The CATALYST Study

__Cataly__zing access to new prevention products to __st__op HIV

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LIST OF ABBREVIATIONS AND ACRONYMS

Ab	Antibody
ADR	Adverse drug reaction
Ag	Antigen
AGYW	Adolescent girls and young women
AHI	Acute HIV infection
AIM	Acceptability of Intervention Measure
ANC	Antenatal care
ART	Antiretroviral therapy
CAB	Cabotegravir, the active agent in injectable cabotegravir for PrEP (CAB PrEP)
CBO	Community-based organization
CI	Confidence interval
CITI	Collaborative Institutional Training Initiative for Research Ethics
CSO	Civil society organization
DBS	Dried blood spot
DCF	Data collection form
DHMT	District health management teams
EDTA	Ethylenediaminetetraacetic acid
EML	Essential Medicines List
FDA	Food and Drug Administration (of the United States)
FTC	Emtricitabine, a common active agent in oral PrEP, along with tenofovir
FGD	Focus group discussion
FHI 360	Organization formerly known as Family Health International
FSW	Female sex worker
GBV	Gender-based violence
HIVDR	HIV drug resistance
INSTI	Integrase strand transfer inhibitors
IDI	In-depth interview
IEC	Independent or institutional ethics committee
IPV	Intimate partner violence
IRB	Institutional review board
IP	Implementing Partner
KII	Key informant interview
M&E	Monitoring and evaluation
MCAZ	Medicines Control Authority of Zimbabwe
MOSAIC	Maximizing Options to Advance Informed Choice for HIV Prevention
MOH	Ministry of Health
NDA	National Drug Authority (Uganda)
NIH	National Institutes of Health
NMRA	National Medicines Regulatory Authority
NNTRI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
PBFP	Pregnant and breastfeeding populations
PCR	Polymerase chain reaction test (test used to determine viral load)
PDSA	Plan-Do-Study-Act
PEP	Post-exposure prophylaxis
PEPFAR	President’s Emergency Plan for AIDS Relief
PEU	Prevention effective use
PHSC	Protection of Human Subjects Committee

PI	Principal investigator
PPB	Pharmacy and Poisons Board (Kenya)
PrEP	Pre-exposure prophylaxis
PSRT	Protocol safety review team
QI	Quality improvement
QIC	Quality improvement collaborative
RDT	Rapid diagnostic test
RNA	Ribonucleic acid
SAE	Serious adverse event
SAHPRA	South African Health Products Regulatory Authority
SMS	Short message service
SOP	Standard operating procedure
STI	Sexually transmitted infection
SUSAR	Suspected unexpected serious adverse reactions
TDF	Tenofovir disoproxil fumarate, an active agent in oral PrEP
TFV-DP	Tenofovir-diphosphate
USAID	United States Agency for International Development
WHO	World Health Organization

KEY DEFINITIONS

Term	Definition
Nested study	CATALYST has several nested studies, which include additional study activities that will take place among a subset of CATALYST study participants. The procedures for each nested study are embedded within the CATALYST protocol.
Study site	The PrEP delivery location, such as a health facility, and surrounding community in which CATALYST activities will take place.
Women	For study purposes, this term is inclusive of individuals assigned female at birth of any gender identity or individuals assigned male at birth who identify as women.

STATEMENT OF COMPLIANCE

This study will be carried out in accordance with the applicable United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56), as well as local legal and regulatory requirements. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted for institutional review board/ institutional ethics committee review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. All personnel involved in the conduct of this study have completed Human Subjects Protection training and all key personnel have completed appropriate Good Clinical Practices training.

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STUDY SUMMARY

Title: The CATALYST Study: Catalyzing access to new prevention products to stop HIV

Study #: 1916056

Design: The overall study goal is to characterize and assess the implementation of an enhanced service delivery package providing informed choice of pre-exposure prophylaxis (PrEP) products among women at U.S. President's Plan for AIDS Relief/U.S. Agency for International Development (PEPFAR/USAID) delivery sites in Kenya, Lesotho, South Africa, Uganda, and Zimbabwe. All products used in the study will have post-regulatory approval; hence, the study will be conducted in two stages, with currently approved oral PrEP and PrEP rings offered in Stage I, and the addition of CAB PrEP in Stage II only after it has been approved by the regulatory authority in each country. We will accomplish the study goal by conducting a mixed-methods implementation study involving several components:

1. **Component 1:** Prospective cohort study of women at PEPFAR/USAID delivery sites that are delivering HIV PrEP, including daily oral PrEP, monthly PrEP rings, and bimonthly CAB PrEP
   a. Descriptive nested cohort study to evaluate the performance characteristics of different HIV testing strategies among participants who initiate CAB PrEP
   b. Descriptive nested cohort study to evaluate the feasibility and validity of a prevention effective use (PEU) measure among a subset of PrEP users
2. **Component 2:** Mixed-methods process evaluation involving implementers and key stakeholders
   a. Nested costing study across Lesotho and Uganda study sites
   b. Nested qualitative study to understand community acceptance of PrEP and informed choice of PrEP products

Population: **<u>Study Population for Component 1 (Cohort of PrEP users)</u>:**
HIV-negative women* attending PEPFAR/USAID-supported facilities who are interested in learning about HIV prevention and are otherwise eligible to participate in the study, including the following subgroups:

- Adolescent girls and young women (AGYW) ages 15–24 years old (lower age boundary will depend on the national guidelines for consent, which may differ across countries)
- Female sex workers (FSWs) ages 18 years and older
- Individuals assigned female at birth of any gender identity, ages 15 years and older
- Individuals assigned male at birth who identify as women, ages 15 years and older
- Pregnant and breastfeeding populations (PBFP) ages 15 years and older

**Presumed HIV-negative based on results from the national testing algorithm. For this study, the term "women" is inclusive of individuals assigned female at birth of any gender identity or individuals assigned male at birth who identify as women.*

Study population for Nested Study 1a (HIV testing strategies): All cohort members who initiate CAB PrEP

Study population for Nested Study 1b (PEU): A subset of PrEP users in the study cohort in South Africa and Kenya in the validation phase (n=400) and all countries in the measurement phase (n=1,000)

Study Population for Component 2 (Process evaluation):
Implementers and other stakeholders involved in informed PrEP choice implementation, including:

- Policymakers, including subnational ministry of health officials (including members of district health management teams (DHMTs), or their equivalent), administrators, supply chain managers, and other key stakeholders within the national government
- Providers and other site staff, including doctors, nurses, other clinicians, counselors, and other personnel involved in the delivery of PrEP-related services within PEPFAR/USAID delivery sites
- Other key stakeholders, such as community leaders, community members, community health service providers, civil society organizations, and key population-led organizations

Study population for Nested Study 2a (costing): All study sites within Lesotho and Uganda

Study population for Nested Study 2b (community acceptance): PrEP influencers (partners and parents/caregivers of existing and potential PrEP users) within select sites across all countries.

Study Duration: Cohort participants will be followed in Stage I until CAB PrEP becomes available (up to 18 months) and up to 24 months in Stage II. All other study activities will be completed within this time frame.

Objectives:

Objective 1: Characterize the implementation of the enhanced service delivery package for informed PrEP choice for women in PEPFAR/USAID public health service delivery sites and assess individual-, provider-, facility-, community-, and health system-level facilitators of and barriers to the implementation process. *(Achieved through process evaluation, and nested costing and community acceptance studies)*

Objective 2: Describe patterns of PrEP use and use effectiveness in the context of informed PrEP choice and assess sociodemographic and contraceptive use correlates of PrEP use patterns. *(Achieved through cohort and nested PEU study)*

Objective 3: Describe clinically relevant indicators among PrEP users, including rates of HIV infection and drug resistance among PrEP users who acquire HIV following PrEP initiation or had undetected HIV prior to PrEP initiation. *(Achieved through cohort, including CAB HIV testing algorithm nested study)*

Outcomes:

Outcomes for Objective 1: Health system feasibility; delivery acceptability among users/providers; cost of delivery at a subset of study sites; community acceptability of HIV prevention, including PrEP and PrEP choice

Outcomes for Objective 2: Overall and method-specific PrEP uptake; periods of use and non-use of PrEP products (e.g., continuation, switching, and discontinuation); product acceptability among users; prevention effective use of PrEP products

Outcomes for Objective 3: Proportion and rates of HIV infection among participants; proportion and rates of HIV drug resistance (HIVDR) mutations among PrEP users who acquire HIV; sensitivity evaluation of multiple HIV testing algorithms prior to CAB initiation; pregnancy and selected infant outcomes among PBFP; frequency of reported side effects by PrEP product

Sites:	Three to ten PEPFAR/USAID PrEP delivery sites in each country (Kenya, Lesotho, South Africa, Uganda, and Zimbabwe)

1 INTRODUCTION

The Maximizing Options to Advance Informed Choice for HIV Prevention (MOSAIC) project is a five-year (2021-2026) global project funded by PEPFAR through USAID to help individuals, especially women, prevent HIV by accelerating introduction and scale-up of new and emerging biomedical prevention products. MOSAIC strives to generate, synthesize, and promote evidence needed by decision-makers to strengthen existing PrEP service delivery platforms and facilitate introduction of new PrEP products aligned with the needs and preferences of women, particularly AGYW, and inclusive of transgender people, PBFP, and FSWs. One way the MOSAIC project will generate evidence is through an implementation study of an enhanced service delivery package for informed PrEP choice—the CATALYST study. This mixed-methods study will be conducted in two stages to capture implementation of each new product when it becomes available (PrEP ring in Stage I and CAB PrEP in Stage II) in Kenya, Lesotho, South Africa, Uganda, and Zimbabwe. These countries were selected based on high HIV incidence among women and current or anticipated introduction of PrEP ring and CAB PrEP, in addition to existing oral PrEP delivery, thus creating feasible settings to study the delivery of informed PrEP choice.

The CATALYST study provides a unique opportunity to assess the acceptability and feasibility of providing an enhanced service delivery approach across stakeholder groups that is tailored to different populations and geographic settings to offer informed PrEP choice. In addition, this study will provide real-world data on PrEP uptake and use in the context of informed choice, including understanding client values and preferences related to PrEP choice (including the role of providers, partners, and parents in facilitating client choice); the feasibility and acceptability of offering PrEP choice from provider and health system perspectives; and additional data on clinical outcomes related to PrEP use across products.

1.1 Background

HIV incidence remains relatively high in eastern and southern African settings, despite expansion of HIV care and treatment. HIV incidence is particularly high among specific groups such as adolescent girls and young women (AGYW), pregnant and breastfeeding populations (PBFP), female sex workers (FSWs), and transgender populations.[1-3] AGYW younger than 25 years of age are estimated to comprise more than 50% of new HIV infections in sub-Saharan Africa, making them five to 14 times more likely to be living with HIV than their male peers.[4,5] Numerous biological, behavioral, and social risk factors for HIV in women have been identified, such as multiple and concurrent partnerships, early sexual debut, age-disparate relationships, gender-based violence (GBV), and unequal gendered power dynamics affecting women's social and economic standing.[6-9] Of note, GBV experienced among AGYW in southern and eastern Africa may contribute to a heightened risk of both unintended pregnancy and HIV.[10] The risk of HIV acquisition also increases during pregnancy and the postpartum period, likely due to a combination of biological[11,12] and behavioral factors.[13,14] Among FSWs, the risk of HIV acquisition is ten times higher than that of the general population,[15] resulting from work-related

factors where greater risk is often incentivized and access to preventive services is often limited.[16] Transgender women also experience elevated risk for HIV: across several African countries, HIV prevalence is over twice as high among transgender women as it is among men who have sex with men.[3] In summary, these and other female populations are at increased risk of HIV. Commonly, women within these groups have multi-level barriers to accessing services that must be considered for tailored HIV prevention methods and service delivery models.

