

LAPIS

**Long-acting HIV Pre-exposure prophylaxis
Integrated with community-based Sexual and
reproductive health services in South Africa
(LAPIS): a hybrid (1a) cluster randomised
controlled phase 3B trial of effectiveness and
implementation**

Statistical Analysis Plan

Date: 21 May 2026

Author: Jacob Busang, Trial Statistician, AHRI

Reviewers: Faith Magut, Trial Statistician, AHRI

Kathy Baisley, Co-Investigator, AHRI/LSHTM

Andrew Copas, Co-Investigator, UCL

Maryam Shahmanesh, Principal Investigator

Protocol version: 8.0 (dated 05 November 2024).

Authorised by:		Role	Date
Name	Maryam Shahmanesh	PI	2026-05-21
Signature			
Name			
Signature			
Name			
Signature			

Table of Contents

1	Introduction.....	2
1.1	Rationale.....	2
1.2	Objectives of the trial.....	3
1.3	Trial design.....	3
1.4	Eligibility criteria.....	5
1.5	Study population and cohorts.....	5
1.6	Study interventions.....	6
1.7	Definition of estimands, primary and secondary outcomes.....	7
1.8	Sample size & power.....	12
1.9	Intervention allocation.....	12
1.10	Data collection schedule.....	13
1.11	Trial reporting.....	13
2	Analysis populations.....	13
2.1	Post randomisation exclusions.....	13
2.2	Analysis principles and population assignment.....	13
3	Detailed definition of outcomes.....	14
3.1	Primary outcomes.....	14
3.2	Secondary Outcomes.....	16
3.3	Implementation (process) Outcomes.....	25
4	Descriptive analyses.....	26
5	Comparative analyses.....	27
5.1	Primary outcome analyses.....	27
5.2	Secondary outcome analyses.....	28
5.3	Pre-specified subgroup analyses.....	29
5.4	Sensitivity analyses.....	29
5.5	Significance levels and adjustment of p-values for multiplicity.....	29
5.6	Missing data.....	30
5.7	Statistical software employed.....	31
6	Miscellaneous.....	31
6.1	Clinical laboratory data analysis.....	31
7	Abbreviations.....	31
8	References.....	32

1 Introduction

We describe the statistical analysis plan (SAP) of the LAPIS trial. LAPIS is a cluster randomised trial (CRT) evaluating the effectiveness and implementation of offering PrEP modality choices through community-based SRH services amongst youth aged 15-30 years living in rural Kwa-Zulu Natal, South Africa (1). LAPIS is nested within *Thetha nami ngithethe nawe* (Let's Talk), a stepped-wedge CRT with two periods investigating the effectiveness, implementation, and cost effectiveness of peer-led social mobilisation into decentralised integrated HIV and SRH services on the population prevalence of sexually transmissible HIV amongst youth. This SAP describes the procedures to be applied to the primary and secondary analyses for the LAPIS trial, once the trial has been completed. A separate SAP has been prepared for *Thetha nami* trial.

This analysis plan was finalised during the LAPIS 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

Recent advances in biomedical HIV prevention tools have significantly enhanced HIV prevention efforts. These tools include HIV point-of-care tests (POCT) and self-tests, the use of daily oral PrEP and long-acting injectable PrEP with cabotegravir (CAB-LA), twice-yearly lenacapavir, and ART for HIV treatment, which eliminates onward transmission of the virus. However, the impact of biomedical prevention such as PrEP depends on its uptake and consistent use by those at greatest risk. This has proven challenging due to several barriers. Retention on oral PrEP also remains a significant issue. Offering a choice of PrEP modalities integrated with peer support and delivered through community-based sexual and reproductive health (SRH) services may overcome these challenges.

1.2 Objectives of the trial

Main objective

To evaluate the effectiveness of real-world implementation of offering a choice of oral PrEP, long-acting PrEP with injectable cabotegravir, dapivirine vaginal ring (DapiRing) or post-exposure prophylaxis-in-pocket (PEP-in-pocket) within community-based integrated HIV and SRH services on PrEP uptake and retention, and population prevalence of sexually transmissible HIV amongst adolescents and young adults in rural KZN, South Africa.

Specific objectives

1. To measure the effectiveness of offering a choice of oral or long-acting injectable cabotegravir (CAB-LA) for PrEP and the availability of DapiRing and PEP-in-pocket on increasing effective uptake, retention and adherence to PrEP, and reducing sexually transmissible HIV and HIV incidence in young people aged 15-30 in rural South Africa.
2. To understand real-world implementation:
 - 2.1. To explore the acceptability, preference, and reach of CAB-LA from the perspective of young people aged 15-30 and their communities in rural South Africa.
 - 2.2. To understand the feasibility, affordability, and scalability of delivering CAB-LA through community-based PrEP with SRH.
 - 2.3. To identify implementation challenges and practical solutions for CAB-LA initiation, laboratory monitoring and safe stopping within nurse-led and rural community-based clinical settings.
 - 2.4. To evaluate the safety and tolerability of CAB-LA compared to oral PrEP.

1.3 Trial design

LAPIS is a phase 3B, hybrid type 1a effectiveness and implementation, parallel-group, two-arm cluster randomised controlled trial (cRCT) designed to evaluate the initial scale-up phase of offering CAB-LA, DapiRing, and PEP as additional options to oral PrEP for HIV prevention in community-based integrated HIV and SRH services. This study is conducted, and will be analysed and reported, according to the Consolidation Standards of Reporting Trials (CONSORT) statement for cluster RCTs (2–4).

LAPIS is embedded within the ongoing stepped-wedge trial, *Thetha nami*, which has two sequences and two periods of 24 months each and is being conducted in the same 40 clusters (administrative areas). The design of the *Thetha nami* trial has been described in detail previously (5). LAPIS is nested in the second period, when all clusters are receiving the *Thetha nami* intervention, a tailored psychosocial support and social mobilisation into community-based SRH and differentiated HIV prevention, including oral PrEP. As part of the *Thetha nami* intervention, each cluster has a pair of peer navigators who reside in the cluster and deliver the intervention to young people in that cluster. Each cluster is visited by a mobile nurse-led integrated HIV and SRH mobile clinic on a monthly basis. At the start of the second period, we randomly allocated the trial clusters to either an expanded differentiated HIV prevention package, in which additional prevention choices including CAB-LA, DapiRing and PEP were offered alongside oral PrEP (intervention, n=20 clusters), or to the standard *Thetha nami* intervention with oral PrEP alone (control, n=20 clusters). Randomisation was stratified by sequence in the *Thetha nami* trial. For the LAPIS primary uptake outcome, documented uptake of oral PrEP through *Thetha nami* services during the second period will contribute to the composite biomedical HIV prevention uptake outcome. The overall trial design is summarised in Figure 1 (1).

