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Pharmacy delivery to expand the reach of PrEP in Kenya: cluster-randomized control trial

Pharm PrEP cRCT

Statistical Analysis Plan

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FINAL

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Contents

Introduction

This statistical analysis plan (SAP) describes the statistical procedures and analyses and data displays that address study objectives specified in protocol version 1.1 of the Pharm PrEP cRCT (a study of pharmacy-delivered PrEP/PEP in Kenya).

New versions of the SAP will be issued to document updates and changes in the plan. Any meaningful changes or additions to this SAP (e.g., in response to protocol amendments or violations of assumptions underlying pre-planned analyses), and the timing of such changes in relation to timing of performing the analysis will be documented in the SAP.

1. Study Objectives and Overview

Protocol title	Pharmacy delivery to expand the reach of PrEP in Kenya: cluster-randomized control trial
Short title	Pharm PrEP cRCT
Design	Cluster-randomized controlled trial
Study exposures	Each pharmacy is randomized to either provision of PrEP/PEP in pharmacies either provided by a pharmacist for free (Arm 1), for a fee (Arm 2), or by an HTS counselor for free (Arm 3); or referral to a clinic for PrEP/PEP (Arm 4, standard of care)
Population	Pharmacies must be registered; pharmacists must be licensed and HTS counselors must be certified; enrolled clients must be adults (≥ 16 years old), at risk of HIV, and eligible for PrEP/PEP (according to the prescribing checklist)
Study size	At least 1,119 PrEP initiations and 2,400 PEP initiations for the cluster-randomized control trial
Study follow-up	At least 20 months for accrual (until sample size achieved) plus follow-up of up to 270 days.
Study sites	60 private pharmacies in Kenya (Nairobi; Kiambu; Kisumu/Siaya; and Homa Bay/Migori).
Objective	Quantify the effect of three models of pharmacy-delivered PrEP/PEP (sustained by clients; sustained by implementors; and sustained by implementors with support from HTS counselors) compared to pharmacy referral to clinic-based PrEP/PEP services (SOC) on PrEP/PEP outcomes and implementation outcomes
Outcomes	<u>Primary</u>: • PrEP initiation within 60 days of enrollment; • PrEP continuation (i.e., one refill) by 60 days

Secondary:

- PrEP initiation within 270 days;
- Any PrEP continuation within 270 days;
- At least 2 PrEP refills within 270 days;
- Any stopping and restarting PrEP (i.e., PrEP reinitiation);
- PEP initiation within 60 and 270 days;
- PEP-to-PrEP transition by 60 and 270 days;
- PrEP-to-PEP transition by 60 and 270 days;
- Recurrent PEP use by 60 and 270 days;
- PrEP adherence at 60 days;
- PrEP/PEP initiation within 60 and 270 days;
- Any PrEP/PEP continuation by 60 and 270 days

Tertiary:

- Follow-up HIV testing by 60 and 270 days;
- Behaviors associated with HIV risk at 60 and 270 days;
- PrEP coverage (exploratory)
- Acceptability; quality of care perceptions; willingness to pay; fidelity (client outcomes); acceptability; feasibility; adaptations; perceived self-efficacy; willingness to charge (provider/counselor outcomes); sustainability (pharmacy outcome)

2. Study Population

Adults at risk of HIV acquisition (determined by screening tools, self-report, and provider assessment) and eligible for pharmacy-delivered PrEP/PEP services (i.e., no medical conditions that might contraindicate PrEP/PEP safety) identified by screening at one of 60 participating pharmacies in Kenya whose data (pharmacy/clinic records, survey, and/or interview) were collected.

Pharmacies

Eligibility criteria:

- Registered with the Kenya Pharmacy and Poisons Board (PPB)
- Premises must comply with the requirements of the Pharmaceutical Society of Kenya and the Kenya Pharmaceutical Association
- Must have ≥1 full-time licensed pharmacist or pharmaceutical technologist on staff
- Must have a private room where HIV testing and PrEP/PEP counseling can occur

- Must be willing to use a study-specific module within a digital platform (Maisha Meds) to record pharmacy PrEP/PEP dispensing
- Owner must agree to allow a trained research assistant to come to the pharmacy on select days to collect data from a random subset of participants
- Owner must agree to allow providers to participate in a monitored WhatsApp group, optional surveys, and in-depth interview (IDI)
- Owner must agree to allow providers to routinely engage with a technical assistant

Pharmacists/HTS counselors

Eligibility criteria:
- ≥ 18 years old
- Licensed pharmacist, licensed pharmaceutical technologist, or NASCOP-certified HTS counselor
- Willing to provide PrEP and PEP services, including HIV testing and associated counseling services
- Completed training on PEP/PrEP service delivery at pharmacies, including certification for rapid diagnostic testing
- Able and willing to provide consent
- Complete study training
- Willing to use a study-specific module within a digital platform (Maisha Meds) to document PrEP/PEP services rendered

Clients

Inclusion criteria:
- ≥16 years old, including emancipated minors 16-17 years old
- Interested in initiating PrEP or PEP
- Meets all criteria for PrEP or PEP initiation on the Prescribing Checklist, including being at risk for HIV and not having any medical conditions that might contraindicate PrEP/PEP safety
- Able and willing to provide informed consent

Exclusion criteria:
- Unwilling to provide a phone number at which an RA can reach them for completing surveys and communicating important study-related information
- Currently enrolled in any other HIV vaccine or prevention trial
- Having a condition that would preclude provision of informed consent, make study participation unsafe, complicate interpretation of outcome data, or otherwise interfere with achieving study objectives

3. Study Outcomes

Planned primary outcomes are PrEP initiation and PrEP continuation. These outcomes will be defined as follows:

- PrEP initiation: the number of participants at each pharmacy that initiated (i.e., were dispensed) PrEP at the pharmacy or clinic **within 60 days** of initial pharmacy-based screening. *Comparisons between intervention arms and the control will rely on self-*

report from the 60-day client survey, while comparisons between intervention arms will employ pharmacy records.