In the last decade, pre-exposure prophylaxis (PrEP) methods have received increased focus as an option for preventing HIV acquisition.[17-21] For example, oral forms of PrEP are becoming more widely available, and additional forms of PrEP, including vaginal rings and long-acting injectables, have proven effective in clinical trials.[18,21-24] Available and upcoming PrEP methods vary by route of administration, efficacy, and personal and clinical considerations, but collectively they offer an array of choices for potential end users and their health care providers. Oral PrEP containing tenofovir disoproxil fumarate (TDF) is highly effective when taken correctly and consistently and is recommended by the World Health Organization (WHO) for individuals at substantial risk of acquiring HIV infection.[25] Currently, most sub-Saharan African countries include TDF-containing PrEP regimens in their HIV prevention programs. However, uptake and effective use of oral PrEP have been suboptimal among vulnerable populations in several countries.[26,27] Rates of seroconversion during PrEP use, as well as frequency of viral resistance mutations to TDF/FTC, are concerning.[28] New PrEP methods are currently in development or nearing market entry. Two methods that may be widely introduced within the next few years include the dapivirine vaginal ring (PrEP ring)[18,21] and injectable cabotegravir for PrEP (CAB PrEP).[22-24]

The PrEP ring is a silicone ring inserted vaginally every month that provides local protection against HIV infection within the vagina using the non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine.[25] In clinical trials, the PrEP ring was found to be approximately 30% efficacious at preventing HIV using an intent-to-treat analysis, with modeling analyses suggesting effectiveness of about 50% with consistent use in subsequent open-label studies.[18,21] The PrEP ring also has few side effects and no product-related serious adverse effects or identified concerns related to HIV treatment resistance.[18,21,29] As such, the WHO recommends the PrEP ring for women at substantial risk of HIV infection who cannot or prefer not to use oral PrEP.[25]

CAB PrEP, which was recently approved by the U.S. Federal Drug Agency (FDA), is a long-acting, systemic injectable PrEP agent requiring dosing every two months.[a] CAB PrEP is highly effective for preventing HIV, with results from two multi-site trials reporting CAB PrEP resulted in a 66% reduction and an 89% reduction in HIV infection compared to oral PrEP among MSM and women, respectively. [22,23] CAB PrEP has a long half-life; supplemental daily oral PrEP was provided within the clinical trials for one year following CAB PrEP discontinuation to prevent

[a] Cabotegravir is administered as a single 600-mg (3-mL) injection given one month apart for two consecutive months (referred to as the "loading dose") and continued with subsequent injections every two months thereafter.

potential drug resistance should infection occur during the tail period.[30] Another issue is if individuals with acute infection who have not yet seroconverted start on PrEP. Exposure to CAB PrEP while infected with HIV[b] may lead to the emergence of resistance mutations.[31] Because dolutegravir, part of the first-line HIV regimen recommended by global guidelines, and cabotegravir are both integrase strand transfer inhibitors (INSTIs), such exposures could lead to resistance across the INSTI class,[32] rendering first-line ART potentially less effective. Global guidance from WHO regarding the use of injectable cabotegravir as PrEP is expected mid-2022; if it is recommended, regulatory approvals are expected in African countries within one to two years of approval.

The expansion of PrEP options provides opportunities for end users, in partnership with their providers, to select the method that will work best for the individual, similar to family planning method choices. Based on the family planning literature, being able to choose from multiple contraceptive options increases the overall use of any contraceptive method for wider public health benefits.[33] As countries move toward epidemic control, where preventing new HIV infections and PrEP implementation feature more prominently, understanding PrEP method choice and service provision preferences across a range of end users and their providers is critical to guiding implementation design for maximum impact. AGYW, FSWs, PBFP, and other women require particular focus for PrEP programming, based both on the need for effective, acceptable HIV prevention methods and specific preferences for and barriers to service access. Scant evidence is available regarding the best PrEP service delivery methods for these groups, and oral PrEP is underutilized and often not used effectively.[4,34,35]

The advent of PrEP methods with different administration routes and less frequent dosing will potentially enable easier access, more effective use, and in some cases more flexible delivery channels. PrEP preferences among women have been assessed in a variety of studies, largely either through hypothetical or placebo discrete choice experiments[36-38] or as part of clinical trials to assess the acceptability of the specific tested method.[39,40] The largest trials to date have been TRIO and Quatro, conducted among women ages 18–30 years in South Africa, Kenya (TRIO), and Zimbabwe (Quatro). These studies compared several different PrEP products, with Quatro comparing four vaginal products (ring, insert, film, and gel) and TRIO comparing tablets, ring, or injection products. Participants in each trial received placebo versions in a randomized allocation followed by method selection (TRIO)[37] or a randomized cross-over trial (Quatro).[36] TRIO findings were notable for preference for a PrEP method over condoms, and of PrEP methods, injectables were most preferred, with no adherence issues, while the reported ring and oral PrEP adherence improved over time. The main findings of the Quatro study included individual-level change in preferred product from baseline (prior to product use). Specifically, preferences for the ring improved considerably once women had experience using it. In both studies, marked differences by country were noted for preferred product. These studies and assessments of acceptability in PrEP clinical trials have been conducted largely among adult

[b] HIV infection can include cases of acute HIV infection at CAB PREP initiation or during post-injection breakthrough infection, as well as post-discontinuation infection during the tail phase.

women ages 18–45 years with variable HIV prevention needs and may not represent subgroups that are particularly vulnerable to infection, including PBFP. There is limited real-world data on the values and preferences of AGYW, especially those younger than 18, as well as other female population groups.

Recent studies from South Africa address PrEP preferences among AGYW ages 15–19 years. The UChoose trial examined PrEP method preference by using hormonal contraceptive methods with similar dosing mechanisms (the contraceptive ring and injectable or oral contraceptive methods) as proxies.[41] Most participants preferred the injectable, though the contraceptive ring was preferred by some and both methods had higher adherence than pills. Other PrEP feasibility studies among youth largely focus on uptake and acceptability of existing services, which are currently limited to oral PrEP.[42,43] However, in implementation cohorts that have measured oral PrEP uptake and adherence among youth, separate considerations have emerged in qualitative research that necessitate a targeted demand generation approach, and these differ substantively by context and age group.[44,45] Recent results from the REACH study (MTN-034), which enrolled 247 HIV-negative AGYW ages 16–21 across sites in South Africa, Uganda, and Zimbabwe, found higher levels of adherence to both oral PrEP and the PrEP ring than observed in previous studies; when given a choice, approximately two-thirds chose the PrEP ring and one-third chose oral PrEP.[46]

For FSWs, studies document high interest and acceptability of PrEP in diverse settings ranging from China to Kenya.[47-51] Most of these studies assessed the feasibility and acceptability of offering oral PrEP only. In Tanzania, Harling et al. presented both oral and injectable PrEP as hypothetical options. Three-quarters of barmaid participants were interested in long-acting injectable (LAI) use compared to 53% interested in oral PrEP; LAIs were preferred to oral PrEP when the preference for a single method was queried.[49] To date, no studies specifically comparing feasibility (i.e., the extent to which PrEP programs can be successfully carried out) of the PrEP ring compared to other PrEP methods among FSWs have been published. Further, more evidence is needed for specific female subpopulations, including PBFP, women in serodifferent (also known as serodiscordant) relationships, people assigned female sex at birth of any gender identity, and transgender women.

1.2 Description of PrEP choice and enhanced service delivery package

The CATALYST study will deliver informed PrEP choice across multiple PrEP products for women in PEPFAR/USAID public health service delivery sites, building on existing PrEP service delivery within sites and in accordance with PEPFAR and national guidelines for PrEP service delivery. Since study sites currently do not offer PrEP choice, the study will implement an enhanced service delivery package that helps support implementation of informed choice among PrEP products that have regulatory approval in each country. The enhanced service delivery package at each study site will include components at the individual, provider, facility, and community levels using a socio-ecological framework (Figure 1 and Table 1). As an implementation strategy to allow for intervention adaptation and tailoring, the study will work through existing quality improvement (QI) mechanisms in each county/district and site,

providing capacity strengthening and support for site QI teams, which will refine the enhanced service delivery package over time using plan-do-study-act (PDSA) cycles and participate in cross-site QI collaboratives[52] and cross-country learning exchanges to identify best practices and core elements of a service delivery package for PrEP choice. These learnings will be critical for the future scale-up and sustainability of informed PrEP choice.

Figure 1. Enhanced service delivery package elements, delineated by individual, provider, facility, and community levels