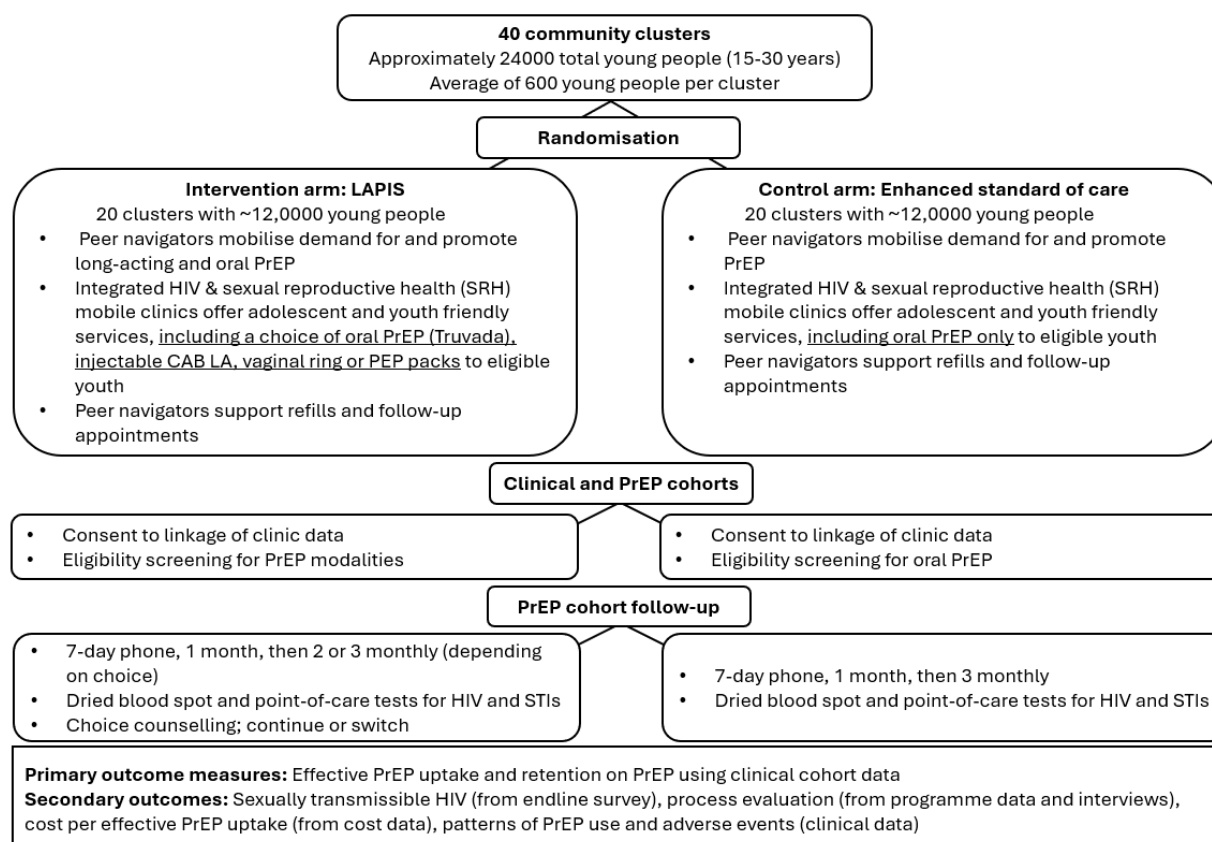


Figure 1 Summary of the trial design

1.4 Eligibility criteria

All 24,000 young people aged 15-30 years residing in the 40 administrative clusters of the health and demographic surveillance site (HDSS) in uMkhanyakude district, rural KwaZulu Natal, during the trial period are eligible for inclusion in LAPIS. Integrated HIV/SRH services, including HIV testing and PrEP, will be offered throughout the study period.

1.5 Study population and cohorts

1.5.1 Trial population

The trial population comprises all individuals aged 15-30 years residing in the 40 trial clusters (intervention and control arms).

1.5.2 Population-based survey population

The population-based survey population comprises participants enrolled in the representative endline survey among individuals aged 15–30 years residing in the trial clusters. Survey-based outcomes, including sexually transmissible HIV, recent HIV infection, contraception use, and pregnancy outcomes, will be assessed within this population.

1.5.3 Screened population

The screened population comprises participants who attended integrated HIV/SRH services during the study period, underwent screening procedures, including HIV testing, and consented to the use of their clinical data for research purposes.

1.5.4 HIV-negative cohort

The HIV-negative cohort comprises screened participants who were confirmed HIV-negative during screening. This cohort contributes to longitudinal HIV incidence analyses and eligibility assessment for PrEP initiation.

Participants within this cohort may additionally participate in exit surveys assessing HIV prevention experiences, service utilisation, and related outcomes.

1.5.5 PrEP cohort

The PrEP cohort comprises participants from the HIV-negative cohort who initiated PrEP during the study period and consented to longitudinal follow-up and use of clinical data for PrEP-related analyses, including retention outcomes.

1.6 Study interventions

Clusters have been randomly allocated to the enhanced SoC (*Thetha nami*) or enhanced SoC with the choice of injectable PrEP, DapiRing and PEP-in-pocket (intervention).

1.6.1 Control (Enhanced SoC): Thetha nami

The *Thetha nami* intervention has been described in detail previously (5). Briefly, it is a peer-led tailored psychosocial support and social mobilisation into community-based SRH and differentiated HIV care and prevention. Area-based peer navigators mobilise youth into nurse-led mobile adolescent and youth-friendly services (AYFS) that visit fixed sites across the clusters every month. Peer navigators are men and women aged 18-30 years, selected by community leaders in each area. They are supervised by a team of peer supervisors and overseen by a committee including a professional nurse and a social worker. They participate in biweekly team debriefings and receive ongoing supervision and training.