- PrEP continuation: the number of participants at each pharmacy that initiated PrEP at the pharmacy or clinic and returned to the pharmacy or clinic and refilled PrEP **within 60 days** of initial pharmacy-based screening. *Comparisons between intervention arms and the control will rely on self-report from the 60-day client survey, while comparisons between intervention arms will employ pharmacy records.*

Secondary outcomes include those related to PrEP initiation, PrEP continuation, PrEP adherence, PEP initiation, PEP-to-PrEP transition, and repeat PEP use.

- PrEP initiation: the number of participants at each pharmacy that initiated (i.e., were dispensed) PrEP at the pharmacy or clinic **within 270 days** of initial pharmacy-based screening
- PrEP continuation:
    - The number of participants at each pharmacy that initiated PrEP at the pharmacy or clinic and returned to the pharmacy or clinic and refilled PrEP **within 270 days** of initial pharmacy-based screening (regardless of any gaps in pill coverage).
    - The number of participants at each pharmacy that initiated PrEP at the pharmacy or clinic and **refilled PrEP at least twice within 270 days** of initial pharmacy-based screening (regardless of any gaps in pill coverage).
    - The number of participants at each pharmacy that initiated PrEP at the pharmacy or clinic and refilled PrEP more than 7 days after their expected refill date (i.e., stopping and restarting, also referred to as "PrEP reinitiation") **within 270 days** of initial pharmacy-based screening.
- PrEP adherence: The median adherence score (0-100) among participants at each pharmacy who initiated PrEP at the pharmacy or clinic –using the Wilson et al. scale (2020, *AIDS*)—as measured at **60 days** following initial pharmacy screening.
- PEP initiation: the number of participants at each pharmacy that initiated (i.e., were dispensed) PEP ≥1 times at the pharmacy or clinic within 3 days, as measured at **60 days** and **270 days** following initial pharmacy screening.
- PEP-to-PrEP transition: the number of participants at each pharmacy that successfully completed PEP (tested negative or self-reported testing negative for HIV between 28 and 45 days after initiating PEP at the pharmacy) **and** initiated PrEP at the pharmacy or clinic as measured at **60 days** and **270 days** following initial pharmacy screening.
- PrEP-to-PEP transition: the number of participants at each pharmacy that initiated (i.e. were dispensed) PrEP and subsequently initiated PEP at the pharmacy or clinic within 3 days, as measured at **60 days** and **270 days** following initial pharmacy screening.
- PEP/PrEP initiation: the number of participants at each pharmacy that initiated (i.e., were dispensed) either PEP or PrEP at the pharmacy or clinic (within 3 days for PEP clients) as measured at **60 days** and **270 days** following initial pharmacy screening.
- PEP/PrEP continuation: the number of participants at each pharmacy that (1) initiated PrEP and refilled PrEP or later were dispensed PEP; or (2) initiated PEP and transitioned to PrEP or later were dispensed PEP again as measured at **60 days** and **270 days** of initial pharmacy screening.

- Recurrent PEP use: the number of participants at each pharmacy that were dispensed PEP ≥2 times as measured at **60 days** and **270 days** of initial pharmacy screening.

Tertiary outcomes include related behaviors as well as implementation outcomes based on a variety of scales:

- Follow-up HIV testing: the number of participants at each pharmacy engaging in HIV testing following the pharmacy PrEP/PEP visit (not including the initiation visit), as measured at **60 days** and **270 days** following initial pharmacy screening.

- HIV risk: the number of participants engaging in specific self-reported behaviors associated with HIV risk reported in the time frame following pharmacy PrEP or PEP delivery, such as any condomless sex in the past month and self-reported perception of HIV risk acquisition in the present and future.

- PrEP coverage (exploratory): duration of time on PrEP based on dates of dispensing and the quantity of pills dispensed at each visit using all longitudinal data available at completion of the cRCT.

- Client implementation outcomes
    - Acceptability: assessed in the extended client survey at different time points over the trial duration using questions that measure different domains of the Theoretical Framework of Acceptability (Sekhon et al., 2017, *BMC Health Serv Res*), which consists of seven component constructs (e.g., affective attitude, burden, perceived effectiveness).
    - Fidelity: the number and proportion of participants that received different core components of the intervention (e.g., counseling on HIV risk, medical history, HIV testing, drug dispensing) as specified in the protocol. Assessed in the extensive client survey at different time points over the trial duration.
    - Willingness to pay: the amount eligible pharmacy PrEP clients are willing to pay for each pharmacy PrEP or PEP visit, as assessed in the extensive client survey at different points in time over the trial duration.
    - Quality of care perceptions: assessed in the extensive client survey at different time points over the trial duration using a modified perceived service quality scale (pSQ-SF6) (Carter et al., 2022, *Res Social Adm Pharm*), with higher score indicating higher perceived service quality.
- Provider/counselor implementation outcomes
    - Acceptability: assessed in the provider survey at different time points over the trial duration using questions that measure different domains of the Theoretical Framework of Acceptability (Sekhon et al., 2017, *BMC Health Serv Res*), which consists of seven component constructs (e.g., affective attitude, burden, perceived effectiveness).

- Feasibility: assessed in the provider survey at different time points over the trial duration using questions based on the Feasibility of Intervention Measure (FIM) (Weiner et al., 2017, *Implement Sci*).
- Perceived self-efficacy: assessed in the provider survey at different time points over the trial duration using statements that assess providers' level of confidence delivering different core components of the pharmacy PrEP intervention (e.g., counseling, HIV testing, referral, etc.).
- Willingness to charge: the amount pharmacy providers are willing to charge for each pharmacy PrEP or PEP visit under different scenarios. Assessed in the provider survey at different time points over trial implementation.

- Pharmacy implementation outcomes
  - Sustainability: comparison of study outcomes during the first half and second half of implementation.
  - Adaptations: measured in the technical assistance reports using the Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies (FRAME-IS) (Miller et al., 2021, *Implement Sci*).