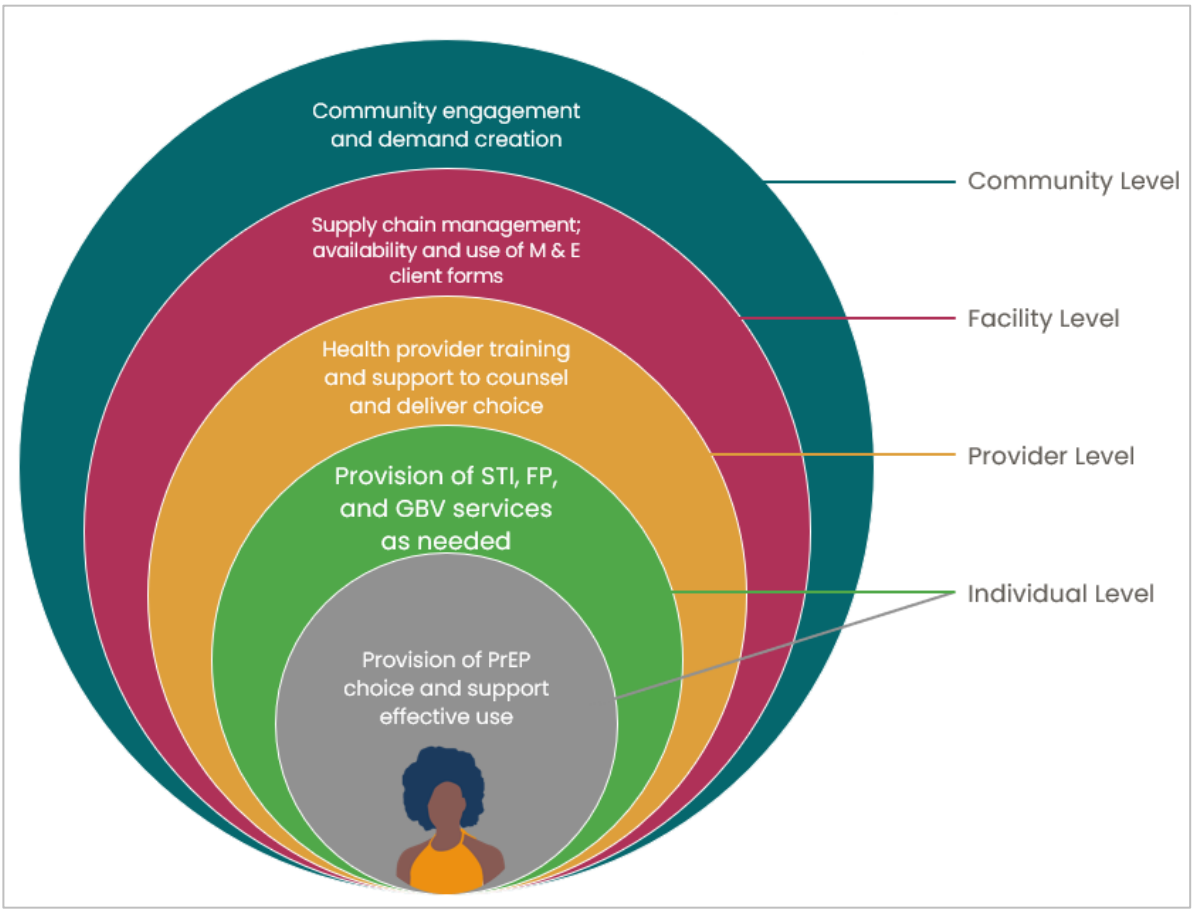


Table 1. Standard of care and the enhanced service delivery package

ELEMENTS	STANDARD OF CARE	ENHANCED CARE*	FREQUENCY
INDIVIDUAL LEVEL - PrEP Service Delivery - targeting PrEP users			
HIV counseling and testing	Counseling and testing for PrEP initiation and at follow-up visits per national guidelines	Additional HIV testing to identify HIV infection before and during CAB PrEP, and then quarterly for up to 12 months after CAB PrEP discontinuation	At PrEP initiation and follow-up visits for all products; quarterly for up to 12 months after CAB PrEP discontinuation
PrEP counseling and provision	Counseling and provision of oral PrEP per national guidelines	Additional offering of counseling on the ring and CAB PrEP; provision of informed choice for clients who do not opt for oral PrEP	All visits
Follow-up for missed visits and PrEP discontinuers	Per site standard of care, which may include: Phone call for those missing scheduled PrEP visits; no additional follow-up for PrEP discontinuers	Encouraged quarterly visits with tracing for up to 12 months after CAB PrEP discontinuation and up to three months for oral PrEP and PrEP ring discontinuation	Phone call for missed PrEP visits per standard of care Encourage quarterly visits for up to 12 months for CAB PrEP discontinuers and up to three months for oral PrEP and PrEP ring discontinuers
Safety laboratory testing	Safety labs for PrEP (as applicable and per national guidelines when available) for each product	No additional enhancements beyond standard of care for each product	Frequency per national guidelines for each PrEP product
Pregnancy testing	At client request or provider recommendation	Urine pregnancy test at initiation and follow-up visits with a provider, except where the need for such testing is clinically implausible, as noted in study specific procedures manual	All provider visits
Provision of STI, FP, and GBV services	Counseling and provision or referral for services per national guidelines	Strengthen bi-directional referral path within communities and between community and facility for referrals using the MOH system	Frequency per national guidelines, typically at PrEP initiation and refills
Product use support	Per site standard of care, which may include: Phone call approximately 7 days after initiation, a call 2 days before refill date, & call on the refill date. Use of peer counselors and support groups	Develop and share materials that describe each product, use considerations (including switching), and side effects; Leverage existing tools (e.g., HIV Prevention Journey Tool) and DREAMS or other community safe spaces for ongoing user support.	Phone call post-product initiation per standard of care Distribute materials at initiation, and then at follow-up visits as needed Varying frequency for leveraging tools and safe spaces

ELEMENTS	STANDARD OF CARE	ENHANCED CARE*	FREQUENCY
PROVIDER LEVEL: Provider Training and Support - targeting facility supervisors, health providers, site staff and lay providers who interact with PrEP clients			
Product-specific training	Initial and refresher oral PrEP training of providers per national program	Additional PrEP ring and CAB PrEP training of site staff and DHMT staff prior to study start with periodic refresher trainings	Prior to study start Refresher trainings as needed
Training on provision of PrEP choice	None	Training on counseling, empathy, providing respectful care, and shared decision-making around PrEP choice (e.g., Empathways training)	Prior to study start Refresher trainings as needed
Job aids for AHI, PEP, PrEP, FP, STI, and GBV	Varies by site	Provide and train on additional job aids as needed and specifically for new product provision and counseling on choice	Prior to study start Refresher trainings as needed
FACILITY LEVEL: M&E and Supply Chain Support – targeting M&E staff, pharmacy staff, and nurses			
M&E tools and client forms	Varies by site, typically to document uptake and refills of oral PrEP	Adapt M&E tools and client forms as needed to accommodate PrEP ring, CAB PrEP, product choice, and switching	Prior to study start, and then ongoing adaptation as needed
Supply chain support: Management of PrEP commodities	Varies by site, typically oral PrEP is stored and dispensed from the facility pharmacy/ dispensary room	Develop a product management plan with each site for study product (PrEP ring and CAB PrEP), using existing product storage and dispensing mechanisms when possible.	Prior to study start, and then ongoing adaptation as needed
COMMUNITY LEVEL: Engagement and Demand Generation – targeting site staff, national and subnational stakeholders, community stakeholders, PrEP users, and key influencers, including antenatal and postnatal care providers			
Community engagement and demand generation	Varies by site; most sites have ongoing PrEP-related community engagement and demand generation activities	Develop study-specific materials that include the PrEP ring and CAB PrEP and promote informed choice; work through existing community and demand generation mechanisms when possible.	Prior to study start, and then continuous

**Enhanced care will be provided only for products that have national regulatory approval in each country.*

1.3 Quality Improvement in CATALYST

QI is a critical aspect of intervention implementation in CATALYST. The CATALYST QI Collaborative will engage QI teams from all CATALYST sites across all five countries — Kenya, Lesotho, South Africa, Uganda, and Zimbabwe — to rapidly test changes and scale up significant improvements to the enhanced service delivery model. Each CATALYST site will establish a multi-professional QI team, which will be supported by QI advisors and coaches who will provide guidance and ongoing support for improvement. QI advisors and coaches will include individuals from local DHMTs, the MOSAIC Consortium and implementing partners. The QI teams will implement the enhanced service delivery package, identify gaps and bottlenecks to implementation, and generate and test change ideas to optimize implementation.

QI teams will go through a structured process of testing change ideas using PDSA cycles and learning sessions to exchange change ideas and report on progress. During the learning sessions, which will take place both within and across CATALYST countries, QI teams will learn about QI models and tools and will share results and practices. In the action periods, the teams will implement, study, and document the interventions and change ideas at study sites using QI tools. Each team in the QI collaborative will communicate regularly at the facility and will be mentored by a QI coach.

The QI collaborative will be a time-limited strategy for the duration of the CATALYST study and will have seven key features:[52]

1. **Common improvement aims and objectives** that are shared by participating sites.
   The **main aim of the CATALYST Quality Improvement Collaborative is** *to optimize for each country the delivery of an enhanced PrEP choice-based delivery package for women, especially AGYW by May 2026.*
   The QI collaborative will include 3 core objectives shared across all five countries:
   i) To increase number of eligible clients that make informed choice for PrEP
   ii) To mitigate early loss among clients on PrEP
   iii) To increase percent of PrEP users reporting a positive experience with the enhanced PrEP delivery package

   and 4 elective objectives:
   iv) To increase percent of PrEP providers having a positive experience with the delivery of the enhanced service delivery package
   v) To ensure that all PrEP clients are screened for STIs and treated as needed
   vi) To ensure that all PrEP clients are screened for FP need and those not desiring fertility are linked to FP services
   vii) To ensure that all PrEP clients are screened for GBV and those requiring support are linked appropriately
2. **A common improvement monitoring system** with measures or indicators shared by all teams to help them compare and learn from each other

3. **An operational structure** organized around teams that perform specific roles and responsibilities: (a) QI teams that will directly implement changes in sites, (b) a quality management team that will play a strategic leadership role and manage the collaborative, and (c) content experts in QI and PrEP implementation
4. **A coaching support** that will regular guidance to the teams to implement changes and measure the effects
5. A **PDSA-based model** for improvement will be used to identify and implement changes and test their impact during specific action periods and a **change package**, which will include the defined enhanced service delivery package and country-specific innovations or adaptation to the package that have been tested and shown to be effective and that can be scaled up. The change package will be detailed in the QI briefs.
6. **Learning sessions** at national level and regionally (through the CATALYST cross-country *PrEP Exchange*) that will provide the opportunity for teams to share their experiences (supported by monitoring data) and to learn about best practices and how they can be replicated.
7. **Experienced-based co-design** (EBCD) to engage clients in an intentional way to improve client and staff experiences of care.

Data sources for QI activities will include routine service data, such as registers and client records. In addition, we will encourage PrEP users to complete an anonymous survey at the end of the visit (i.e., a tablet-based end-user feedback system). From this system we will obtain feedback on waiting time, whether PrEP clients received adequate information, and whether they felt treated with respect by providers. Questions to assess providers' experiences implementing the enhanced service delivery package will be incorporated in provider surveys that will be conducted as part of the CATALYST study. Coaching reports generated by the QI coaches summarizing their findings at the end of QI visits will be another source of QI data. Lastly, data from the improvement efforts across five countries will be aggregated, analyzed and summarized in 6 monthly QI briefs.

As part of the QI Collaborative, we will use experience-based co-design (EBCD)[c] to engage clients in an intentional way to influence and shape service quality. The EBCD method is consent based and includes listening to patient stories and co-designing improvements in service delivery with clients and health providers. We will invite a diversity of consenting PrEP users to share stories of their experience with the enhanced service delivery package and the health provider, and in this way reveal unexpected areas for improvement. These experiences will also be shared with health providers. The PrEP users and health providers will then work together to design potential improvements to the service delivery package.

[c] EBCD processes used are adapted from: Rakhmanova N, Bouchet B. Health care Quality Improvement Handbook: A Guide to Enhancing the Performance of Quality Improvement Efforts in Cambodia. In: FHI 360; 2017.

1.4 PrEP products offered in the study

The intervention involved in this study comprises the enhanced service delivery package for offering PrEP choice. The three PrEP products that will be offered include the following:

- Oral PrEP containing tenofovir (tablets containing 300 mg of TDF and possibly other active agents based on products available in each country, such as emtricitabine or lamivudine)
- PrEP ring (a silicone vaginal ring containing 25 mg of dapivirine)
- CAB PrEP (an intramuscular injection containing 600 mg cabotegravir) and possibly oral CAB (tablets containing 30 mg of CAB) provided as an optional or mandatory lead-in (depending on country guidelines).

Oral PrEP is currently available in all the countries in which CATALYST will be implemented. The PrEP ring has national regulatory approval in all the countries in which CATALYST will be implemented but is not yet widely available. CAB PrEP will be implemented through CATALYST once in-country regulatory approval has been obtained. The study will procure PrEP rings and receive donated CAB PrEP from the drug manufacturers. During the study, trained health care providers will administer oral PrEP, PrEP rings, and CAB PrEP within study delivery sites. Additional laboratory-based HIV testing will be conducted among participants initiating and using CAB PrEP, which is discussed in detail in Section 5. Providers will be trained by study staff using a curriculum reviewed and approved by the Ministry of Health of each country in which study activities will occur. More detailed information about these products is presented in Table 2.

Table 2. Information on PrEP products used in CATALYST

Product	Manufacturer	Active agents	Storage	Form, route of administration	Dosing scheme
Daily oral PrEP	Varies by country (oral PrEP will be provided through existing standards of care)	Fixed-dose combination product containing 300 mg TDF and other active agents that may vary by country	Room temperature (25°C, excursions permitted 15–30°C)	Oral tablet	Once daily
PrEP ring	International Partnership for Microbicide (IPM)	25 mg of dapivirine per ring	Room temperature (15–30°C)	Flexible silicone ring containing 25 mg of dapivirine	Worn continuously inside the vagina for approximately 1 month, and then replaced with a new ring
CAB PrEP	ViiV Healthcare	Injectable: 600 mg/3 mL (200 mg/mL) of cabotegravir in single-dose vial	Injectable: 2–25°C (exposure up to 30°C is permitted)	Injectable: Intramuscular injection in the gluteus medius, provided in single dose vials	Injectable: Administered every 2 months[a]
		Oral: 30mg tablet	Oral: Room temperature below 30°C	Oral: Oral tablet	Oral: Once daily with food. Duration varies with indication

[a] *The loading dose for CAB PrEP is administered as a single 600-mg (3-mL) injection given 1 month apart for 2 consecutive months and continued with subsequent injections every 2 months thereafter. Of note, CAB PrEP could potentially involve an optional or mandatory oral lead-in period (based on the local label) in which daily oral CAB is taken for a period of 4- to 5-weeks to gauge tolerability prior to the first injection. In clinical trials, participants were provided oral PrEP for 12 months following CAB PrEP discontinuation to cover the pharmacokinetic tail. Participants in CATALYST who choose to discontinue CAB will also be offered and encouraged to use an alternative effective method for HIV prevention during the tail phase. Procedures for restarting CAB PrEP following a delayed injection visit (>7 days of scheduled visit) will follow the national medicines regulatory authority (NMRA) label per country. Following study completion, participants will be transitioned to standard of care PrEP care.*

1.4.1 PrEP uptake, discontinuation, and switching

Study participants will be offered a choice of PrEP products, depending on which products have received national regulatory approval, including within the specific context of PBFP. Therefore, each study component will be implemented in two stages. In Stage I, participants will be offered a choice among oral PrEP and PrEP ring. When approval for CAB PrEP has been received, Stage II will be initiated. In Stage II, participants will be offered a choice among oral PrEP, the PrEP ring, and CAB PrEP. Participants will be allowed to discontinue PrEP or switch PrEP methods at any time during the study. For those discontinuing CAB PrEP, participants will be

encouraged to use an alternative effective method of HIV prevention during the tail phase while/if they continue to need HIV prevention, or as otherwise directed by the NMRA-label, which may differ by country.