Young people attending the mobile AYFS are offered self-taken vaginal swabs or urine tests for sexually transmitted infections (STIs), including gonorrhoea, chlamydia, trichomonas (in women), and syphilis. They also receive testing for hepatitis B and C, pregnancy testing and family planning support if female, syndromic and etiological management for STIs, HIV counselling and testing, and, if male, a referral for voluntary male medical circumcision. Those living with HIV are immediately initiated on ART, while those who test negative and are suitable according to South African National PrEP guidelines are offered oral PrEP. The initial visit is followed by a 7-day phone call and 3-monthly follow-ups. Each follow-up includes repeat HIV testing, pregnancy testing, syndromic management of STIs, and referral to peer navigators for adherence support and PrEP/ART, and contraception refills if applicable.

1.6.2 Intervention: Choice of PrEP modalities

In addition to the enhanced SoC, the nurses in the mobile AYFS within the intervention clusters will offer the choice of long-acting injectable cabotegravir (CAB-LA) to be delivered to AYA at risk of HIV acquisition or 3-

monthly DapiRings. If they choose not to take PrEP, they are offered take-home PEP-in-pocket. A PEP-in-pocket kit includes an HIV self-test, a 28-day supply of a fixed dose combination of generic Tenofovir Lamivudine and Dolutegravir (TLD), a pregnancy test and emergency contraception (for females), along with a card containing the clinic hotline and peer navigator contact information. For those who choose or switch to CAB-LA (if already on oral PrEP), the initial visit will be followed by a planned visit for the first injection. This will be followed by a one-month visit for the second injection, and then bi-monthly injections. Each visit will include repeat HIV testing, pregnancy testing, and referral to peer navigators for adherence and retention support. Safety bloods collection (full blood count, creatinine, liver function tests) will follow national guidelines.

Peer navigators in the intervention clusters promote long-acting PrEP alongside oral PrEP during community-based health promotion activities. As part of the peer mentorship package, they remind young people of their follow-up visits and if feasible, accompany those on CAB-LA to their first follow-up injection (1 month) and subsequent bi-monthly injections at the mobile clinics. With support from their supervisors and oversight committee, peer navigators trace individuals who have missed their scheduled visits. They assist clinical teams in ensuring that young people who have discontinued CAB-LA receive regular HIV testing and remain protected from acquiring HIV during the CAB-LA tail period

1.7 Definition of estimands, primary and secondary outcomes

1.7.1 Primary estimands

The primary estimand for effective uptake is a population-level implementation estimand: the effect of allocation to the LAPIS intervention, compared with control, on uptake (documented receipt) of any biomedical HIV prevention intervention through study-linked HIV/SRH services among young people aged 15–30 years residing in the trial clusters during the observation period. This estimand reflects population-level reach or coverage of the intervention package, rather than uptake conditional on HIV-negative status or individual clinical eligibility, irrespective of the level of implementation of the intervention. Participants will be analysed according to their allocated trial cluster irrespective of actual engagement with HIV prevention services (policy estimand).

The primary estimand for retention is a post-initiation engagement estimand: the effect of allocation to the LAPIS intervention, compared with control, on attendance at least one follow-up HIV prevention service visit after PrEP/PEP initiation among individuals who initiated PrEP/PEP through study-linked services at least 4

months before trial end, irrespective of the level of implementation of the intervention. Participants will remain analysed according to their allocated trial cluster irrespective of subsequent patterns of service utilisation following PrEP/PEP initiation (policy estimand).

Intercurrent events such as death, withdrawal of consent, or movement outside the HDSS area may result in incomplete outcome ascertainment and will be addressed as part of missing outcome handling.

1.7.2 Primary outcomes

a) Effective uptake of PrEP/PEP: this is defined as the proportion of young people who have received any biomedical HIV prevention intervention through study-linked HIV/SRH services during the LAPIS observation period, including oral PrEP, injectable PrEP (CAB-LA), vaginal ring (DapRing) or PEP-in-pocket.

- Oral PrEP was available in both trial arms through the *Thetha nami* trial platform, while CAB-LA, DapiRing, and PEP-in-pocket were additionally offered in intervention clusters as part of the LAPIS differentiated HIV prevention package.

This outcome is defined based on documented initiation or dispensing through study-linked HIV/SRH services. Individuals aged 15-30 years residing in the trial clusters (irrespective of HIV status) for whom no clinical uptake data are available will be classified as not having initiated PrEP or PEP for the primary analysis.

b) Retention on PrEP/PEP: this is defined as attending at least one follow-up appointment after PrEP/PEP initiation, including appointments for HIV testing. Retention will be assessed among individuals who initiate any form of PrEP or PEP as part of the trial at least 4 months before the end of the trial.

1.7.3 Secondary outcomes (see Table 1 for definitions):

- a) Prevalence of sexually transmissible HIV
- b) Uptake of universal risk informed HIV prevention intervention
- c) Cost per effective PrEP uptake
- d) Adverse events associated with CAB-LA compared to oral PrEP
- e) Patterns of PrEP/PEP use
- f) Risk of HIV acquisition or transmission
- g) Access to sexual and reproductive health services (STI prevalence, uptake of contraception, teenage pregnancy, voluntary male medical circumcision (VMMC))

- h) Recent HIV infection using recency assays
- i) Common mental health disorder as measured by PHQ9

1.7.4 Implementation (process) outcomes:

- a) Reach
- b) Effectiveness
- c) Adoption
- d) Implementation
- e) Maintenance

This SAP describes the analysis of the above outcomes except for the secondary outcome: 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 summarise the outcomes, source of data, 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 and Secondary outcomes (detailed definitions in Section 3)