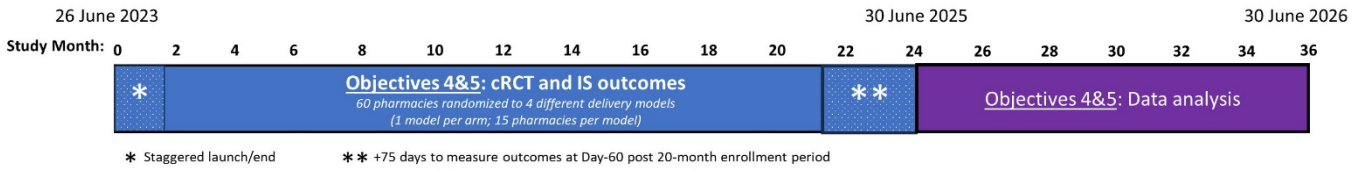
4 Study Design

The study is a cluster-randomized control trial (cRCT). The intervention will be introduced in a parallel fashion with a brief ramp-up period (i.e., staggered launch).

4.2 Trial

The study is a cRCT in 60 pharmacies. Fifteen pharmacies will be assigned to each of the four study arms: 3 involving pharmacy-delivered PrEP/PEP services (Arms 1-3) and 1 SOC (Arm 4). These pharmacies will have at least 20 months to enroll participants, **Figure 1**, with the option to extend this longer if needed to achieve target sample size.

Figure 1. Overview of study implementation activities over duration of the cRCT.



4.3 Intervention

Implementation of the intervention will begin with training of pharmacists, pharmaceutical technologists, and HTS counselors who will be involved in the delivery of PrEP/PEP and associated counseling and HIV testing services. This will culminate in an observed practice session. Throughout the study, research assistants will visit the pharmacies to monitor activities and provide support.

4.4 Randomization

4.4.1 Randomization design

Stratified permuted block randomization will be performed to ensure balance by key prognostic covariates in the first stage of the randomization. Specifically, the goal is to achieve balance across the 4 arms by county or county group (4 counties/county groups, each with 15 participating pharmacies plus 5 back-up pharmacies). Randomization will proceed as shown in **Table 1**, which describes the number of pharmacies that will be in each arm by county.

Of note, implementation was originally planned in 2 counties in Western Kenya (e.g., Kisumu and Homa Bay), this was expanded to 2 additional neighboring counties to ensure the pharmacies selected for study participation were spaced far enough away from one another and an ongoing cRCT in the region testing different models of pharmacy-delivered PrEP services for adolescent girls and young women seeking contraception (i.e., to prevent potential contamination).

This randomization strategy results in balance of treatment assignment by county/county group (in each county/county group, 3-4 pharmacies are in each of the 4 arms) and overall (15 pharmacies assigned to each arm). Within each of these stratified blocks, treatment assignment can be permuted. For instance, consider the 20 urban pharmacies in Kiambu County. Three of these will be assigned to Arm 1, 4 will be assigned to each of Arms 2-4, and 5 will be assigned as back-up pharmacies; the arm assignments will be randomized within this block. Note that by pursuing a stratified randomization scheme, analyses must adjust for county/county group (categorical). In addition to determining which arm a given pharmacy is in, it is necessary to determine whether it will be designated as a cRCT pharmacy or a back-up pharmacy.

Table 1: Randomization scheme for the cRCT and back-up distribution.

County	Arm 1	Arm 2	Arm 3	Arm 4	Back-up pool	Total # pharmacies
Kiambu	3	4	4	4	5	15 cRCT + 5 back-up
Nairobi	4	4	3	4	5	15 cRCT + 5 back-up
Kisumu/Siaya	4	3	4	4	5	15 cRCT + 5 back-up
Homa Bay/Migori	4	4	4	3	5	15 cRCT + 5 back-up
TOTAL	**15**	**15**	**15**	**15**	**20**	**60 cRCT + 20 back-up**

4.4.2 Randomization process

Each pharmacy will select an opaque envelope at the end of the training session; the contents of the envelope will indicate which arm the pharmacy is randomized to or if it will be a back-up pharmacy. The training will be done by county. For the county groups, whatever envelopes are not selected at the first training will be available for selection at the second training. Thus, the following envelopes are proposed:

Kiambu County: Arm 1 envelopes: n = 3; Arm 2 envelopes, n = 4; Arm 3 envelopes, n = 4; Arm 4 envelopes: n = 4; back-up pharmacy envelopes: n = 5

Nairobi County: Arm 1 envelopes: n = 4; Arm 2 envelopes, n = 3; Arm 3 envelopes, n = 4; Arm 4 envelopes: n = 4; back-up pharmacy envelopes: n = 5

Kisumu/Siaya Counties: Arm 1 envelopes: n = 4; Arm 2 envelopes, n = 4; Arm 3 envelopes, n = 3; Arm 4 envelopes: n = 4; back-up pharmacy envelopes: n = 5

Homa Bay/Migori Counties: Arm 1 envelopes: n = 4; Arm 2 envelopes, n = 3; Arm 3 envelopes, n = 4; Arm 4 envelopes: n = 3; back-up pharmacy envelopes: n = 5

4.4.3 Replacement of dropped pharmacies

During implementation, it is anticipated that some participating pharmacies may have to drop from or be dropped from the study (by the research team) for a variety of reasons, including provider/ownership turnover, inability to follow study procedures, request of pharmacy provider, a gap in service delivery (>1 month), etc. In these instances, these pharmacies will be replaced with one from the pool of back-up pharmacies for each county/county group. When replacement is needed, a pharmacy from this back-up pool will be randomly selected. The back-up pool will ideally not drop below 2-3 pharmacies, with backup pharmacies identified and trained as needed.