1.4.2 Clinical safety management

Clinical safety management for all PrEP products will adhere to national guidelines. The CATALYST study will use only PrEP products that have national regulatory approval for commercial use. For oral PrEP, existing country-specific clinical safety management will be followed. For the PrEP ring, no additional clinical safety management is required above regular HIV testing, STI screening, and counseling. National requirements for clinical safety management of CAB PrEP are currently unknown. As guidelines are developed on the national level, the study team will work with providers to ensure that all clinical safety monitoring is followed appropriately.

Additionally, the study will attempt to screen for pregnancy using a urine pregnancy test at initiation and follow-up visits with a provider, except in cases where the need for such testing is clinically implausible, such as in cases where a female participant has undergone sterilization, as noted by study-specific procedures. This additional screening will allow the identification of pregnancies at an early stage to facilitate PrEP eligibility determination and method switching (if necessary, based on national guidelines) and documentation of product exposure among study participants who become pregnant. We will attempt to collect certain pregnancy and infant outcomes for study participants who are or become pregnant during study participation and have been exposed to one or more PrEP products during the course of the study.

For CAB users, additional HIV testing will be conducted at each clinic visit (as described under Study Component 2b), and for those who discontinue, participants will be encouraged to return for quarterly HIV tests (for up to 12 months or until the end of the study) and to switch to an alternative effective method of HIV prevention during the tail phase. If participants return for quarterly testing or alternative PrEP product refills, data will be captured at these clinic visits. For all study participants, the study team will document HIV infections.

Any participant who acquires HIV while on any PrEP product during the study will be provided with post-test HIV counseling and facilitated referral to HIV treatment, including prevention of vertical transmission for PBFP. A standard HIV drug resistance (HIVDR) test will be done on a blood sample collected at the time of HIV diagnosis, with results returned to the treatment care provider when possible.

Participants can decline any study procedure or withdraw from the study at any time. A participant will not be actively withdrawn from the study, unless requested by the participant or following HIV diagnosis (exit may be deferred until HIV infection is confirmed by CATALYST if an HIV diagnosis, learned of through self-report, occurred at a site external to CATALYST; exit may also be deferred until completion of HIVDR procedures). Otherwise, participants will be considered exited from the study once they have been enrolled for the maximum follow-up period per Stage, or the study ends (whichever comes first). In cases of voluntary withdrawal, participants will be asked if they are willing to complete one final visit prior to exiting. In the

event that participants who voluntarily withdraw from the study wish to re-join the study, they may do following reconsent.

In addition, we will collect data on serious adverse events (SAEs) and social harms for study participants, including product-related and non-product-related events. Please refer to Section 14.6 for safety monitoring and reporting plans.

1.4.3 Post-trial access to PrEP products

CATALYST will be conducted only in countries where oral PrEP and ring PrEP are already approved and national regulatory approvals for CAB PrEP are actively being sought. Products will not be introduced in the study without national regulatory approval nor used in populations not included in the regulatory approval, e.g., by age or pregnancy status**.** The study team will work in close consultation with each country's MOH throughout study preparation, implementation, and dissemination. As a part of these consultations, the study team will work with the MOHs to facilitate ongoing access to all relevant PrEP products at CATALYST sites or through other sites in the national health system. However, it is possible that some PrEP products, such as the PrEP ring or CAB PrEP, might not be available to participants following study completion. In these instances, participants will be counseled as to their available HIV prevention options following study completion. This information will be covered during informed consent for study participation.

1.5 Implementation science and research utilization frameworks

1.5.1 Implementation science frameworks

As described above, this study involves the implementation of an enhanced service delivery package — refined and tailored for each country's context through a QI approach — that leverages existing procedures and standards of care to allow for delivery of PrEP choice. Because its primary focus is on implementation of informed PrEP choice, the study is grounded in several implementation science frameworks, including Proctor's Taxonomy for Implementation Outcomes,[53] and the Consolidated Framework for Implementation Science (CFIR).[54]

Proctor's Taxonomy of Implementation Outcomes provides a comprehensive, evidence-informed set of outcomes critical to understanding and evaluating aspects of an implementation strategy. In this case, the implementation strategy involves many of the enhanced care measures listed in Table 1, such as enhanced provider training and creation of job aids, as well as the overall QI approach used to allow for intervention adaptation, contextual tailoring, peer to peer influence, knowledge sharing, and involvement of local stakeholder advisory mechanisms.

CFIR will be used to inform the development of qualitative interview guides for the process evaluation using the major CFIR domains, including intervention characteristics, inner and outer settings, and characteristics of individuals. Utilizing the construct on intervention characteristics,

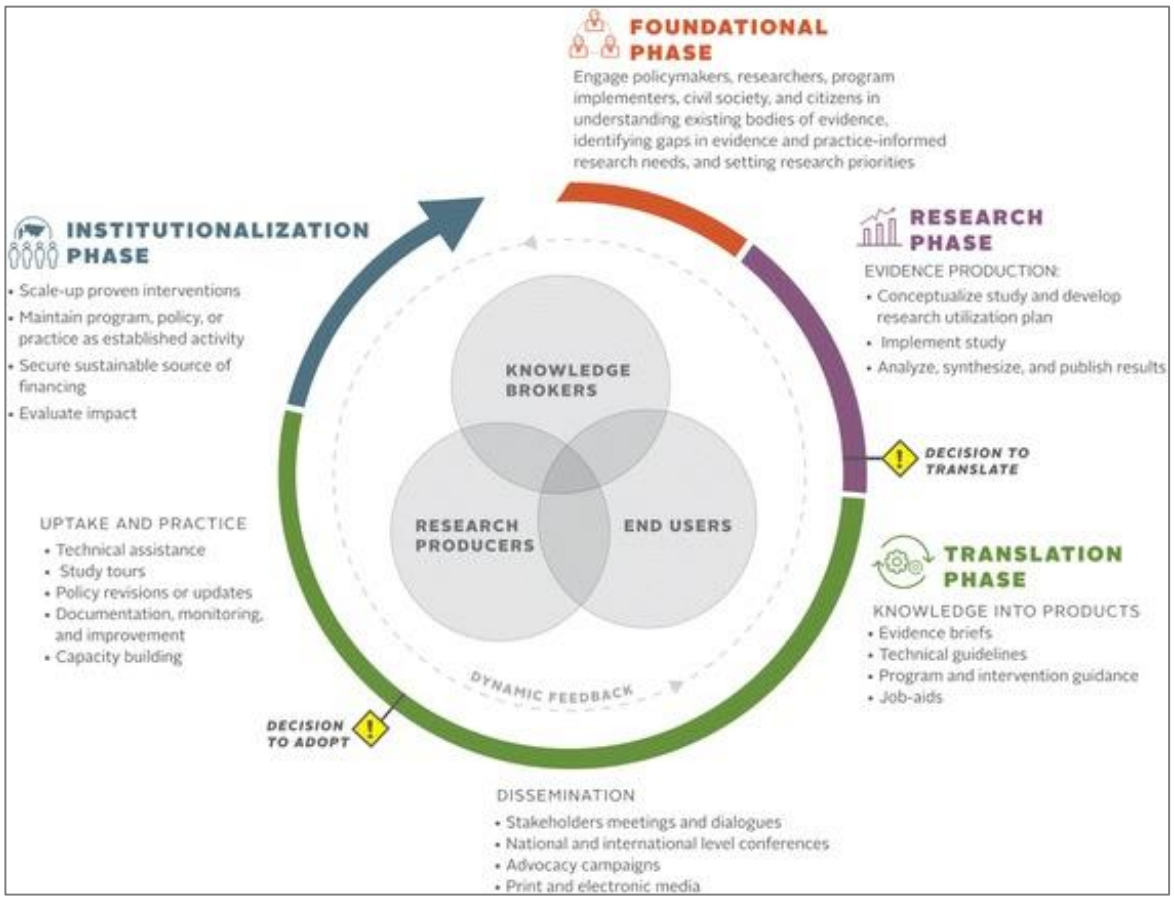
we will assess intervention aspects such as adaptability, complexity, and costs. Using the inner setting construct, we will examine organizational characteristics, such as implementation climate, compatibility, learning climate, and readiness for implementation. For the outer setting, we will utilize measures of policies and incentives as well as broader user needs and resources.

As demonstrated in recent research,[55] using Proctor's Taxonomy of Implementation Outcomes *and* CFIR — complementary implementation frameworks—can help researchers identify common metrics to assess the success of implementation across sites as well as understand the most salient, modifiable considerations for implementation.

1.5.2 Research utilization framework

Using FHI 360's Research Utilization (RU) Framework as a guide (Figure 2), CATALYST will apply a systematic and dynamic approach to accelerate the transition from research to program and policy change and potential scale-up of interventions.[56] The RU framework illustrates our approach before, during, and after research findings are produced, from the foundational and research phases to the translation and institutionalization phases, with opportunities for continuous collaboration, learning, and adaptation within and between phases. The framework also centers key actors who are essential to the progress of each phase — namely, research producers, knowledge brokers, and end users of research – and highlights critical decision points for research translation and adoption. See Sections 11 and 15 for more information on research utilization activities.

Figure 2. Research utilization framework



2 STUDY GOALS AND OBJECTIVES

2.1 Study Goal

The overall goal of the study is to characterize and assess the implementation of an enhanced service delivery package providing choice of PrEP products among women at PEPFAR/USAID delivery sites in Kenya, Lesotho, South Africa, Uganda, and Zimbabwe. For this study, the term "women" is inclusive of individuals assigned female at birth of any gender identity or individuals assigned male at birth who identify as women.

2.2 Objectives

The study has three primary objectives:

Objective 1: Characterize the implementation of the enhanced service delivery package for informed PrEP choice for women in PEPFAR/USAID public health service delivery sites and assess individual-, provider-, facility-, community-, and health system-level facilitators of and barriers to the implementation process. *(Achieved through process evaluation, and nested costing and community acceptance studies)*

Objective 2: Describe patterns of PrEP use and use effectiveness in the context of informed PrEP choice and assess sociodemographic and contraceptive use correlates of PrEP use patterns. *(Achieved through cohort and nested PEU study)*

Objective 3: Describe clinically relevant indicators among PrEP users, including rates of HIV infection and drug resistance among PrEP users who acquire HIV following PrEP initiation or had undetected HIV prior to PrEP initiation. *(Achieved through cohort, including CAB HIV testing algorithm nested study)*

3 METHODS

3.1 Overall study description

CATALYST is a mixed-methods study, grounded in implementation science, that utilizes a prospective cohort design and a process evaluation to assess an enhanced service delivery package providing informed PrEP choice. The study will describe feasibility, acceptability, uptake, patterns of use, and use effectiveness from end-user, community, and health system perspectives in the context of providing informed PrEP choice across five countries: Kenya, Lesotho, South Africa, Uganda, and Zimbabwe. In addition, this study will collect clinical outcomes of PrEP use (i.e., HIV infections, HIV drug resistance among participants who acquire HIV, and pregnancy-related outcomes among participants with PrEP exposure during pregnancy).