Domain	Measure	Method of aggregation	Metric	Source for outcome ascertainment
Primary outcomes				
Uptake of PrEP	Taking up any form of PrEP (oral, injectable, ring) or PEP-in-pocket in the study clinics during the trial period	Frequency and percentage	Odds ratio	Clinic data
PrEP retention	Receiving at least one PrEP prescriptions among those who reported PrEP use during the trial period	Frequency and percentage	Odds ratio	PrEP cohort
Secondary outcomes				
Sexually transmissible HIV	Having HIV viral load of ≥ 400 copies/mL (yes/no)	Frequency and percentage	Odds ratio	Endline survey
Universal risk informed HIV prevention intervention uptake	On antiretroviral therapy (ART) if living with HIV or on PrEP if HIV negative (yes/no)	Frequency and percentage	Odds ratio	Endline survey + Clinic data
Sexually transmitted infections	Positive test for chlamydia and/or gonorrhoea	Frequency and percentage	Odds ratio	Endline survey
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?”	Frequency and percentage	Odds ratio	
	Self-reported current pregnancy among females younger than 20; based on answer to the question, “are you currently pregnant?”	Frequency and percentage	Odds ratio	
	VMMC – self reported VMMC in adolescent boys and young men (yes/no)	Frequency and percentage	Odds ratio	
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).	Frequency and percentage	Odds ratio	Endline survey + Clinic data
Recent HIV infection	Individuals living with HIV and have a positive recency assay (within 6 months)	Frequency and percentage	Odds ratio	Endline survey

Domain	Measure	Method of aggregation	Metric	Source for outcome ascertainment
HIV incidence rate	Number of participants with a new HIV infection within the HIV-negative cohort	Count of new infections over person-time at risk	Incidence rate per 100 person-years	Clinic data
Common mental health disorder (depression screening)	Patient Health Questionnaire-9, total score	Mean and SD	Mean difference	Endline survey
	Patient Health Questionnaire-9, total score ≥ 10	Frequency and percentage	Odds ratio	
Patterns of PrEP/PEP use		Frequency and percentage	Odds ratio	PrEP cohort
Adverse events	Frequency and severity of adverse events (AEs) reported among participants who initiated CAB-LA compared to those on oral PrEP.	Frequency and percentage	Odds ratio	PrEP cohort

1.8 Sample size & power

Based on our current data, we estimate that 20% of young people aged 15-30 years in the enhanced SoC arm will attend a clinic to undergo an HIV risk assessment, and 20-30% will start or continue PrEP (primary outcome 1), i.e., 4%-6% (0.20×0.20 - 0.30) of all young people in the control clusters. With 12,000 AYA in the control clusters we estimate that ~600 will start/continue oral PrEP. Assuming intracluster correlation coefficients (ICCs) values between 0.05-0.15, with 12,000 young people in the control clusters and 12,000 in the intervention clusters, we will have 80% power to detect an increase in PrEP uptake from 4% to 9% (at ICC 0.05) or 14% (at ICC 0.15). We will have 90% power to detect an increase in uptake to 10% (ICC 0.05) or 16% (ICC 0.15) (Supplementary figure 1). Similarly, we will have 80% power to detect an increase in PrEP uptake from 6% to 12% (at ICC 0.05) or 17% (at ICC 0.15).

If uptake increases to 9%–14% in the intervention arm, this will result in 1100–1700 (55-85 per cluster) young people starting PrEP or PEP over 14 months. However, our second primary outcome (retention on PrEP) is assessed only among those who have at least four months of follow-up time by the end of the trial. Therefore, we have used a more conservative estimate of the numbers per cluster in our power calculations. The current retention in those who start PrEP is 20%. With a sample size of 400 (20 per cluster) in the enhanced SoC arm and 780 (39 per cluster) in the intervention arm, and assuming ICC values between 0.05 and 0.15, we will have 80% power to detect an increase in retention from 20% to 31% at an ICC of 0.05 or to 37% at an ICC of 0.15. We will have 90% power to detect an increase in retention from 20% to 33% (ICC = 0.05) or 40% (ICC = 0.15).

1.9 Intervention allocation

The 40 trial clusters were randomly allocated in a 1:1 ratio to the LAPIS intervention or enhanced standard of care. Randomisation was stratified by early or delayed roll-out of the *Thetha nami* intervention in the first period of the stepped-wedge trial. In addition to this stratification, we applied covariate-based restricted (or constrained) randomisation to ensure that the clusters are reasonably balanced between arms with respect to key characteristics namely: population size of the 15-30-year-olds, proximity to the major road, and geographical location in the northern or southern part of the study area. A random sample of 10,000 possible allocations of clusters to two groups (labelled A or B) was selected from a total of approximately 500,000 possible allocations that met the restriction criteria, from which one was randomly selected at a public randomisation ceremony.

1.10 Data collection schedule

Data for outcome ascertainment are/will be collected from the following sources outlined in **Table 2**: i) population-based endline survey data; ii) exit survey of the participants within the HIV-negative cohort; iii) programme, process, and clinical data; iv) qualitative data collected during the process evaluation; v) records of resource utilisation (such as consumables, medicines, diagnostics) and cost data including financial reports for staff and overhead costs.

1.11 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 (2–4). The final analysis for the main results will be conducted once the exit surveys have 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 arm, and the reasons summarised. The following 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 Analysis principles and population assignment

Population definitions used for specific outcomes are described in Section 1.5. Comparative analyses of intervention effects will follow the intention-to-treat principle, whereby participants will be analysed according to the cluster corresponding to their area of residence within the trial clusters during the study period, irrespective of the location at which services were accessed during follow-up. Attendance at study clinics or mobile services outside the participant's cluster of residence will not alter cluster assignment for analysis purposes. This preserves the integrity of the cluster randomisation. Outcome-specific analyses will be conducted within the relevant predefined study populations described in Section 1.5.

Table 2 Schedule of enrolment, interventions, and assessments for LAPIS cluster randomised trial

	STUDY PERIOD		
	Allocation (clusters)	Intervention delivery	Endline survey
TIMEPOINT	Month 0	Month 1-15	Month 16-24
ENROLMENT:			
Eligibility screen		X	X
Informed consent		X	X
Restricted randomisation of N=40 clusters	X		
Allocation	X		
INTERVENTIONS:			
<i>Choice of long-acting injectable PrEP with cabotegravir, DapiRing or post-exposure prophylaxis-in-pocket (PEP-in-pocket) within community based integrated HIV (PrEP/ ART) and SRH services</i>		20 clusters	X
<i>Enhanced standard of care: Peer-led mobilisation into community based integrated HIV (oral PrEP or ART) and SRH services</i>		20 clusters	X
ASSESSMENTS:			
<i>Blood sample for HIV testing & viral load if positive</i>			X
<i>Urine and self-taken vaginal swabs for STI testing</i>			X
<i>20–30-minute interview- administered questionnaire (uptake of HIV & SRH services, sexual risk, reproductive health, mental health etc.)</i>			X
<i>Clinical data from clinical management tools</i>		X	X
<i>Programme data from peer navigators' support management tools</i>		X	X
<i>In-depth interviews with peer navigators, clinic staff and young people</i>		X	X
<i>Costing Data</i>		X	X

3 Detailed definition of outcomes

3.1 Primary outcomes

The primary outcomes will be assessed using routinely collected clinical data from study-linked HIV/SRH services, including electronic medical records, dispensing logs, and clinic visit records from our mobile study clinics. Outcome analyses will be conducted within the relevant predefined study populations described in Section 1.5.