4.5 Sample size and power

We had planned to analyze the PrEP and PEP initiation and continuation outcomes as binary outcomes, using an individual-level analysis. However, in September 2023, it became apparent that the denominators that would be used in these estimates (number enrolled) would vary greatly across arms (and indeed would be affected by which arm a pharmacy was randomized to) and would likely lead to biased estimates of the proportions initiating/continuing in each arm. In particular, the intervention is thought to (a) have an effect on likelihood of enrollment and (b) have an effect on likelihood of PrEP/PEP initiation (and thus continuation); we would like to capture the total effect of the intervention, i.e., both (a) and (b). However, by only considering individuals who were enrolled (which corresponds to the previous analytic approach), we would only capture (b), and would be ignoring (a).

Thus, we are instead pursuing a cluster-level analysis of the initiation and continuation outcomes, where each cluster (pharmacy) is summarized by the number of initiations/continuations over the course of the study, accounting for pharmacy size (i.e., pharmacy flow). This is reflected in the analytic approach described below.

The anticipated number of PrEP and PEP initiations and continuations within 60 days of pharmacy screening per pharmacy in each study arm over 16 months of implementation are given in **Table 2**. Estimates of the total counts per pharmacy in each arm were based on those observed in pilot studies of pharmacy-delivered PrEP and PEP services: (1) one which offered PrEP for a fee of 350 KES in 4 pharmacies—informing Arm 1 PrEP initiation and continuation estimates (Ortblad et al., J Int AIDS Soc. 2023), and (2) another which offered PrEP and PEP services for free in 12 pharmacies—informing Arm 2 PrEP initiation and continuations estimates, as well as PEP initiation and continuation estimates (Roche et al., CROI 2023). The estimates in other arms were based on the hypothesized difference between the arms—with the hypothesis that Arm 3 (implementor-sustained with HTS counselor support) would perform best, followed by Arm 2 (implementor-sustained), Arm 1 (clients-sustained), and Arm 4 (SOC referral). The PrEP continuation estimates in Arm 4 (SOC referral) were additionally informed by the Partners Scale-up Project, with delivered PrEP services in 24 public clinics in Kenya. Based

on the hypothesized number of PrEP/PEP initiations, proportion of PrEP initiators who would continue PrEP, and proportion of PEP users who would transition to PrEP ("PEP continuation"), the number of PrEP/PEP continuations was determined.

Table 2: Hypothesized number of pharmacy-based PrEP, PEP, and PrEP/PEP initiations and continuations per pharmacy (k=60) and arm, based on pilot and implementation studies

Study arms:	1: Client-sustained	2: Implementor-sustained	3: HTS-supported	4: Referral (SOC)
PrEP initiations: over 16 months (monthly)	128 (8 monthly)	176 (11 monthly)	208 (13 monthly)	80 (5 monthly)
PrEP continuations: over 16 months (% of initiators)	64 (50% initiators)	123 (70% initiators)	166 (80% initiators)	48 (60% initiators)
PEP initiations: over 16 months (monthly)	32 (2 monthly)	48 (3 monthly)	64 (4 monthly)	16 (1 monthly)
PEP continuations: over 16 months (% of initiators)	4.34 (14% initiators)	9.12 (20% initiators)	13.90 (23% initiators)	2.61 (17% initiators)
PrEP/PEP initiations: over 16 months	160	224	270	96
PrEP/PEP continuations: over 16 months	68.34	132.12	179.90	50.61

The numbers in Table 2 were originally used to estimate power, yielding power of nearly 100% for the comparison of each direct pharmacy delivery arm (Arms 1-3) to Arm 4 (SOC). However, in Fall 2024, it became apparent that far more individuals were initiating PEP as opposed to PrEP, and the target number of PrEP initiations was not feasible. Given the very high power in the original design, the PrEP initiation numbers in Table 2 were scaled such that the power for PrEP initiations (one of the primary outcomes) for the smallest comparison—Arm 1 (client-sustained) vs. Arm 4 (SOC)—was 80%. This would thus guarantee power >80% for the comparisons of Arms 2 and 3 vs. Arm 4 (**Table 3**). The estimated power for each comparison is then given in **Table 4**.

In particular, to estimate power, it was assumed that the average pharmacy flow was the same across the four arms; there is no a priori reason to assume otherwise. We further assumed a coefficient of variation (CV) of 0.25. The coefficient of variation characterizes the variability in number of PrEP initiations (relative to pharmacy size) across pharmacies. While this is difficult to know ahead of time, it is typically <0.25 (Hayes and Bennett, *IJE*, 1999). A CV of 0.25 would roughly correspond to a situation where, for example, the average number of PrEP initiations was 20/pharmacy, and 95% of pharmacies had between 10 and 30 initiations (assuming equal flow across pharmacies); this seems to be a reasonable degree of variability in our setting. Given that the analyses will include comparisons of Arms 1, 2, and 3 vs. 4, we used a Bonferroni correction to our alpha level (two-sided alpha = 0.05/3) for the PrEP 60-day initiation/continuation outcomes and the combined PrEP/PEP outcomes (primary and key secondary outcomes).

Based on the hypothesized number of PrEP/PEP initiations and continuations in **Table 3**, we estimated the power would be very high for comparing Arms 2 and 3 to Arm 4 for PrEP initiation

and continuation (primary outcomes) and the combined PrEP/PEP initiation and continuation outcomes (key secondary outcomes; **Table 4**). For the Arm 1 vs. Arm 4 comparisons, the power is estimated to be 80% for PrEP initiation (as designed), 100% for the combined PrEP/PEP initiation outcome, and lower for the continuation outcomes.

→ Primary outcome assessment will be completed after a total of 1,119 PrEP initiations are achieved. A study duration of 20 months of implementation is targeted.