The study will be divided into two stages, because national regulatory approvals for CAB PrEP are expected at different times across participating countries. Having two stages will allow for a comparison of PrEP uptake as additional PrEP products become available. Stage I will assess delivery of informed PrEP choice among two products — oral PrEP and the PrEP ring. Stage II will assess delivery of informed PrEP choice among three products — oral PrEP, the PrEP ring, and CAB PrEP. The PrEP ring currently has national regulatory approval in all five study countries. The implementation of Stage II is conditional upon in-country regulatory approval of CAB PrEP. Implementation of Stage II will not commence in each country until the in-country regulatory approval for CAB PrEP has been granted in that country. Of note, oral PrEP is currently available through routine service delivery at all selected sites, and oral PrEP will continue to be available outside of the research context during the study.

The study also includes several nested studies, two related to the prospective cohort and two related to the process evaluation. These study components are described in more detail below.

3.2 Study design

The two main study components include the following:

1. **Component 1. Prospective cohort** (Section 4) of individuals eligible for the study (e.g., interested in learning about HIV prevention with screening for entry at time of HIV testing) and followed at all PrEP-related clinic visits throughout the study period, and for a limited time after PrEP discontinuation: Data collection will include quantitative and qualitative methods. Several subpopulations, including PBFP, people who acquire HIV, and those initiating and using CAB PrEP will have additional laboratory testing and/or data collected.

2. **Component 2. Mixed-methods process evaluation** (Section 7): This evaluation will document implementation of the enhanced service delivery package (including quality improvement adaptations), assess ongoing perceptions of enhanced service delivery (i.e., acceptability and feasibility, barriers and facilitators) among providers and key

stakeholders, and document other important implementation considerations (e.g., opportunities for PrEP and FP integration)

In addition, this study involves four nested studies, described briefly here:

Component 1a. Descriptive evaluation of alternative HIV testing algorithms for CAB PrEP in Stage II (Section 5): Delayed HIV diagnosis and the risk of drug resistance is a concern for individuals who are HIV positive or acquire HIV while using CAB PrEP. This nested study will address a key implementation question for CAB PrEP by evaluating combinations of antibody, antigen, and nucleic-acid-based HIV tests to determine if HIV diagnostic accuracy and sensitivity in CAB PrEP users can be improved using feasible and implementable HIV testing methods.

Component 1b. Prevention effective use nested study (Section 6): A two-stage descriptive study will assess (1) the feasibility and validity of collecting PEU data among CATALYST participants in the validation phase (occurring early in the study), and (2) will then measure PEU by PrEP method and compare cost-effectiveness of preventive use (e.g., per episode of condomless sex) for each PrEP method in the measurement phase (occurring later in the study). Results will inform the conceptualization of PrEP coverage as a function of temporal adherence and risk, which will inform the design of service delivery approaches to optimize PEU.

Component 2a. Nested costing studies for PrEP choice in Lesotho and Uganda in Stage II (Section 8): The objective for this component is to determine the average and incremental unit costs of providing oral PrEP, the PrEP ring, and CAB PrEP for women seeking health services (e.g., HIV prevention and family planning) in Lesotho and Uganda. All study sites within the two countries will participate in the costing analysis.

Component 2b. Qualitative nested study on community acceptance of PrEP choice in Stage II (Section 9): The objective of this nested study is to understand the community acceptability of informed PrEP choice, especially among primary PrEP influencers of AGYW (partners and parents/caregivers of PrEP users and potential PrEP users). The objective will be accomplished by leveraging the qualitative in-depth interviews (IDIs) being conducted among community members and leaders as part of the process evaluation, as well as the IDIs among PrEP users conducted within the cohort, and by conducting IDIs and focus group discussions (FGDs) with parents and partners of existing PrEP users (identified through snowball sampling through PrEP user interviews and community-based sampling for partners/peers of potential PrEP users).

3.3 Study setting

The study will take place across five countries (Lesotho, Kenya, South Africa, Uganda, and Zimbabwe), with approximately 3-10 sites chosen per country. Study sites for introduction of

new PrEP products will be purposively selected in consultation with USAID and MOHs within those five countries. Sites will need to meet the following criteria:

- Supported by PEPFAR/USAID-funded implementing partners (IPs) and have PEPFAR/USAID PrEP targets.
- Have established oral PrEP service delivery, concurrent demand generation activities in catchment areas, and services catering for selected populations, e.g., AGYW and FSWs.
- Other criteria include on-site phlebotomy, sample storage and transport; an HIV RNA viral load point-of-care testing or referral system; an on-site or nearby affiliated pharmacy; research experience (preferred) and concurrence from the USAID Mission, the MOH, and the district/county health authority.

3.4 Study populations

The study involves four distinct populations: 1) PrEP users, 2) providers and other facility staff, 3) PrEP influencers (partners, parents/caregivers), and 4) other relevant key stakeholders, including policymakers and community leaders. More details about these populations are included in Table 3 below and in the sections on each study component.

Table 3. Descriptions of study populations and approximate sample sizes

Population	Study component	Approx. sample size
HIV-negative women attending PEPFAR/ USAID-supported facilities who are interested in learning about HIV prevention and otherwise eligible to participate in the study, including the following subgroups: • Adolescent girls and young women (AGYW) ages 15–24 years old[a] • Female sex workers (FSWs) ages ≥18 years • Individuals assigned female at birth of any gender identity, ages ≥15 years • Individuals assigned male at birth who identify as women, ages ≥15 years • PBFP, ages ≥15 years	Component 1: Cohort Component 1a: CAB testing algorithms *(subset of cohort members who initiate CAB PrEP)* Component 1b: PEU nested study *(subset of cohort members selected for PEU data collection)*	Complete cohort (Stages I and II): 2,800 participants in Stage I and 8,465 in Stage II Qualitative subcohort[b]: 190 individual IDIs and 240 participants involved in FGDs CAB testing algorithms: 4,225 PEU: 400 in validation phase and 1000 in measurement phase
Providers and other health facility staff at study sites, including doctors, nurses, other clinicians, counselors, pharmacists, and other facility personnel involved in the delivery of PrEP-related services	Component 2: Process evaluation	600 providers across all sites for quantitative data collection 90 providers for qualitative data collection[b]
Primary PrEP influencers, including: • Parents/caregivers and partners of existing PrEP users • Parents/caregivers and partners of potential PrEP users, with partners sub-divided into younger (ages 18–25 years) and older (25 years and older) groups.	Component 2b: Community acceptance	30 parents/caregivers and 30 partners of existing PrEP users involved in IDIs[b]; 80 parents/caregivers, 80 younger partners, and 80 older partners of potential PrEP users involved in FGDs[b]
Key stakeholders who meet the following criteria will be eligible to participate in stakeholder IDIs: • Key Informants: Serve in an official capacity (such as MOH official, district health management team representative) or serve as a manager at a study site. • Community stakeholders: Represent a population, community, or other group interested in PrEP delivery.	Component 2: Process evaluation	75 key informants[b] 75 community stakeholders[b]

[a] *For national and regional consultation to have consensus around balancing rights and need for inclusion of AGYW with established norms for service delivery. If 15–17-year-olds are included, we would seek a waiver of written parental consent (see Section 14 for more detail).*

[b] *All participants involved in qualitative data collection must be willing to be audio-recorded to participate in the qualitative study components.*

3.5 Outcomes to be measured

The main study outcomes are described in Tables 4 and 5. The implementation outcomes (Table 6) are organized according to Proctor's Taxonomy of Implementation Outcomes.

4. Service and patient outcomes

Outcome description	Measurement method(s)	Level of measurement	Measurement time point(s)	Study component and objective
Initial uptake of PrEP methods – cohort *Defined as: Proportion of cohort members who initiate oral PrEP, the PrEP ring, CAB PrEP, or decline all PrEP or are ineligible for PrEP*	Chart abstraction; structured questionnaire	Individual service user (cohort members)	Month zero (or month of initial PrEP uptake if PrEP uptake is initially deferred)	Cohort ***Objective 2***
Uptake of PrEP methods – site *Defined as: Proportion of eligible PrEP users receiving PrEP services from the facility, disaggregated by method*	Aggregated, deidentified, routinely collected facility data on PrEP use	Health service facility	Service statistics obtained during implementation	Process Evaluation ***Objective 2***
Patterns of PrEP use and non-use over study duration *Defined as: Person-time of continued use of a certain PrEP method, until switching to another method or missed resupply; Person-time of pause between missed resupply and reinitiation or switching (subset). Use of oral CAB as a lead-in or as a bridge between doses of CAB PrEP will also be recorded.*	Chart abstraction; structured questionnaire	Individual service user (cohort members)	Month zero and at least quarterly thereafter; those who discontinue will be followed for 3 months post-discontinuation (for oral and ring) and up to 12 months for CAB	Cohort ***Objective 2***
HIV infections among those exposed to PrEP *Defined as: Number of study cohort members who become infected with HIV at any point during the study disaggregated by PrEP use status after enrollment (but not including the enrollment visit).*	Chart abstraction; results from laboratory testing	Individual service user (cohort members)	Throughout the follow-up period	Cohort ***Objective 3***

Outcome description	Measurement method(s)	Level of measurement	Measurement time point(s)	Study component and objective
Drug resistance *Defined as: Number and type of HIV drug resistance-associated polymorphisms and/or mutations identified among participants who become infected with HIV and were exposed to PrEP*	Results from laboratory testing	Individual service user (cohort members)	Throughout the follow-up period	Cohort ***Objective 3***
Pregnancy outcomes *Note: To determine pregnancy outcomes, pregnancy status will be determined among all study participants through urine pregnancy tests conducted at all clinic visits among women of reproductive potential.* *Among pregnant participants: type and frequency of pregnancy outcomes (term live birth [≥37 weeks], preterm live birth [<37 weeks], pre-term birth, stillbirth, birth weight and sex, spontaneous abortion, congenital anomalies, gestational age, neonatal death)*	Chart abstraction (from relevant facilities), hand-held data, and structured questionnaire	Individual service user (cohort members who are or become pregnant during follow-up, known based on results of routine pregnancy testing)	Throughout the follow-up period	Cohort ***Objective 3***
Contraception outcomes *Defined as: 1) the proportion of study participants who report contraceptive use, including type, during study participation; 2) proportion of study participants who are referred to PrEP from FP or vice versa; 3) proportion of participants seeking and receiving integrated PrEP/FP services*	Structured questionnaire	Individual service users	Throughout the follow-up period	Cohort ***Objective 2***
Side effects *Defined as: The type, number, and perceived severity of patient-reported side effects from PrEP product use*	Structured questionnaire; qualitative interviews	Individual service user (cohort members)	Throughout the follow-up period	Cohort ***Objective 3***

Outcome description	Measurement method(s)	Level of measurement	Measurement time point(s)	Study component and objective
Testing algorithm characteristics *Defined as: Sensitivity, specificity, negative predictive value, positive predictive value will be calculated dependent on sample size; alternatively, descriptive statistics will be used to compare tests and testing algorithms*	Chart abstraction; laboratory results	Diagnostic device/ algorithm (results among cohort members initiating or using CAB)	Throughout the follow-up period	Nested study on CAB testing algorithms ***Objective 3***
Prevention effective use (proxy measure) *Defined as: Recent exposure and use of PrEP product within 30 days*	Structured questionnaire	Individual service user (cohort members)	At all clinic visits	Cohort ***Objective 2***
Prevention effective use (actual measure) *Defined as: % of risk-days (days with condomless sex) when participants were protected from HIV acquisition by taking PrEP*	Daily short questionnaire through SMS text messaging (PEU sub-cohort)	Individual service user (subset of cohort members)	Daily (PEU sub-cohort during 6-week intervals)	PEU nested study ***Objective 2***