3.1.1 Effective uptake of PrEP or PEP

Definition:

Effective uptake of PrEP or PEP is defined as the proportion of individuals aged 15-30 years residing in the trial clusters who received any biomedical HIV prevention intervention either oral PrEP, injectable PrEP (CAB-LA), vaginal ring (DapiRing), or PEP-in-pocket at a study clinic at least once during the observation period.

Numerator:

Number of participants aged 15-30 years who have received any form of PrEP (oral, injectable, vaginal ring) or have received PEP-in-pocket from study clinics, as documented in clinical records.

Denominator:

Total number of individuals aged 15-30 years who are residents of the trial clusters, regardless of HIV status, during the study period.

Measurement period:

Uptake will be assessed over 14 months post-intervention roll-out.

Data source:

- Electronic medical records from study-linked HIV/SRH services
- Dispensing logs for oral PrEP, CAB-LA, DapiRing, and PEP-in-pocket
- Clinic attendance and visit records from mobile and linked study clinics

Operational notes:

- Uptake is measured at the population level within the HDSS trial population, with all residents aged 15–30 years in the trial clusters contributing to the denominator irrespective of clinic attendance or HIV status.
- A participant will be considered to have initiated PrEP or PEP if there is documented evidence of medication being dispensed, regardless of the number of doses or whether follow-up visits occurred.
- PEP-in-pocket refers to the provision of a 28-day PEP course, a pregnancy test and emergency contraception (for females), along with a card containing the clinic hotline and peer navigator contact information to participants assessed to be at ongoing risk but who may not consistently attend clinic or may have episodic risk exposures.

- Multiple modality initiations will count only once for this primary outcome (i.e., binary indicator per individual: initiated vs not initiated).

3.1.2 Retention on PrEP

Definition:

Retention is defined as the proportion of individuals who attend at least one follow-up appointment after PrEP/PEP initiation.

Numerator:

Number of participants who initiated PrEP/PEP and attended at least one follow-up appointment at a study clinic during the trial observation period, with initiation at least 4 months before trial close.

Denominator:

All participants who initiated PrEP/PEP during the trial observation period, and at least 4 months before trial close.

Measurement period:

Retention will be assessed over 14 months post-intervention roll-out.

Operational notes:

- A follow-up visit is defined as any documented clinic attendance for PrEP/PEP refills after the initial PrEP or PEP dispensing, including visits for HIV testing, PrEP refills, PEP-related follow-up, or reassessment for HIV prevention services.
- This outcome reflects continued engagement with study-linked HIV prevention services following initiation and does not necessarily represent sustained long-term adherence or persistence on PrEP
- This measure captures any return visit post-initiation, not sustained use or exact dosing intervals (which may be explored in secondary outcomes or sensitivity analyses).

3.2 Secondary Outcomes

3.2.1 Sexually transmissible HIV

Definition:

Sexually transmissible HIV is defined as the proportion of participants aged 15-30 years who have a

detectable viral load (≥ 400 copies/mL) at the time of dried blood spot (DBS) specimen collection during the endline survey.

Numerator:

Number of participants aged 15-30 years with a confirmed HIV-positive result and a viral load ≥ 400 copies/mL from DBS testing.

Denominator:

Total number of participants aged 15-30 years who provided a DBS sample as part of the endline survey.

Measurement period:

Assessed at a single timepoint during the endline survey, conducted after full intervention implementation and follow-up.

Operational notes:

The composite outcome reflects both newly acquired HIV infections (incident cases) and established infections not virologically suppressed, regardless of ART status.

3.2.2 Uptake of universal risk informed HIV prevention intervention

Definition:

Uptake of universal risk-informed HIV prevention is defined as the proportion of survey participants aged 15-30 years who are aware of their HIV status and are either:

- On antiretroviral therapy (ART) if living with HIV, or
- Have ever taken up PrEP following a risk assessment if HIV-negative.

This composite outcome is designed to reflect the extent of appropriate biomedical prevention coverage in the population.

Numerator:

Number of participants meeting one of the following criteria:

- **HIV-positive** and either:
 - Have a viral load < 400 copies/mL on DBS, or
 - Are documented as being on ART based on clinical data (from mobile clinics) and have consented to data linkage.

- **HIV-negative** and documented to have initiated PrEP based on linked clinical data following risk assessment.

Denominator:

All participants aged 15-30 years enrolled in the population survey who consented to DBS collection and data linkage for clinical records.

Measurement period:

Assessed at a single timepoint during the endline survey, conducted after full intervention implementation and follow-up.

Data sources:

- Survey-collected DBS for HIV and viral load testing
- Linked clinical data, including PrEP/ART dispensing and treatment records from the study clinics

Operational notes:

- HIV-negative individuals are classified as having taken up PrEP if clinical records show evidence of initiation at any time prior to the survey.
- HIV-positive individuals are considered on ART if this is indicated in any available linked clinical data source, or if viral suppression (VL <400 copies/mL) is observed.
- Individuals on PrEP or with VL <400 copies/mL are assumed to be aware of their HIV status.
- Those with detectable viremia (VL ≥400 copies/mL) and no record of ART, or HIV-negative individuals with no PrEP record, are considered to have not taken up a HIV risk-informed prevention intervention.

3.2.3 Access to SRH services

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

3.2.3.1 Curable Sexually Transmissible Infections (STI)

Definition:

Prevalence of *any* curable STIs is defined as the proportion of participants who test positive for at least one of the following infections: *Chlamydia trachomatis* (CT) or *Neisseria gonorrhoeae* (NG), based on Cepheid GeneXpert CT/NG testing conducted at the endline survey.