Table 3: Number of PrEP, PEP, and PrEP/PEP initiations and continuations per pharmacy (k=15/arm, k=60 total) for >80% power in our PrEP outcomes of interest

	1: Client-sustained	**2: Implementor-sustained**	**3: HTS supported**	**4: Referral (SOC)**	**TOTAL** (across 60 pharms)
PrEP initiations	**16.13**	**22.18**	**26.21**	**10.08**	**1,119**
PEP initiations	32	48	64	16	2,400
Total PrEP/PEP initiations	*48.13*	*70.18*	90.21	26.08	*3,519*
PrEP continuations	**8.06 (50% of initiations)**	**15.52 (70% of initiations)**	**20.97 (80% of initiations)**	**6.05 (60% of initiations)**	**759**
PEP continuations	4.34 (13.6% of initiations)	9.12 (19.0% of initiations)	13.90 (21.7% of initiations)	2.61 (16.3% of initiations)	450
Total PrEP/PEP continuations	*12.40*	*24.64*	*34.87*	*8.66*	*1,209*

Table 4: Estimated power for PrEP initiation and continuation and the combined PrEP/PEP initiation and continuation outcomes

	Arm 1 vs. Arm 4	**Arm 2 vs. Arm 4**	**Arm 3 vs. Arm 4**
PrEP initiations	80%	100%	100%
PrEP continuations	23%	100%	100%
Total PrEP/PEP initiations	*100%*	*100%*	*100%*
Total PrEP/PEP continuations	*48%*	*100%*	*100%*

Sample sizes for other aspects of the study (e.g., extended surveys, provider surveys, costing data, IDIs), were chosen based on feasibility and ability to obtain a representative sample. The extended client surveys will include 1,340 participants across the four arms. One provider and/or HTS counselor from each pharmacy will be asked to participate in the provider survey at baseline, 60 days, and 270 days post-launch of PrEP/PEP service delivery at their pharmacy. IDIs will be conducted with up to 88 PrEP and 60 PEP candidates (with product candidacy determined by providers at enrollment following an HIV risk assessment, medical safety assessment, and counseling session). We will also interview 40 pharmacy providers, 15HTS counselors (supporting Arm 3 pharmacies), and the study's remote clinician. IDI sampling will be done using random stratified purposeful sampling, with PrEP client sampling stratified by PrEP

initiation and continuation, PEP client sampling stratified by PEP initiation and PEP-to-PrEP transition, and provider sampling stratified by pharmacy performance (high/low performer based on PrEP initiation rates relative to other pharmacies in the same arm).

In order to achieve our targeted number of PrEP (1,119) and PEP (2,400) initiations, we anticipate needing to enroll 5,865 client participants (1,865 pharmacy PrEP candidates and 4,000 pharmacy PEP candidates). This assumes that 75% of enrolled client participants will complete the brief client survey at 60 days, and of those, 80% will initiate PrEP/PEP. Combining this target with the other types of participants (60 pharmacy providers, 15 HTS counselors, 4 remote clinicians), our total enrollment target is 5,944 participants.

5 Planned Analyses

No formal interim analyses are planned. Data listings and summaries similar to those described here may be provided to the Data Safety and Monitoring Board (DSMB), but statistical testing will not be included. The DSMB was provided with the total number of PrEP initiations per arm and per pharmacy to determine whether enrollment should be extended to 20 months or beyond; this was shared with the DSMB in a closed session partway through implementation. Given relatively low enrollment at this time, it was decided to extend the study to 20 months. Analyses described in this plan are final analyses to be performed on the final dataset for the study.

6 General Statistical Considerations

6.2 Data sources

The following data sources will be used to address the objectives (detailed in **Table 5**):

- Pharmacy records: intervention arms only, Arms 1-3 (i.e., not SOC arm, Arm 4)
    - Items on Prescribing Checklist, including PEP/PrEP dispensing data, age, sex, marital/relationship status, behaviors associated with HIV risk, HIV test result
    - Other services/products purchased
- Clinic records: SOC arm only
    - Items on the Clinical Encounter Form akin to those in the study's Prescribing Checklist
- Brief client surveys: all arms
    - Brief demographics
    - Whether the participant initiated PrEP and/or PEP and, if so, where
    - Whether the participant has refilled PrEP and, if so, where
    - Whether the participant is still taking PrEP/PEP as of today
    - If the participant is still taking PrEP/PEP, how many PrEP/PEP pills they swallowed in the past 7 days
    - PrEP adherence
    - Select HIV risk behavior questions

- Extended client survey: all arms
    - Extended demographics
    - Alcohol use
    - Sexual and mental health
    - HIV risk behaviors
    - Fertility
    - Social harm
    - Acceptability of pharmacy model in which they received PrEP/PEP services
    - Quality of care perceptionsFidelity of services received
    - Willingness to pay
- Provider surveys: all arms
    - Provider demographics
    - Acceptability of pharmacy-delivered PrEP/PEP
    - Feasibility of pharmacy-delivered PrEP/PEP
    - Self-efficacy to delivery PrEP/PEP services at pharmacies
    - Organizational Readiness for Change (ORIC)
    - Willingness to charge
- Client in-depth interviews: all arms
    - Model acceptability
    - Model appropriateness
    - Acceptability of modifications
    - Appropriateness of modifications
- Provider in-depth interviews: all arms
    - Acceptability
    - Feasibility
- Techincal assistance (TA) reports
    - Adaptations

Data from the Maisha Meds application on PrEP/PEP delivery/dispensing, survey data, audio files from interviews, and interview transcripts will be stored on secure electronic platforms that meet all data security requirements (e.g., REDCap, Dedoose). Table 5 below summarizes the outcomes and data sources.