Table 5. Implementation outcomes

Framework Taxonomy[a]	Outcome description	Measurement method(s)	Level of measurement	Measurement time point(s)	Relevant study component and objective
ACCEPTABILITY	**Product acceptability** *Defined as: Perception that PrEP product is agreeable or satisfactory*	Structured questionnaire; qualitative interviews	Individual service user	All clinic visits during follow-up; a subset will be invited for IDIs/FGDs	Cohort Process evaluation ***Objective 2***
	Acceptability of services received *Defined as: Perception that PrEP-related services are agreeable or satisfactory*	Structured questionnaire; qualitative interviews	Individual service user	All clinic visits during follow-up; a subset will be invited for IDIs/FGDs	Cohort Process evaluation ***Objective 1***
	Community acceptability *Defined as: Perception that PrEP (and PrEP choice) are agreeable, satisfactory, and welcomed in the community, especially among primary PrEP influencers (partners and parents)*	Qualitative interviews and focus groups	PrEP influencers (partners and parents/care-givers of existing and potential PrEP users)	Once (During Stage II)	Qualitative nested study on community acceptance ***Objective 1***
	Intervention acceptability *Defined as: Perception that intervention, including PrEP products, offering informed choice, and provision of the enhanced service delivery package is agreeable or satisfactory in this setting (e.g., FP, ANC, RH, ART, one-stop-shop, etc.)*	Acceptability of Intervention Measure (AIM);[28] qualitative IDIs using CFIR-based interview guides	Service provider	Every 6 months during implementation; IDIs will occur up to 3 times during implementation	Process evaluation ***Objective 1***

Framework Taxonomy[a]	Outcome description	Measurement method(s)	Level of measurement	Measurement time point(s)	Relevant study component and objective
APPROPRIATENESS	**Intervention appropriateness** *Defined as: A given provider's perception of the fit of the enhanced service package and offering PrEP choice*	Intervention appropriateness measure; qualitative IDIs using CFIR-based guides	Service provider	Every 6 months during implementation; IDIs will occur up to 3 times during implementation	Process evaluation ***Objective 1***
FIDELITY	**Fidelity of informed choice counseling** *Defined as: The proportion of cohort members who report: 1) being counseled on the efficacy, side effects and dosing schedule of all methods, 2) told what to do about side effects, and 3) told they could switch methods (as appropriate)*	Structured questionnaires from cohort participants reporting on being offered informed choice and quality of counseling; provider IDIs	Service provider (via reports from clients and from providers themselves)	At cohort enrollment and follow-up	Process evaluation ***Objective 1***
	Fidelity of provision of respectful care (proxy for client-centered service) *Defined as: The proportion of cohort members, including AGYW and FSW, who report being treated respectfully*	Structured questions from cohort participants	Individual cohort members	At cohort enrollment and follow-up	Cohort ***Objective 1***
FEASIBILITY	**Feasibility of informed choice counseling** *Defined as: The average time spent counseling a client on informed choice at PrEP initiation and follow-up; staff time available for counseling;*	Structured questions from providers, and site assessment; Costing time/motion study;	Site	Throughout implementation using cohort and provider interviews, and	Cohort Process evaluation ***Objective 1***

Framework Taxonomy[a]	Outcome description	Measurement method(s)	Level of measurement	Measurement time point(s)	Relevant study component and objective
FEASIBILITY	*estimated number of PrEP clients requiring counseling post-study; number of additional staff required to extend informed choice counseling to all PrEP clients*			Site assessments	
	Feasibility of laboratory services for PrEP choice provision *Defined as: The extent to which existing site laboratories can accommodate additional requirements of providing PrEP choice.*	Laboratory capacity and staffing,	Site	Site assessments	Process evaluation ***Objective 1***
	Health system feasibility *Defined as: The extent to which PrEP choice and the enhanced service delivery package can be successfully carried out at a facility within a health system*	Qualitative interviews with stakeholders	Site and system	Throughout implementation using site staff and key informant interviews	Process evaluation ***Objective 1***
	CAB testing algorithm feasibility *Defined as: The extent to which the additional HIV testing for CAB PrEP can be successfully carried out at a facility within a health system*	Provider questionnaires; routine data from facility (turn-around time for non-batched HIV RNA tests to providers and to clients as required	Providers and health facility	Questionnaires every 6 months; provider IDIs Process data collected per HIV RNA test	Nested study on CAB HIV testing algorithms ***Objective 1***

Framework Taxonomy[a]	Outcome description	Measurement method(s)	Level of measurement	Measurement time point(s)	Relevant study component and objective
		by national guidelines)			
COST	**Cost** *Defined as: The cost of the implementation effort, including average unit cost estimates for oral PrEP, the PrEP ring, and CAB PrEP in Lesotho and Uganda and the incremental unit cost of adding PrEP ring and CAB PrEP at sites already providing oral PrEP*	Interviews with facility staff; process data (commodity costs, product continuation data); time-motion data	Health facility	At one time point during implementation and at least 4 months after CAB PrEP introduction	Nested costing studies ***Objective 1***
SUSTAINABILITY	**Identification of core service delivery requirements** *Defined as: The extent to which the enhanced service delivery package is maintained or institutionalized within a health facility*	QI briefs from study sites (service delivery adaptations); qualitative interviews with providers and key informants; program assessment sustainability tool (PSAT) completed during facility assessment	Health facility	Quarterly QI briefs during implementation; sustainability assessed at site assessment conducted towards the end of Stage II	Process evaluation ***Objective 1***

[a] The implementation outcome "adoption", which is an outcome included in Proctor's Taxonomy, will not be included in the evaluation as all PrEP providers across all study sites will be trained in the provision of offering PrEP choice.

4 STUDY COMPONENT 1: COHORT OF PREP USERS

4.1 Overview

This study component, following a cohort of PrEP users for up to 18 months in Stage I and 24 months in Stage II, will contribute data to address all three of the research objectives, including: assessing facilitators of and barriers to implementation (Objective 1), defining patterns and correlates of PrEP use and use effectiveness in the context of PrEP choice (Objective 2), and describing clinically relevant indicators among PrEP users (Objective 3).

Data collection for all cohort members will involve quantitative surveys completed at enrollment and at every clinic visit and data extraction from their medical records during study implementation (i.e., chart/register review). A subset of cohort members will participate in qualitative IDIs, described in further detail below. In addition, several subpopulations, including PBFP, people who become HIV infected, and those initiating and using CAB PrEP will have additional laboratory testing and data collected.

Schematics for cohort activities across stages I and II are presented in figures 3 and 4.

Figure 3. Study schema for Stage I

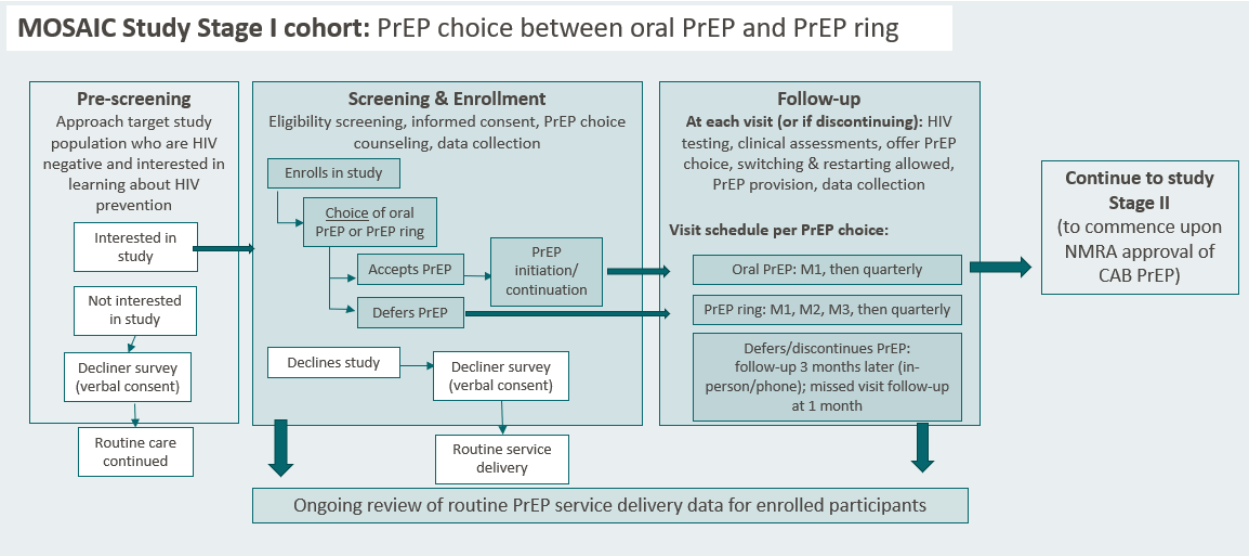
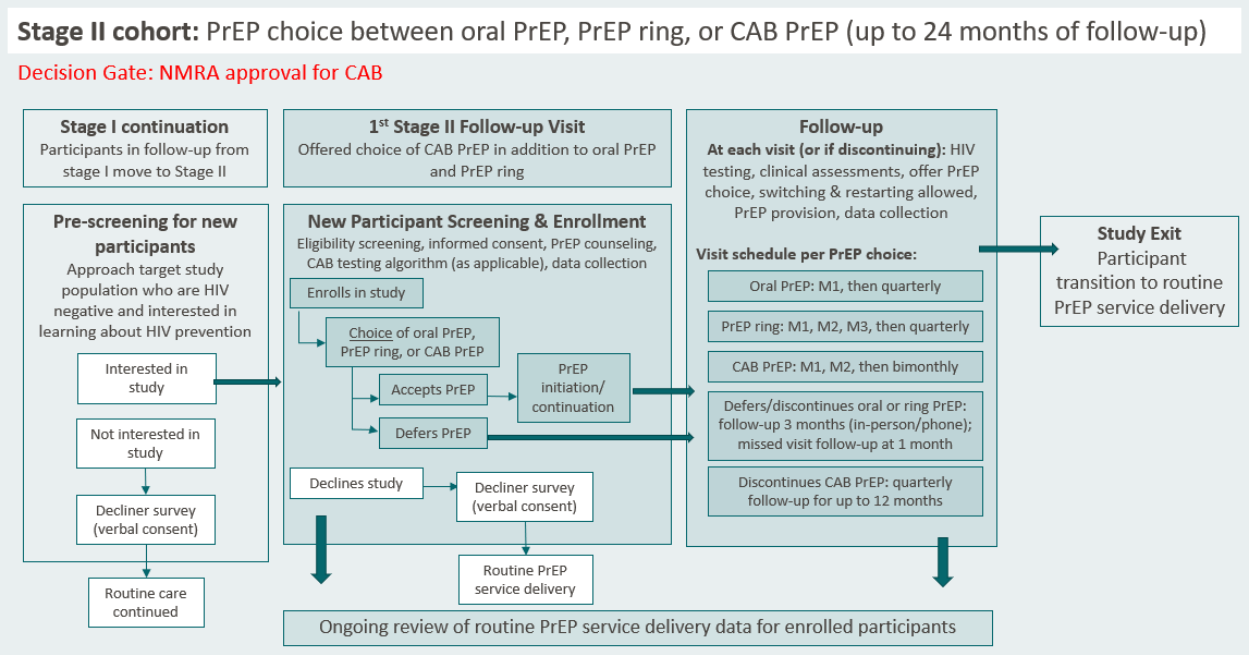


Figure 4. Study schema for Stage II



4.2 Selection of study population

4.2.1 Inclusion and exclusion criteria for cohort participation

Eligibility criteria to enroll in the study cohort for Stages I and Stages II are:

1. Tested HIV-negative as determined by the national HIV testing algorithm at a CATALYST site on the same day as enrollment

2. Self-identify with at least one of the following populations:
    a. Adolescent girl or young women (AGYW) ages 15–24 years
    b. Female sex worker (FSW) ages 18 years and older
    c. Pregnant and breastfeeding populations (PBFP) ages 15 years and older
    d. Individuals assigned female at birth of any gender identity ages 15 years and older
    e. Individuals assigned male at birth who identify as women ages 15 years and older
    f. Other women ages 25 years and older

3. Interested in learning about HIV prevention

4. Willing to be contacted for follow-up by phone or other means (e.g., through a community health worker)

5. Willing and able to provide informed written consent for participation

Participants will be excluded based on the following criteria:

1. For participants ages 15–17 years, potential participants under the age of 18 may be excluded from study participation based on country guidelines and the age of consent. This determination will vary by country, including countries' definitions of emancipated minors. Country-specific informed consent forms will outline the country-specific inclusion criteria related to age.