Numerator:

Number of participants with a positive test result for chlamydia and/or gonorrhoea.

Denominator:

Number of participants who provided a valid biological sample (urine or vaginal swab) and were tested for both infections.

Measurement period:

Assessed at a single timepoint during the endline survey, conducted after full intervention implementation and follow-up.

Data sources:

Clinical data of specimens collected: male urine samples and female self-collected vaginal swabs or urine

Additional Reporting:

- Prevalence of *any* curable STI (composite outcome)
- Prevalence of each STI separately (chlamydia and gonorrhoea)
- Disaggregated reporting by sex, age group, and trial arm (in stratified or adjusted analyses)

3.2.3.2 Uptake of contraception, defined as current contraception use**Definition:**

Proportion of women aged 15-30 years who report currently using any contraceptive method to prevent pregnancy.

Numerator:

Number of women aged 15-30 years classified as currently using contraception. Women will be classified as using contraception if they either:

1. respond “yes” to the question: *“Are you currently using any contraceptive methods to prevent pregnancy?”*
2. or have documented contraception delivery through linked clinical data

Denominator:

Number of women participating in the population survey who provided a response to the contraception use question.

Measurement period:

Assessed at a single timepoint during the endline survey, conducted after full intervention implementation and follow-up.

3.2.3.3 *Teenage pregnancy***Definition:**

Proportion of adolescent girls aged 15-19 years who self-report currently being pregnant.

Numerator:

Number of adolescent girls aged 15-19 years who respond “yes” to the pregnancy status question in the survey or have a linked clinical pregnancy data.

Denominator:

Number of adolescent girls aged 15-19 years who completed the survey and provided a pregnancy response.

Measurement period:

Assessed at a single timepoint during the endline survey, conducted after full intervention implementation and follow-up.

3.2.3.4 *Voluntary male medical circumcision (VMMC)***Definition:**

Proportion of male participants who report ever having undergone circumcision.

Numerator:

Number of men who report ever being circumcised.

Denominator:

All male survey participants who responded to the circumcision question.

Measurement Period:

Assessed at a single timepoint during the endline survey, conducted after full intervention implementation and follow-up.

3.2.4 Risk of HIV acquisition or transmission

Definition:

Composite outcome capturing individuals at risk of acquiring or transmitting HIV, among participants aged 15-30 who provided DBS during the endline survey or underwent HIV testing during a clinic visit during the trial.

- **Acquisition risk:** HIV-negative individuals, reporting any condomless sex (regardless of partner type), with no record of PrEP use.
- **Transmission risk:** HIV-positive individuals with a viral load ≥ 400 copies/mL and who report any condomless sex.

Numerator:

Number of participants meeting either acquisition or transmission risk definition.

Denominator:

All participants aged 15-30 who provided a DBS or clinic HIV test result and completed sexual behaviour questions in the endline survey.

Measurement period:

Assessed at a single timepoint during the endline survey, conducted after full intervention implementation and follow-up.

Data sources:

- Survey-collected DBS for HIV and viral load testing, self-reported condom use and behaviour from endline survey
- Linked clinical data, including PrEP/ART dispensing and treatment records from the study clinics
- HIV status is derived from the DBS if available, and otherwise from most recent HIV test at clinic.

3.2.5 Recent HIV infection using HIV recency assays

Definition:

Proportion of individuals living with HIV who are classified as having a recent HIV infection (within 6 months) based on laboratory recency testing of DBS samples.

Numerator:

Number of HIV-positive participants with a positive recency assay.

Denominator:

All participants who provided DBS sample for HIV testing at the endline survey.

Measurement period:

Assessed at a single timepoint during the endline survey, conducted after full intervention implementation and follow-up. Recency reflects approximate infection within ~6 months prior to endline; it does not capture infections earlier in follow-up that have progressed beyond the recency window.

Data source:

Laboratory recency assay data on DBS samples.

Operational notes:

- Recency assay algorithm: We will use Maxim HIV-1 LAg-Avidity DBS EIA for recency classification according to the manufacturer's protocol. A sample will be classified as 'recent' only if:
 - (1) the recency assay result falls within the recent range (~6 months prior to the endline survey);
 - (2) viral load ≥ 400 copies/mL; and
 - (3) no antiretroviral drugs detected on ARV assay.
- Recency outcomes will primarily be reported descriptively as indicators of recent HIV infection at the population level.

3.2.6 HIV incidence rate

Definition:

The rate of new HIV infections among all participants in the HIV-negative cohort, regardless of PrEP initiation.

Numerator:

Number of participants with a first confirmed HIV-positive test (seroconversion) during follow-up.

Denominator:

Total person-time at risk contributed by participants confirmed HIV-negative at enrolment. Person-time is accrues from the date of the baseline HIV-negative test (at screening) until the earliest date of seroconversion, death, withdrawal, loss to follow-up, or administrative censoring.

Measurement period:

From date of the HIV-negative test confirming eligibility for enrolment into the HIV-negative cohort until last recorded HIV test during follow-up, censoring at the date of infection or study exit.

Data source:

- Negative HIV status: Determined from screening/enrolment HIV testing records (point-of-care rapid tests confirmed by DBS tests and/or laboratory-based HIV ELISA).
- Follow-up HIV tests: Derived from clinic visit records and laboratory confirmations of positive results during follow-up.

Operational notes:

- Date of HIV infection will be estimated as the midpoint between the last negative and first positive HIV tests.
- Participants lost to follow-up will be censored at the date of their last HIV-negative test.
- Incidence rate will be reported per 100 person-years. If few seroconversions occur, exact Poisson confidence intervals or permutation-based inference will be considered.

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

Definition:

Prevalence of depression symptoms among participants based on the Patient Health Questionnaire-9 (PHQ-9) screening assessment tool.

Scoring:

Each of the 9 items is scored from 0 ("Not at all") to 3 ("Nearly every day"). Total score ranges from 0 to 27. Categories: 1-4 none/minimal; 5-9 mild; 10-14 moderate; 15-19 moderately severe; 20-27 severe.

Primary inferential outcome:

Binary indicator using a threshold of PHQ-9 score ≥ 10 (moderate or worse depression).

Denominator:

Participants who complete the PHQ-9 questionnaire at endline survey with ≤ 2 missing responses.