Table 5. Data sources

PRIMARY/ SECONDARY	OUTCOME	TIMING	DATA SOURCE
Primary	PrEP initiation	By 60 days	*Brief client survey* Pharmacy records* Clinic records*
	PrEP continuation	By 60 days	
Secondary	PrEP initiation	By 270 days	
	Any PrEP continuation	By 270 days	
	At least 2 PrEP refills	By 270 days	
	Any stopping and restarting PrEP (i.e., PrEP reinitiation)	By 60 and 270 days	
	PEP initiation	By 60 and 270 days	
	PEP-to-PrEP transition	By 60 and 270 days	
	PrEP-to-PEP transition	By 60 and 270 days	
	Repeat PEP use	By 60 and 270 days	
	PrEP/PEP initiation	By 60 and 270 days	
	PrEP/PEP continuation	By 60 and 270 days	
	PrEP adherence	At 60 days	Brief client survey (self-report)
Tertiary	HIV risk behaviors	At 60 and 270 days	Brief client survey Extended client survey
	Follow-up HIV testing	At 60 and 270 days	Brief client survey
	PrEP coverage	Over study duration	*Brief client survey* Pharmacy records* Clinic records*
	Client: acceptability	At 60 and 270 days	Extended client survey Client interviews
	Client: quality of care perceptions	At 60 and 270 days	
	Client: willingness to pay	At 60 and 270 days	
	Client: fidelity		
	Provider: acceptability	At baseline, 60, and 270 days	Provider interviews Provider surveys
	Provider: feasibility	At baseline, 60, and 270 days	
	Provider: willingness to charge	At baseline, 60, and 270 days	
	Provider: perceived self-efficacy	At baseline, 60, and 270 days	
	Pharmacy: adaptations	Over study duration	TA reports
	Pharmacy: sustainability		*Brief client survey* Pharmacy records* Clinic records*

**The pharmacy records and client records will be used for comparison of outcomes between intervention arms and other secondary analyses; see Section 7.5 for details.*

6.3 Descriptive statistics

Continuous variables and count data will be described with mean (SD) or median (Q1, Q3). Categorical variables will be described with N (%).

6.4 Statistical testing and models

Statistical tests will be 2-sided tests and considered statistically significant if $p < 0.05$ (i.e., $\alpha = 0.05$), with the exception of the analyses of the PrEP initiation and continuation outcomes and the combined PrEP/PEP initiation and continuation outcomes, which constitute the primary and key secondary outcomes. These will utilize a significance threshold of $0.05/3 = 0.0167$ to account for the three comparisons of Arms 1, 2, and 3 versus Arm 4.

6.5 Exposure groups

The exposure groups are the 4 study arms, (determined by randomized group assignment of the clinic) which will be treated as a categorical variable throughout the analyses.

6.6 Analysis populations

- *Cluster-Randomized Control Trial Client Population*

  All pharmacy clients enrolled in the cluster-randomized controlled trial phase of the study. Data from these individuals includes data from pharmacy records, clinic records (of referral facilities), and client surveys—including brief surveys among all clients at 60 and 270 days post enrollment, and extensive surveys among select clients at 0, 60, and 270 days post-enrollment.

- *Extended Client Survey Population*

  Clients enrolled in the study who were randomly selected and completed the extended client survey.

- *Client Interview Population*

  PrEP and PEP clients randomly selected for an in-depth interview.

- *Provider Interview Population*

  Pharmacy providers and HTS counselors randomly selected to provide an in-depth interview.

- *Provider Survey Population*

  Pharmacy providers and HTS counselors randomly selected to complete the provider survey.

- *Enrolled Pharmacies Population*

  All pharmacies included in the study. All pharmacies in the study will contribute pharmacy records for the estimation of costs.

- *Costing Population – Provider, Costing Population – Pharmacy*

  One provider from each pharmacy in the Enrolled Pharmacies Population (costing survey) and 10 pharmacies randomly selected from the Enrolled Pharmacies Population (time-in-motion studies).

6.7 Missing values

Missing data in the primary outcomes, i.e., PrEP initiation and continuation, are of greatest concern.

The primary analysis of the PrEP outcomes (described more fully below) will rely on data from the brief client surveys to create uniformity between the intervention arms (for which pharmacy dispensing data will also be available) and the SOC arm (for which clinic dispensing data will also be available). To accommodate missing PrEP outcomes, we will impute missing values as failures (i.e., did not initiate or did not continue, depending upon the outcome under consideration). This same strategy will also be applied to our secondary PrEP/PEP outcomes. Note that since the primary analysis relies on pharmacy-level counts of individuals who initiated/continued PrEP/PEP, for the primary analysis, this imputation procedure will be equivalent to a complete case analysis.

In addition to the analyses above, for the analysis of PrEP initiation at 270 days, we will perform a **sensitivity analysis** where PrEP initiation at 60 days is used to impute missing PrEP initiation at 270 days. For instance, if a participant reports initiating PrEP at 60 days, but PrEP initiation status at 270 days is unavailable, we will consider this participant to have initiated PrEP at 270 days.This would be expected to reduce recall bias in the 270 day outcome.

7 Data Analysis

7.2 Study enrollment

The number of clients enrolled at each pharmacy.

Analysis population: Cluster-Randomized Control Trial Client Population

7.3 Pharmacy characteristics

Characteristics of enrolled pharmacies, both overall and by study arm/modification, will be presented.

Analysis population: Enrolled Pharmacies

7.4 Characteristics at enrollment

Tables will show descriptive statistics for characteristics at enrollment for all pharmacy clients and forpharmacy PrEP and pharmacy PEP candidates, with product candidacy determined by providers following HIV risk screening and counseling, with breakdowns by study arm. Similar tables will also be presented separately for those who initiated PrEP and those who initiated PEP to understand differences in demographics among those who initiated these products across the study arms.

Analysis population: Cluster-Randomized Control Trial Client Population

7.5 Outcomes

7.5.1 Primary outcomes

Our analyses of the primary outcomes of PrEP initiation and PrEP continuation by 60 days will

use cluster-level data for all participants enrolled in the cluster-randomized control trial.

7.5.1.1 Effect of intervention on PrEP initiation at 60 days

Analysis Population: Cluster-Randomized Control Trial Population

The primary analysis will aim to estimate the effectiveness of the pharmacy-delivered PrEP intervention as measured by the number of PrEP initiations by 60 days at each pharmacy in the cluster-randomized control trial phase of the study.

If data are available from pharmacies that dropped out after a period of time in the study, we will attempt to include these data. We will do so by modifying the offset term (see "Inference" below) to reflect the amount of time the pharmacy participated in the study. For instance, if the study lasts for 16 months and a given pharmacy dropped out after 8 months, the offset for that pharmacy would be half of what it would have been if the pharmacy had completed the study. We will seek to obtain measures of pharmacy volume from all pharmacies, even those that drop out; if obtaining volume measures is not possible for some pharmacies, we will impute these measures using pharmacy-level characteristics.