The above criteria describe eligibility for entry into the study cohort. Eligibility for specific PrEP products will be determined by providers. Product-specific eligibility criteria will be outlined in site- and/or country-specific standard operating procedures (SOPs), as criteria may differ across countries and across products, depending on the NMRA-label and country guidelines. Providers will receive training on eligibility criteria for PrEP products that are being introduced as part of the study.

4.2.2 Sampling and recruitment

Sampling for prospective observational cohort: Once enrollment begins, participants will be selected sequentially at all participating sites. Sampling for the cohort will vary depending on the study stage. Enrollment in each stage will be monitored to help ensure sufficient numbers of participants are new initiators of PrEP, thereby facilitating unbiased comparisons of uptake, continuation, and acceptability between PrEP methods.

Potential participants at each CATALYST site will be screened for HIV infection using standard-of-care HIV tests following each country's national HIV testing algorithm as applicable. Individuals with a negative HIV test result interested to learn more about the study will be directed to an on-site study staff member. The study staff member will obtain verbal permission from interested individuals to administer a brief eligibility screening. To maintain privacy, interactions between study staff and potential participants will occur in private or semi-private areas of the study site where auditory privacy can be maintained. If the participant is eligible, a trained study staff member will go through the informed consent process with the potential participant. Following obtaining informed consent, the participant will see the PrEP provider. All study staff members involved in the screening and consent process will be trained in research ethics.

In Stage I (choice between oral PrEP and PrEP ring), all eligible clients attending the clinic (see eligibility criteria in Section 4.2.1) will be invited to enroll in the study by a trained study staff member. Enrollment in Stage I will continue until the target number of ring initiations is achieved (n=approximately 280 per country), 12 months of recruitment per country have elapsed, or CAB PrEP is approved and enrollment in Stage II begins, whichever occurs sooner. Follow-up for participants in Stage I will last up to 18 months, or until Stage II begins. Enrollment in Stage II (choice among oral PrEP, PrEP ring, and CAB PrEP) will commence in each country once

NMRA approval of CAB PrEP has been granted in that country (approval timeline will vary by country). Stage II eligibility criteria (Section 4.2.1) and enrollment will be the same as in Stage I. Cohort participants enrolled in Stage I will be re-consented to continue follow-up in Stage II and will be offered the additional choice of CAB PrEP. If a Stage I participant does not consent to Stage II, they will be exited from the study (unless pregnant — in which case we will continue to track their pregnancy outcomes until the birth of their child — or if we are currently following up with an adverse event for that client, in which case we will follow until resolved or until the end of the study, whichever comes first). Recruitment into Stage II will continue until the targeted number of CAB PrEP initiations is achieved (n=approximately 845 per country) or until 12 months of recruitment have elapsed per country. Follow-up for Stage II will last up to 24 months.

Sampling and recruitment for qualitative data collection: A subset of cohort participants will be purposively selected in Stage II to complete a qualitative IDI or participate in an FGD. The populations that will be recruited for these IDIs and FGDs are described in Table 6 and will be based on experience with informed choice PrEP counseling; PrEP-related experiences following choice counseling, and population-specific experiences (e.g., AGYW, FSW). For most categories, purposive sampling will be used to identify participants meeting the target profiles, taking into consideration participant characteristics (such as PrEP method), data collector availability, site, and other logistical considerations. Within the sites conducting qualitative research, study staff will have regular meetings during Stage II to review participants eligible for the various sub-categories of interest for the qualitative subcohort. In preparation for these meetings, study analysts monitoring data collection will compile a list of participants meeting the criteria for each category of interest. A participant may be selected for only one category. Site staff will review the lists and will purposefully select participants based on a number of potential criteria, including knowledge that certain participants might be 'information-rich' (e.g., known to have interesting, relevant stories to tell), PrEP product to ensure variation, and timing (e.g., an event of interest such as product switching, recently occurred). If more eligible participants meeting all criteria are identified than needed, remaining participants per sub-category will be chosen randomly. Research assistants will then contact potential qualitative subcohort participants using their preferred contact method to offer participation in an additional IDI or FGD. To maintain privacy, the research assistant will not disclose that the call is related to the study until the participant has confirmed their identity. If contacted participant is interested, the research assistant will schedule the interview or FGD.

Table 6. Description of qualitative data collection within cohort of PrEP users to occur during Stage II[a]

Category	Sub-categories and definitions used for inclusion criteria	Target sample size	Sampling	Timing
Experiences informed PrEP choice counseling through CATALYST	CATALYST participants who go through choice counseling, with variation sought in terms of choice made (no PrEP, oral, ring, and CAB). Interviews will occur approximately one month of undergoing initial choice counseling. There will be a focus on new PrEP initiators (i.e., those deciding to use PrEP for the first time after undergoing choice counseling as a part of CATALYST).	40 IDIs (8 per country, 2 per choice per country)	Purposive sampling based on participant profile (typical case with variation sought in terms of choice made, including oral PrEP, ring PrEP, CAB PrEP, and choosing no PrEP), availability of participants, and data collectors.	Early in Stage II
PrEP user experiences following choice	• ≥6 months continuous PrEP use on one product (all refills/ injections provided within 2-weeks of scheduled visit), with variation sought in terms of product (oral, ring, and CAB) • Intermittent PrEP users: At least one break from PrEP of ≥1 month over 6-12 month period (on the same PrEP product after break), with variation in terms of product (oral, ring, and CAB) • Switching: Those who report switching PrEP method during follow-up, interviewed approximately 2-3 months after switching	90 IDIs overall, with 30 per sub-category (6 per country, 2 per method choice per country).	Purposive sampling based on participant profile (variation sought in terms of PrEP product and user experience) and availability of participants and data collectors	At least 6-months into Stage II for continuous and intermittent use; anytime in Stage II for switchers.
PrEP user experience involving pregnancy	• Pregnant at enrollment and choose PrEP • Breastfeeding at enrollment and choose PrEP • Becomes pregnant during PrEP use, with a focus on those using new	30 IDIs (10 per sub-category), with variation in PrEP product sought for those P/BF at enrollment, and focus	Purposive sampling based on participant profile (variation sought in terms P/BF status and PrEP products) and	Anytime during Stage II

and/or breastfeeding	methods (ring and CAB PrEP) at time of pregnancy discovery	on women using PrEP ring or CAB PrEP for those who become pregnant during follow-up[b]	availability of participants and data collectors at sites	
Unique experiences	• HIV infection discovered during PrEP use • Chose PrEP method but never used • Dual method (used/wanted to use more than one PrEP method simultaneously) • Other experiences deemed unique or noteworthy by the study team	No set targets, estimating approximately 30 (6 per country)	Deviant case sampling, with decisions made by site/country team	Anytime during Stage I and Stage II
AGYW, FSW, and PBFP experiences	• FGDs with AGYW, FSW, and PBFP to understand population-specific experiences, including barriers and facilitators to use (6-10 participants per group)	10 AGYW FGDs (2 per country) 10 FSW FGDs (2 per country) 10 PBFP FGDs (2 per country)	Homogenous sampling based on population with some variation sought in terms of PrEP product if possible.	Anytime during Stage II

[a]*Most qualitative interviews with the cohort will be conducted during Stage II. However, it is possible that some participants will be interviewed in Stage I for the "unique experiences" category. Approximately two sites per country will be selected for qualitative data collection. Sites selected for the population-specific FDGs may differ from the other sites selected for the IDIs.*

[b] *If certain countries do not allow PBFP to initiate PrEP ring and/or CAB PrEP, interviews may be shifted to countries that do allow PBFP to initiate ring PrEP and/or CAB PrEP within the total sample size included in the PBFP category listed above.*

4.2.3 Sample size for cohort

4.2.3.1 Sample size for quantitative components of cohort

The number of participants enrolling in CATALYST will depend on several factors, including but not limited to: the timing of NMRA approval of CAB PrEP across countries and PrEP uptake across sites during enrollment. Recognizing these unknowns, we anticipate enrolling approximately 11,265 PrEP users across all sites and countries in Stages I and II. In Stage I, we anticipate enrolling 2,800 PrEP users, including 1,400 ring initiators (280 per country) and a similar number of oral PrEP users. In Stage II, we expect to enroll 8,465 PrEP users (1,693 per country). However, these totals are approximations since Stage I participants will remain in follow-up when Stage II begins and will have the option to continue into Stage II. Of note, having a large sample size for Stage II will help ensure that sufficient numbers of participants are included to provide meaningful results for the HIV drug resistance testing and alternative CAB PrEP testing algorithms (described further in Section 5). If the maximum sample size is not attained for either Stage I or Stage II, we will retain our ability to describe all primary study outcomes, although with decreased precision of estimates. Also of note, it is possible that individuals who enroll in the study will not choose a PrEP method initially. Although unknown, we anticipate this occurring among up to 5-10% of enrolled participants. These participants may choose to take-up PrEP later during the study period.

A key objective for both Stage I and Stage II is a comparison of uptake rates, overall and by important subgroups of participants. The primary comparisons of method uptake will be restricted to participants who are new adopters of PrEP, since the inclusion of experienced users with established preferences or dislikes would bias comparisons with the newly available methods. Recognizing this restriction, we have approximately 80% power to detect a 10% difference in method uptake in Stage I (45% for one method and 55% for the other) based on chi-squared goodness of fit tests conducted at the 0.05 significance level, so long as there are at least 700 new PrEP initiators in each relevant subgroup of participants. There will also be approximately 90% power to detect modestly higher CAB PrEP adoption rates (e.g., 40% versus 30% for each other method; Table 7) in subgroups with at least 600 new PrEP adopters in Stage II.

We will also have excellent precision when estimating probabilities of other events (e.g., method discontinuation), overall and by relevant subgroups, in both Stage I and Stage II. For example, with only 200 PrEP users (considerably less than number expected per PrEP type in each country), the half-width of 95% confidence intervals for a given outcome will be at most 7.1% (see Table 8). Finally, there is at least an 80% chance of detecting 10% differences in event rates between any two PrEP groups with at least n=400 evaluable participants per group based on two-sided 0.05 level chi-squared tests.

Table 7. Power to detect differences in PrEP adoption rates in Stage II

True PrEP Adoption Probabilities				
CAB	**Ring**	**Oral**	**N[1]**	**Power[2]**
0.40	0.30	0.30	400	71 (71)
			500	80 (80)
			600	88 (88)
			700	92 (92)
0.40	0.35	0.25	400	94 (83)
			500	98 (88)
			600	99 (90)
			700	99 (93)

[1] *Number of new PrEP initiators in Stage II who choose among all three methods*
[2] *Power to conclude a difference in PrEP choice, based on a 0.05 level chi-squared test of homogeneity (number in parentheses is the probability that the test rejects and CAB is the most chosen method)*

Table 8. Maximum half-width of 95% Cis as a function of evaluable sample size

Number of Participants	Maximum half-width for 95% CI
100	+/-10.2%
200	+/-7.1%
280 (anticipated ring users per country in Stage I)	+/-6.0%
400	+/-5.0%
600	+/-4.1%
845 (anticipated CAB users per country in Stage II)	+/-3.4%
1000	+/-3.2%
2000	+/-2.2%

4.2.3.2 Sample size for qualitative components of cohort

In-depth interviews: Recent evidence suggests that 80% saturation can be reached within eight IDIs and 90% saturation can be achieved with 16 IDIs.[57] Balancing these considerations with practical constraints and with recognition that the research is being conducted across five countries, we set per country targets of approximately 6 to 8 IDIs per sub-category as listed in Table 6. Across the five countries, this means we will have a sample size of approximately 30 to 40 IDIs per category of interest, which should be sufficient to reach thematic saturation. Although of note, our sampling scheme prioritizes seeking variation in PrEP product by category

and sub-category of interest given the focus of PrEP product choice and use of PrEP following choice within CATALYST. Therefore, we will have limited ability to comprehensively understand themes that are specific to other potentially important perspectives, such as experiences in urban vs. rural settings, experiences by specific sub-population (e.g., older vs. younger women), and country-specific experiences.