Measurement period:

Assessed at a single timepoint during the endline survey, conducted after full intervention implementation and follow-up.

Analysis notes:

- Prevalence will be reported in categories.
- Mean and SD scores will be summarized.
- If ≤ 2 items are missing, scores will be imputed using the median of completed items.
- Internal consistency assessed with Cronbach's alpha.
- Binary outcome (score ≥ 10) used for regression analyses.

3.2.8 Patterns of PrEP/PEP use

Definition:

Longitudinal patterns in PrEP and PEP initiation, continuation, stopping, switching, or restarting across study participants.

Key descriptors:

- Initiation: First documented receipt of PrEP or PEP.
- Continuation: Ongoing use without a gap exceeding the expected refill or dosing interval for the specific prevention modality.
- Stopping: No further documented receipt of the prevention modality beyond the expected refill or dosing interval.
- Switching: Transitioning from one PrEP modality to another, or from PEP to PrEP.
- Restarting: Re-initiation of PrEP or PEP following a period classified as stopping.

Denominator:

All participants with at least one clinic record indicating PrEP or PEP use.

Data source:

Clinic visit data including PrEP dispensing medical records.

Measurement period:

From first PrEP/PEP uptake to study end (clinic-recorded period, including all follow-ups).

Analysis notes: Stratified analyses by sex, age group, and PrEP modality.

3.2.9 Adverse events associated with CAB-LA compared to oral PrEP

Definition:

Frequency and severity of adverse events (AEs) reported among participants who initiated CAB-LA compared to those on oral PrEP.

Outcome measures:

- Proportion of participants experiencing any adverse event.
- Proportion experiencing severe (Grade 3+) adverse events.
- Type and frequency of reported adverse events (e.g., injection site reactions, systemic reactions).

Denominator:

Participants who initiated either CAB-LA or oral PrEP and had at least one follow-up visit or contact where AE reporting was possible.

Numerators:

- Any AE: Number of participants reporting ≥ 1 AE.
- Grade 3+ AE: Number reporting ≥ 1 severe AE.
- Specific AE types: Counts of each adverse event reported.

Measurement period:

Ongoing during PrEP follow-up for each modality user.

Data source:

- Clinical monitoring data from mobile clinics.
- Structured adverse event reporting forms.
- Participant interviews or follow-up questionnaires.

Analysis notes:

- Stratified comparisons by product (CAB-LA vs. oral PrEP).
- AE incidence rates may be calculated per person-time if follow-up duration varies.
- Summary tables will report number (%) by AE category and grade.

3.3 Implementation (process) Outcomes

We will evaluate key implementation outcomes using the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation, Maintenance) to complement our analysis of the intervention's clinical effectiveness. Each implementation outcome is described below

3.3.1 Reach

We will measure reach as the extent to which key populations at risk of HIV acquisition such as out-of-school youth, recently migrated, those living in remote areas, and other hard-to-reach groups that are aware of and take up PrEP. This will be assessed using survey data collected at endline, focusing on the proportion of the target population who are aware of PrEP and have initiated PrEP. We will also describe the patterns of PrEP and PEP uptake and retention stratified by intervention arm and subgroup.

3.3.2 Effectiveness

For this we use our primary outcome, see section 3.1, and compare across arms, with subgroup analyses by sex and age group.

3.3.3 Adoption

Adoption reflects the acceptability and appropriateness of PrEP modalities and HIV testing strategies among 15–30-year-olds. This will be assessed using both quantitative survey data and qualitative interview data. Quantitative data will include participant preferences and attitudes towards oral PrEP, CAB-LA, and the DapiRing, as well as HIV self-testing. Qualitative data will explore the underlying reasons for these preferences and perceptions of acceptability.

3.3.4 Implementation

We will assess the fidelity and feasibility of delivering CAB-LA and associated services in the intervention arm. This includes examining how CAB-LA is implemented in practice, including the use of HIV self-testing at initiation, during continuation, and at stopping.

3.3.5 Maintenance

To evaluate the sustainability and scalability of the intervention, we will explore the affordability and resource needs for delivering a choice of PrEP modalities through both mobile and primary care services.

4 Descriptive analyses

Following CONSORT guidelines for cluster randomised trials, we will include a flow diagram detailing the number of individuals aged 15-30 years who are residents of the trial clusters during the study period, the number completing the endline survey, the number screened for PrEP/PEP initiation and study enrolment, the number deemed eligible, and the number enrolled to the PrEP cohort, disaggregated by trial arm. Reasons for ineligibility and non-enrolment will also be summarised.

For continuous variables:

- If approximately normally distributed, we will report number of observations (n), mean, standard deviation (SD), minimum, and maximum, with summary statistics presented to one more decimal place than the raw data.
- If non-normally distributed, we will report count, median, lower quartile (Q1), and upper quartile (Q3).

For categorical variables, we will report count and percentage, with percentages presented to one decimal place.

To describe the total study population and the PrEP cohort, and assess baseline comparability across arms, we will summarise key sociodemographic characteristics by trial arm. These will include age group, sex, area of residence (rural vs. urban/peri-urban), socio-economic status, highest educational attainment, and employment status.

5 Comparative analyses

5.1 Primary outcome analyses

For each of the two primary outcomes, we will report the number and percentage of participants with the outcome by trial arm. To estimate the intervention effect, we will fit population-averaged logistic regression models using Generalized Estimating Equations (GEE) with a logit link and binomial distribution. Clustering at the cluster level will be accounted for using an exchangeable working correlation structure and robust (sandwich) standard errors. These models will yield odds ratios (ORs) and 95% confidence intervals (CIs).

Models will adjust for:

- **Design factors:** exposure to the first period of *Thetha Nami* and the factors used in the restricted randomisation:
 - Population size of 15–30-year-olds
 - Proximity to the major road
 - Geographical location (north/south)

To improve statistical efficiency and account for potential chance imbalance, we will also adjust for the following individual-level covariates that may be associated with PrEP uptake:

- Age (continuous)
- Sex
- Area of residence (rural/urban)

The odds ratio for the intervention from these fully adjusted models will be considered the primary estimate of effect. Unadjusted models will also be reported for completeness.

If the GEE model with exchangeable working correlation fails to converge, we will refit the model using an independence working correlation structure.