The primary analysis will include data from all partially completing pharmacies from the time the pharmacy is enrolled to drop out or end of study (intent-to-treat analysis). We will additionally perform a **sensitivity analysis** where dropout pharmacies in which there is evidence of no effort to implement the intervention (e.g., stated lack of interest on the part of the pharmacist, pharmacy provider rarely available and present in the pharmacy to deliver the intervention, failure of pharmacy provider to follow protocol, no participants enrolled, etc.) are excluded; other dropout pharmacies will be included (per-protocol analysis). We will also conduct a **sensitivity analysis** where temporary pauses in implementation (not drop outs) are incorporated by adjusting the denominator.

Descriptive statistics

A table will be produced giving descriptive statistics of number of PrEP initiations by study arm (i.e., 1: client-sustained, 2: implementor-sustained, 3: HTS counselor-supported, 4: SOC referral). To aid in interpretation of the number of PrEP initiations accounting for pharmacy size, we will also present PrEP initiation rates standardized to the median monthly volume among Arm 4 (SOC) pharmacies. The table below shows an example of how the standardization would work for an Arm 1 pharmacy, assuming the median monthly volume among Arm 4 pharmacies is 1000. The formula for the standardized number of initiations is as follows: let n be the observed number of initations in a pharmacy, and N is that pharmacy's monthly volume. Let N* be the median monthly volume in Arm 4. Then the standardized number of initiations, n*, is

$$n^* = n \times \frac{N^*}{N}.$$

Then n* is divided by the number of months of implementation for the particular pharmacy to get the standardized rate per month. These estimated rates would be reported by pharmacy (graphically) and averaged by arm (in a table).

Arm 1 Pharmacy: Observed Data	***Standardized Data***	***Reported estimated rate***
100 PrEP initiations	50 PrEP initiations	50 initiations/6 months = **8.3 initiations/month**
2000 clients/month	1000 clients/month (tied to the median in Arm 4 pharmacies)	

6 months of implementation	6 months of implementation

Inference

We will estimate the ratio of PrEP initiation rates (number of initiations per clients served at the pharmacy, accounting for pharmacy volume over the implementation period) comparing each intervention arm to the SOC arm using a Poisson generalized linear model with log link and robust standard errors. The model will allow for overdispersion to account for increased variability in rates. The outcome will be number of self-reported PrEP initiations from the 60-day brief client survey in each pharmacy. A cluster-level analysis was chosen for the outcome of PrEP initiation because the number of individuals enrolling in the study at a given pharmacy was found to be heavily dependent upon the study arm of the pharmacy. Thus, the available denominator for the individual-level PrEP initiation outcome, number of individuals enrolled in the study, was a poor proxy for the quantity of interest, number of pharmacy PrEP candidates (i.e., individuals determined at risk of HIV acquisition who meet the pharmacy PrEP prescribing checklist criteria). Instead, we will pursue a cluster-level analysis where the outcome is number of initiations at each pharmacy and we account for pharmacy volume as a way to make fair comparisons across pharmacies.

The model will include study arm as a four-level categorical (nominal) variable and a continuous offset variable reflecting pharmacy volume (number of clients per unit time). Pharmacy volume will be measured as the number of transactions per month. Estimates of monthly volume will be obtained up to three times in each pharmacy during the course of the study (to account for seasonal variations); missing observations will be imputed, and we will take the average of the three assessments. To account for the stratified randomization procedure, we will adjust for county as a categorical (nominal) variable. As noted in Section 6.7, our missing imputation strategy (i.e., imputing missing outcome data as failures) will not affect the primary analysis of the pharmacy-level count data and will only influence the secondary analysis described in Section 7.5.1.3.

To address potentially large variability in pharmacies, a **sensitivity analysis** will be conducted removing extreme outlier pharmacies to evaluate how the primary results are impacted. To address difference in when participants were reached for follow-up, another **sensitivity analysis** will be conducted that restricts follow-up data to just include those within 30 days (+/-) of their scheduled follow-up visit (the primary analysis will not restrict timing of follow-up data). An additional **sensitivity analysis** will use non-parametric permutation testing to understand the robustness of the findings of the main analysis. To account for possible imbalances across study arms, a common challenge in cluster-randomized trials, we will perform **sensitivity analyses** repeating the analyses with adjustment for pharmacy-level factors considered to be strongly predictive of PrEP initiation and continuation. Finally, a **sensitivity analysis** will be conducted repeating the primary analysis with adjustment for pharmacy-level average time to survey completion to account for delays in survey completion allowing for additional time to engage with PrEP and PEP.

7.5.1.2 Effect of intervention on PrEP continuation at 60 days

Analysis Population: Cluster-Randomized Control Trial Population

The primary analysis will aim to estimate the effectiveness of the pharmacy-delivered PrEP intervention as measured by the number of PrEP continuations by 60 days at each pharmacy

among the clients enrolled in the cluster-randomized control trial phase of the study who initiated PrEP.

Descriptive statistics

A table will be produced giving descriptive statistics of PrEP continuation by study arm. A figure similar to that described in 7.5.1.1 will be generated.

Inference

The primary analysis (including sensitivity analyses) will utilize the same approach as described for PrEP initiation (7.5.1.1).

