use the process data to assess the acceptability and reach of peer support. This outcome will be defined as the proportion of all 15–30-year-olds residing in the HDSS who undergo at least one peer navigator needs assessment per year, disaggregated by gender, age, and other sociodemographic factors.

3.3.2 Acceptability and reach of mobile SRH clinics

We will use the clinical data to assess the acceptability and reach of mobile SRH clinics, defined as the proportion of all 15–30-year-olds residing in the HDSS who attend at least one mobile clinic per year, disaggregated by gender, age, and sociodemographic factors.

3.3.3 Fidelity

Fidelity of the intervention will be assessed based on the engagement with the intervention components listed in **Table 3**. We define successful fidelity as the proportion of all participants who engaged with or participated in at least 60% of the intervention components offered to them.

Table 3 Components of the nurse-led SRH mobile clinics and peer navigator support

Mobile SRH services	**Peer support**
1) PrEP initiation if suitable	1) Needs assessment
2) ART uptake if living with HIV	2) Safe spaces
3) STI testing	3) Youth groups social mobilisation
4) Contraception uptake	
5) Provision of condoms	
6) Provision of HIV self-tests	
7) POCT including pregnancy tests	
8) Referral to VMMC	
9) Health promotion counselling	

4 Descriptive analyses

Following the extended CONSORT guidelines for stepped-wedge cluster randomised trials, a flowchart will illustrate the number of individuals sampled, the number of eligible individuals, and the number enrolled in each of the surveys. Reasons for non-eligibility and non-enrolment will be presented.

For normally distributed continuous data, the following statistics will be provided: number, mean, standard deviation (SD), minimum and maximum, and will be reported to 1 more decimal place than the original data. For non-normally distributed continuous data, number, median, lower quartile, and upper quartile will be provided, unless otherwise stated. Categorical data will be summarised in terms of numbers and percentages, with percentages to 1 decimal place.

To provide a comprehensive description of the study sample and assess the balance from randomisation, demographic variables will be summarised by exposure condition, pooled across the surveys. Sociodemographic variables, such as age group, sex, area of residence (rural or urban/peri-urban), socio-economic status, highest level of education attainment, and employment status, will be included.

5 Comparative analyses

5.1 Primary outcome analysis

We will present the number and percentage with the outcome by intervention exposure condition for the two primary outcomes. To quantify the effect of the intervention on the primary outcomes, a logistic regression model will be fitted using data from all three survey waves. These models will estimate an odds ratio (OR) for intervention exposure relative to control along with 95% confidence intervals (CI). The analysis will account for design factors including population size of young people aged 15-30 years, location (northern or southern part of the study area), and proximity to a major road, for the final wave, the LAPIS trial allocation, survey wave, and the clustered nature of the data using the generalised estimating equation (GEE) framework, giving what we term an ‘unadjusted’ intervention effect. The working correlation structure will be exchangeable.

To enhance statistical power and address any potential imbalance in the distribution of HIV risk factors between the intervention exposure conditions, adjustments will additionally be made (main effects) for location (rural/urban), age (continuous variable), and sex, and the odds ratio for intervention from these

fully adjusted models will be considered primary, whilst unadjusted ORs will also be reported for completeness. These predictors are known to be associated with HIV transmission risk within this population. The fitted models will follow the same general form:

$$\boldsymbol{logit}(\boldsymbol{\pi_{ict}}) = \mathbf{log}\left(\frac{\boldsymbol{\pi_{ict}}}{\mathbf{1}-\boldsymbol{\pi_{ict}}}\right) = \boldsymbol{\alpha} + \boldsymbol{\beta x_{ct}} + \boldsymbol{\gamma Z} \qquad (5.1)$$

Where i =individual 1, 2, …, 80 c =cluster 1, 2, …, 40 t = time-period (survey wave) 1, 2, and 3