The fitted marginal models will follow the general form:

$$\text{logit}\left(P(Y_{ij} = 1)\right) = \beta_0 + \beta_1 \cdot \text{Intervention}_j + \sum_{k=2}^K \beta_k \cdot X_{ijk} \quad (5.1)$$

Where:

Y_{ij} = binary outcome for individual i in cluster j (e. g. PrEP uptake)

Intervention_j = binary indicator for whether cluster j was allocated to the intervention arm (1=intervention, 0=control)

X_{ijk} = k^{th} individual-level or cluster-level covariate (e.g., age, sex, rural/urban residence, etc.)

β_0 = intercept (log-odds of the outcome in the reference group)

β_1 = fixed effect of the intervention (our primary parameter of interest)

β_k = fixed effect for k^{th} covariate

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 will be analysed to assess the broader impact of the intervention across domains of HIV prevention, sexual and reproductive health, and mental health. We will present the number and proportion of individuals with each outcome by trial arm. The effect of the intervention will be quantified using regression models appropriate to the type of outcome, adjusting for clustering and relevant covariates, as described in section 5.1.

5.3 Pre-specified subgroup analyses

To assess the consistency of the intervention effect on the primary outcomes across key population subgroups, we will conduct pre-specified subgroup analyses. These analyses will test for statistical interaction between the intervention and subgroup variables by including interaction terms in the adjusted models used for the primary outcome analyses. The subgroup variables are:

- Sex (male vs. female)
- Age group (<21 years vs. ≥21 years)

For each subgroup:

- We will present effect estimates (odds ratios) and 95% confidence intervals for the intervention effect within each level of the subgroup.
- We will report the p-value for interaction, with $p < 0.05$ indicating evidence of differential effect across subgroup levels.

5.4 Sensitivity analyses

As a pre-specified sensitivity analysis, primary and secondary outcomes will be re-analysed among participants aged ≥18 years to assess the potential impact of consent-related and implementation barriers affecting participation and access to intervention components among participants aged <18 years. These analyses will be interpreted as sensitivity analyses and will not replace the primary analyses conducted in the full eligible population.

5.5 Significance levels and adjustment of p-values for multiplicity

All statistical analyses will be conducted using a two-sided significance level of 5%, and 95% confidence intervals (CIs) will be reported for all primary and secondary outcomes, as well as subgroup analyses. No formal correction for multiplicity will be applied to primary or secondary outcomes, as these outcomes span

different domains of interest (e.g., effectiveness, implementation, and safety), and each addresses distinct trial objectives.

Subgroup analyses are exploratory in nature and will likewise not be adjusted for multiplicity. However, the issue of multiple comparisons will be explicitly considered when interpreting the findings to avoid overinterpretation of statistically significant results that may arise by chance.

Interpretation of results will be guided by:

- The strength and consistency of observed effects,
- Pre-specified hypotheses,
- The biological plausibility and relevance of observed subgroup differences,
- And alignment with findings from related trials or literature where applicable.

5.6 Missing data

We will distinguish between (i) item-level missingness within completed questionnaires or scales and (ii) outcome-level missingness due to non-attendance at visits, missing DBS samples, or loss to follow-up. We will report the proportion of missing data for all collected variables, including baseline covariates and outcome measures, by trial arm. The extent and pattern of missingness will be assessed to determine informally whether the missing data are likely to be missing completely at random (MCAR) or not.

Item-level missingness: For outcomes based on validated scales such as the PHQ-9, we will follow standard scoring rules. For example, PHQ-9 scores will be calculated if at least 7 of 9 items are completed, with imputation of missing items as described in Section 3.2.7.

Outcome-level missingness: For primary and secondary outcomes, the main analysis will be complete case. Participants without outcome data at the relevant timepoint will be excluded from that analysis. As a sensitivity analysis, we will use multiple imputation (MI) under a missing at random assumption if the proportion of missing exceeds 10%.

All imputation models will include:

- Trial arm,
- Variables associated with missingness and the outcome of interest,
- And auxiliary variables that may improve imputation accuracy.

- For time-to-event outcomes (e.g., HIV incidence), we will not impute event times; participants with no follow-up HIV test will be censored at their last observed HIV-negative test.

We will report the extent and pattern of missingness by trial arm and compare MI results with complete case results to assess robustness.

5.7 Statistical software employed

The statistical software Stata/SE version 18 or higher version for Windows will be used for all analyses. Software R 4.2.1 or higher version will be used for graphics where necessary.

6 Miscellaneous

6.1 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.

7 Abbreviations

AE	Adverse Event
ART	Antiretroviral Treatment
AHRI	African Health Research Institute
CONSORT	Consolidated Standards of Reporting Trials
CI	confidence interval
DBS	Dried blood spot
HIV	Human Immunodeficiency Virus
ICC	Intracluster correlation coefficient
KZN	Kwa-Zulu Natal
OR	Odds ratio
PHQ-9	Patient Health Questionnaire-9
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
VL	Viral load
VMMC	Voluntary male medical circumcision

8 References

1. Busang J, Zuma T, Chimbindi N, Ngoma N, Herbst C, Okesola N, et al. Long-acting HIV pre-exposure prophylaxis integrated with community-based sexual and reproductive health services in South Africa (LAPIS): study protocol for a hybrid (1a) cluster randomised controlled phase 3B trial of effectiveness and implementation. BMC Public Health. 2026 Jan 20;26(1). doi:10.1186/S12889-025-24889-1 PubMed PMID: 41559582.
2. Hopewell S, Chan AW, Collins GS, Hróbjartsson A, Moher D, Schulz KF, et al. CONSORT 2025 statement: updated guideline for reporting randomized trials. Nat Med. 2025 Apr 15. doi:10.1038/S41591-025-03635-5 PubMed PMID: 40229553.
3. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar 27;340(mar23 1):c332. doi:10.1136/bmj.c332 PubMed PMID: 20332509.
4. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340(mar23 1):c869. doi:10.1136/bmj.c869 PubMed PMID: 20332511.
5. Busang J, Zuma T, Herbst C, Okesola N, Chimbindi N, Dreyer J, et al. 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. BMC Public Health 2023 23:1. 2023 Aug 15;23(1):1–14. doi:10.1186/S12889-023-16262-X