7.5.1.3 Secondary Analyses

For the outcome of PrEP continuation at 60 days, we will conduct a **secondary analysis** of the proportion of participants continuing PrEP at 60 days among those who initiated PrEP. In particular, we will estimate the risk difference of PrEP continuation between each intervention arm and the SOC arm using a Poisson generalized estimating equations (GEE) model with identity link and robust standard errors (Pedoza and Truong, BMC Med Res Methodology, 2016). The outcome will be self-reported PrEP continuation from the brief client survey. The model will include study arm as a four-level categorical (nominal) variable and adjust for county to account for the stratified randomization procedure. To account for varying cluster size (number of PrEP initiators), we will use an independent working correlation matrix and weights for cluster size (Wang et al., Contemp Clin Trials, 2022). Missingness will be addressed as described in Section 6.7. In the event that this model does not converge or yields invalid estimates (e.g., risk differences or confidence intervals outside of +/- 1), we will instead fit a modified Poisson GEE model—i.e., a GEE with log link and robust standard errors (Yelland et al., AJE, 2011)—to estimate the relative risk comparing each intervention arm to the SOC arm. Importantly, as this analysis is restricted to those who have initiated PrEP, randomization is not maintained. Thus, we would need to adjust for factors related to initiation in order to remove the bias incurred by selecting only those who initiate (Hernan and Hernandez-Diaz, Clin Trials, 2012).

Additionally, **secondary analyses** for PrEP initiation and continuation at 60 days will be conducted to evaluate whether the effect of the intervention differs by urban/rural pharmacy status, location in Western vs. Eastern Kenya, or by the proportion of enrolled individuals who (1) are female or (2) over the age of 25. This will be done by adding two terms to the model described in Section 7.5.1.1: the main effect of the subgroup variable (e.g., percent female) and an interaction between the categorical intervention variable and the subgroup variable. As part of this analysis, we will estimate the intervention effects within each subgroup.

In addition, **secondary analyses** for both PrEP initiation and PrEP continuation with 60 days among the clients in the three intervention arms will be performed to compare each of the three intervention arms to each other. The approaches will be identical to that described in Sections 7.5.1.1, with the caveat that the outcome (PrEP initiation or PrEP continuation) will be computed from the pharmacy records, which is available for all three intervention arms and will be a more complete data source than the 60-day follow-up survey. Because the pharmacy data precisely reflects the day initiation or refill takes place, the computation will use a cutoff of exactly 60 days from initial pharmacy-based screening.

A **secondary descriptive analysis** will be performed to compare the data on PrEP initiation by 60 days and PrEP continuation by 60 days from the brief clients surveys versus clinic records

among those in the SOC arm (Arm 4). In particular, we will compare the number (1) initiating PrEP within 60 days and (2) continuing PrEP by 60 days between these two data sources. A similar analysis will be performed for the three intervention arms to compare the number of PrEP initiations and continuations based on the brief client surveys versus the pharmacy records.

7.5.2 Secondary and tertiary outcomes

The analysis of the secondary outcomes of PrEP initiation within 270 days, any PrEP continuation within 270 days, at least 2 PrEP refills, any stopping and restarting PrEP, PEP initiation, PEP-to-PrEP transition, recurrent PEP use, PrEP/PEP initiation, PrEP/PEP continuation, PrEP adherence and the tertiary outcome of follow-up HIV testing will be similar to those described in Sections 7.5.1.1. Furthermore, the secondary analyses proposed in Section 7.5.1.3 will be performed for these outcomes (as appropriate for the outcome), with the exception of the secondary analysis investigating interactions. For the analysis of PrEP initiation with 270 days, the sensitivity analysis described in Section 6.7, in which PrEP initiation at 60 days is used to impute missing PrEP initiation at 270 days, will be performed.

For the exploratory outcome of PrEP coverage, descriptive statistics in each arm will be provided.

The tertiary outcomes (including acceptability, appropriateness, willingness to pay/charge, feasibility, and adaptions) will be summarized using descriptive statistics when assessed quantitatively and analyzed using a combination of inductive and deductive approaches (e.g., thematic content analysis) when assessed qualitatively. Similarly, the HIV risk behavior outcomes will be analyzed descriptively. No formal statistical comparisons will be performed for these tertiary outcomes.

7.6 Safety

7.6.1 HIV seroconversion

Seroconversion will be determined by local HIV testing guidelines. A listing of participants who seroconvert will be maintained.

7.7 Post-unblinding update: December 16, 2025

The study team was unblinded to the results of the analysis on November 6, 2025 prior to the final DSMB meeting on November 13, 2025. The last version of this SAP, with all sections finalized with the exception of this post-unblinidng update, was on November 5, 2025—prior to unblinding of any study team members. Summary statistics generated for the November DMSB meeting showed notable variability in completion of 60-day surveys across the 4 study arms. To understand the source of this heterogeneity, pharmacy data for the three intervention (i.e., non-SOC) arms were evaluated. These data indicated that a large number of individuals who did not complete the 60-day survey did in fact initiate/continue PrEP/PEP. This indicated that the planned outcome imputation approach, in which individuals who did not respond to the survey were assumed to have failed (i.e., not initiated/continued PrEP/PEP), likely did not reflect the nature of missingness. Following conversations with DSMB members and other experts, the study team decided to change the imputation approach.

The new imputation approach would impute PrEP/PEP outcomes for individuals who did not complete the survey using the proportion of PrEP/PEP initiations/continuations among individuals in the same pharmacy who did respond to the survey. Thus, if Pharmacy A enrolled 100 participants, 70 of whom responded to the survey and 14 of whom (20%) indicated they had initiated PrEP, then the PrEP initiation outcome for the 30 non-responders would be imputed as a binomial random variable with a success probability of 20%. As indicated above, evaluation of the pharmacy record data in the three intervention (i.e., non-SOC) arms indicated that the proportion of individuals who, per pharmacy records, initiated PrEP (for instance) was similar among those who did and did not complete the survey (42.8% and 40.5%, respectively). Thus, while the analysis based on the imputation procedure proposed in Section 6.7 will be reported in the main results manuscript as the pre-specified analysis, emphasis in that paper will be placed on the results from the analysis using the new imputation approach described in this paragraph, noting that this was not prespecified. We note that the decision to shift focus to this new imputation approach was made prior to seeing the results with the new imputation approach.

Finally, based on discussions regarding the policy impact of the results of this study, the study team decided to include all PrEP initiations, even among those who had previously been dispensed PEP, and vice versa. All of these decisions were made prior to the study team seeing the results with these changes incorporated.