$\boldsymbol{logit}(\boldsymbol{\pi_{ict}})$ refers to the log-odds of the outcome for the ith individual in the cth cluster at time-period t

$\boldsymbol{\alpha}$ is the expected log-odds in the first period under the control condition

$\boldsymbol{\beta}$ is the intervention effect

$\boldsymbol{x_{ct}}$ is the intervention indicator that equals to 1 if cluster c receives intervention during period t and 0 otherwise

$\boldsymbol{\gamma}$ parameters represent the effects of a set of covariates, $\boldsymbol{z_1, z_2, \ldots, z_L}$, each of which may be measured at individual or cluster level

Besides reporting odds ratios, we will also report the intervention effect on the risk difference scale, though marginalisation based on the fully adjusted model.

5.2 Secondary outcome analyses

Secondary outcomes (STI prevalence, contraception use, teenage pregnancy, VMMC, risk of HIV transmission, PrEP uptake, PrEP retention, recent HIV acquisition, depression) will be analysed using logistic regression with GEE, as described for the primary outcomes. For the components of the risk of HIV acquisition or transmission outcome, we will report the descriptive statistics by trial arm without inferential statistics.

5.3 Pre-specified subgroup analyses

The consistency of the intervention effect on the primary outcomes will be assessed across specific subgroups using the statistical test of interaction. Effect estimates and 95% confidence intervals will be presented for each subgroup, plus the interaction p-value. The grouping factors for subgroup analysis are sex (male/female), age (<21 or ≥21 years), and location (rural/urban).

5.4 Significance levels and adjustment of p-values for multiplicity

For all primary and secondary outcomes, and subgroup analyses, 95% confidence intervals will be used. A formal correction for multiplicity will not be applied because the outcomes reflect different trial domains (effectiveness and process). Subgroup analyses are considered exploratory so no formal correction for multiplicity will be applied; however, multiple comparisons will be taken into account when interpreting the findings.

5.5 Missing data

We will report proportions of missing values for all collected variables. For missing items in the outcome measurements that are based on summing items to give overall scores (PHQ9) refer to section 3.2 for the treatment of missing data.

5.6 Statistical software employed

The statistical software Stata/SE version 17 or higher version for Windows will be used for all analyses. Software R 4.2.1 or higher version will be used for drawing plots if applicable.

6 Safety data analysis

All serious adverse events (SAEs) and adverse events (AEs), their relationship to research procedures, expectedness and date of occurrence will be listed by intervention exposure condition, along with number (%) of SAEs and AEs, overall and by type.

Since this trial is an implementation study and all tests and drugs used are approved for clinical use in South Africa, the number of safety events to be detected and reported is expected to be low. Additionally, all clinical care adheres to South African clinical guidelines. As such, inferential statistics will not be performed in the analysis of safety events.

7 Miscellaneous

7.1 Clinical laboratory data analysis

Laboratory tests included HIV and viral load tests, STI tests, and urinalysis. For viral load, results that are below the lower limit of quantitation will be given a value of half that limit. For instance, if a viral load test

result is recorded as "<50" then it will be summarised as a value of "25", for the purpose of summary statistics.

8 ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Treatment
AHRI	African Health Research Institute
AUDIT-C	Alcohol Use Disorders Identification Test
BIC	Bayesian Information Criterion
CONSORT	Consolidated Standards of Reporting Trials
CI	confidence interval
GEE	Generalised estimating equation
HIV	Human Immunodeficiency Virus
ICC	Intracluster correlation coefficient
KZN	Kwa-Zulu Natal
OR	Odds ratio
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
POCT	Point-of-care tests
PrEP	Pre-exposure prophylaxis
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	Standard of Care
SRH	Sexual and reproductive health
STI	Sexually Transmissible Infection
SW-CRT	Stepped-wedge cluster randomized trials
TSC	Trial Steering Committee
UTT	Universal test and treat
VL	Viral load
VMMC	Voluntary male medical circumcision
WHO	World Health Organization

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