For practical reasons, IDIs may be conducted in a limited number of study sites per country. However, to allow some variation in experiences and service delivery contexts, women will be selected from at least two different sites per country. Final target profiles are subject to change based on the number of women within each target profile and other preliminary findings.

Focus group discussions: To better understand the experiences of three key populations groups, AGYW, FSWs, and PBFP, two FGDs per group will be conducted per country (10 FGDs in total for AGYW, 10 FGDs for FSW, and 10 for PBFP). Evidence suggests that the majority of themes are found within the first focus group and that all themes are identified within three FGDs.[58] Approximately 6–10 participants will take part in each FGD, although fewer or more may participate. The FGD will proceed with a minimum of four participants and a maximum of 12. If fewer than four participants are present at the specified time, the FGD will be rescheduled.

As with the IDIs, FGDs may be conducted within a limited number of sites per country, which may or may not be the same as the sites selected for the qualitative IDIs. The exact number of IDIs and FGDs conducted will depend on thematic saturation, logistical considerations, and participant availability. Table 6 (above) provides the sample sizes for the cohort IDIs and FGDs. The qualitative data will help support the understanding of the quantitative data.

4.3 Study procedures for cohort

Client-facing data collection tools will be translated into languages of interest in each country. Interviewers interfacing with clients will be fluent in English and the language spoken in the assigned region so that clients may choose the language of the interview.

Teams of quantitative and qualitative interviewers will be trained in human subjects' research ethics, study procedures, and use of study tools. Trainings will be led by the local partners in collaboration with FHI 360 staff and will cover both general research practice (e.g., ethics, data quality) and study-specific procedures (objectives, methods, survey instruments, sampling, and data storage and transfer). The trainings will be conducted in person to the extent that local COVID regulations permit. Initial trainings will occur prior to study start, with refreshers conducted as necessary to coincide with the ebb and flow of data collection activities (e.g., periods of qualitative interviewing). Trainings will include a pretest component during which data collectors will practice interviewing volunteers. This pretest will be used to assess the clarity, translation, contextualization, and flow of interview questions, correct implementation of the informed consent process, and submission of electronic data. Areas for improvement identified during the pretest will be strengthened prior to and during field work. All data collection forms that will be administered to participants will be pretested. Feedback on forms that are completed

by providers will be sought from providers involved in the study who volunteer to offer their comments.

4.3.1 Procedures at enrollment

Following providing informed consent, which will take place at the study site, the participant will see a PrEP provider at the same site, where they will receive an assessment of PrEP readiness, including screening for acute HIV infection (AHI), screening for recent HIV exposure within 72 hours (in which case post-exposure prophylaxis will be offered per standard of care), and a urine pregnancy test. Testing for additional product-specific eligibility, such as tests for kidney function or liver function, may also be conducted by providers according to national guidelines and standard of care. If a participant is eligible for PrEP, they will be counseled on PrEP choice, with available options potentially limited by the NMRA-label of PrEP products (example: pregnant women may not be allowed to take PrEP ring or CAB PrEP per NMRA-label and will therefore be counseled only on oral PrEP). Providers will counsel PBFP about the risks and benefits of using PrEP methods, including CAB PrEP, during pregnancy and/or while breastfeeding. In cases where the local NMRA-label is ambiguous and does not specifically comment on whether CAB PrEP can be used during pregnancy and/or while breastfeeding, PBFP should only be allowed to take CAB PrEP *if the user and provider agree that* the benefits outweigh the potential risk to the fetus or breastfeeding infant. Providers will document each participant's eligibility for each PrEP product and the product prescribed on a study-specific form. On the same form, providers will also indicate the results of rapid HIV tests, the pregnancy test, and STI screening (if applicable). The form that providers complete might be paper-based or electronic, depending on the preferences of study sites. All paper-based forms will be handed directly to study staff following the participant visit. The study staff member will input all information into electronic format. Paper copies of the form will be stored securely, in a locked cabinet, either at the study site or the local study office.

Following counseling and method selection, a trained research assistant will administer the enrollment questionnaire to each participant in a location where auditory privacy can be maintained. Questionnaires will be administered in the participant's preferred language, on an electronic tablet using a secure, cloud-based electronic data capture program. Participants will be asked to provide contact information, such as a mobile phone number, and permission to be contacted using the means provided for study-related purposes. For AGYW ages 15–17 years, a waiver of parental consent will be sought (see Section 14 for more detail) when feasible. There will be a separate informed consent process for IDIs and FGDs in addition to the main study cohort informed consent process.

4.3.2 Quantitative data collection for cohort participants

Cohort members will have data collected at all PrEP-related clinic visits (visit schedules will vary by PrEP product but will occur at least quarterly for each method), including the study enrollment visit. Clinic-based data collection will include an electronic, structured questionnaire

administered by a trained research assistant at the end of each visit, chart/register review of participant records conducted quarterly, and a paper-based form containing results from any tests or procedures not included in the chart/register that will be completed by a provider or a trained study staff member at each visit for each cohort participant.

If the quarterly chart review identifies a participant who came to the clinic for a PrEP-related visit but was not identified as a study participant (i.e., the participant did not have additional study data collected during the visit), a trained research assistant will attempt to contact the participant by phone (or by an alternative, preferred means of contact) to obtain responses to the structured questionnaire typically administered at the clinic visit.

In addition, if a participant misses a clinic visit by one month, a research assistant will attempt to reach the participant by phone (or other preferred means of contact) to collect the structured follow-up questionnaire data. During the missed visit calls, research assistants will encourage the participant to return to the clinic for HIV testing. If the participant returns for HIV testing, all clinic visit study procedures will be followed.

- Research assistants will also attempt to contact participants to obtain responses to an abbreviated follow-up questionnaire either approximately 3 months of no contact following a decline of PrEP at enrollment or a visit in which a participant does not get a resupply of PrEP or approximately 3 months following a missed clinic visit with no recontact with the clinic. If a participant returns to the clinic after a period of declining PrEP during the study period, in-clinic data collection will resume.
- Participants discontinuing CAB who are not using another study-provided PrEP method will be contacted by phone quarterly for up to one year, or until the end of the study, whichever comes first, to respond to the abbreviated follow-up questionnaire. For those discontinuing PrEP ring or oral PrEP, participants will only be followed for three months post-discontinuation. The difference in post-discontinuation follow-up times for oral PrEP/PrEP ring users and CAB PrEP users is due to the length of the pharmacokinetic tail of CAB PrEP, which is not applicable to other PrEP methods.

Participants will also be contacted approximately one week after initiation of any new PrEP product (defined as approximately seven days from the clinic visit in which PrEP was dispensed or injected), and trained research assistants will administer a brief questionnaire to ask about PrEP initiation, possible early discontinuation, and side effects. Additional data will be collected from PBFP. All data collection methods are detailed below.

4.3.2.1 Quantitative data collection for cohort members

- The enrollment questionnaire will capture demographics, membership in subgroups of interest, history of PrEP use, knowledge of PrEP methods, receipt of PrEP services, reasons for PrEP method selection, FP use, sexual behavior, pregnancy/breastfeeding status, awareness of PrEP messaging within the community, and pregnancy information for those who are pregnant at time of enrollment. The survey will be completed at the enrollment clinic visit.

- A brief one-week post-PrEP initiation questionnaire administered by phone approximately seven days following the prescribing of any new PrEP product to ask whether PrEP was initiated and experience of side effects.
- A structured follow-up questionnaire conducted at each clinic visit (visit schedules may vary by PrEP method but will occur at least quarterly across methods) or by phone to gather information on use of HIV prevention methods (including reasons for continuation, discontinuation or switching methods), side effects, attitudes towards product use and services received, barriers to use, sexual behavior, pregnancy-related information, and FP use.
    - For those who miss regularly scheduled clinic visits by one month, a missed clinic visit interview will be conducted, most likely by telephone. These interviews will involve asking participants the same follow-up questions asked during regular clinic visits and will be conducted approximately 1 month after the missed clinic visit.
- The follow-up questionnaire will be abbreviated when given to those who decline PrEP or discontinue PrEP that will be conducted approximately three months following PrEP decline at enrollment or discontinuation. A CATALYST Cohort Visit Form will capture test results from study procedures (e.g., HIV rapid, pregnancy testing, screening for and presence of STI (if available), HIV testing, the provider's assessment of whether or not a participant is eligible for each PrEP method, and the PrEP method prescribed and amount dispensed). This form may be paper-based or electronic; when paper-based forms are used by providers, results will be entered into the study database by data collectors. Each site and laboratory will outline procedures related to this form in a standard operating procedure (SOP) prior to study start.

4.3.2.2 Additional data collection for PBFP

Pregnant participants will be asked to provide additional information on select pregnancy and infant outcomes. Several potential methods will be used to collect this information. Initially, members of the research team will ask pregnant participants to bring in their hand-held records related to antenatal care, delivery, and infant care to a regularly scheduled clinic visit(s) at the study site. If participants have no scheduled PrEP-related clinic visits (e.g., because they chose to discontinue PrEP), participants will be contacted by phone to provide this information. In addition, during the informed consent process, women will be asked if the study team has their permission to abstract their clinic records from antenatal clinic (ANC) and relevant delivery site facility records. When feasible and necessary to complete data collection, the study team will attempt to collect this information directly from facilities through chart/register abstraction with participants' permission. Maternal deaths are not anticipated in this study, but in cases of maternal death, care providers would be contacted to provide relevant outcome data. Source(s) of outcome data will also be collected. If the participant exits the study prior to their pregnancy outcome, but their due date falls within the study period, we will attempt to obtain this information when it is available via chart review or by contacting the participant.

4.3.2.3 Data collection among those who decline study participation

A brief (five-minute), anonymous survey will be administered among those who decline study participation. Collecting these data will help ensure we document potential selection bias (i.e., clients already taking oral PrEP might be disinclined to join the study), as well as to better understand reasons for not wanting to participate in the study or use PrEP.

4.3.3 Qualitative data collection (qualitative subcohort)

IDIs and FGDs will be conducted among a subset of cohort members who meet certain profiles of interest during Stage II when all PrEP method options will be available. Selected participant will be contacted by a study team member via their preferred contact method to gauge interest and availability. If participants are interested and available, the study staff member will schedule the IDI or FGD and will also contact those participants a few days prior to the IDI or FGD to remind them of the appointment. During these interviews, the interviewer will ask about multi-level facilitators of and barriers to PrEP initiation and use, experiences with the enhanced service delivery package and the experience of being offered PrEP choice, perceptions of PrEP, and what influences PrEP decision-making. IDIs could take place at various locations, including the clinic, or another location of the participant's choosing. IDIs could be conducted face-to-face or, if necessary, by phone. Each interview will take approximately 60 minutes to complete and will use a semi-structured IDI guide. Individuals will provide written informed consent prior to participating in the interview. If the IDI is conducted by phone, the interviewer will sign and acknowledge obtaining informed consent from the participant. IDIs will be audio-recorded, pending permission of the participant. If an IDI participant does not come to the scheduled IDI, attempts will be made to reschedule the interview. If the participant does not come to the rescheduled IDI, they will be replaced with another eligible participant.

Focus group discussions will be conducted with participants within specific subgroups (e.g., AGYW, FSWs, and PBFP) who have used PrEP across selected project sites. Participants in the FGDs will be asked about PrEP choice, facilitators of and barriers to PrEP use, strategies used to confront challenges, experiences with the enhanced service delivery package, and the role of social influences. Study staff conducting the recruitment will confirm availability at the specified time for the FGD to ensure adequate participation. FGDs will proceed if at least four participants are present; otherwise, they will be rescheduled. Each FGD will comprise approximately 6–10 participants and will take approximately 90 minutes to complete. A semi-structured interview guide will be used. Individuals will complete written informed consent prior to participating in an FGD. FGDs will be conducted in person and will be audio-recorded, pending permission of the participants.

4.3.4 Interventions

- Cohort participants will receive the components of the enhanced service delivery package described in Section 1.2, as adapted and tailored to the site in which they are receiving services. Given the different country and site contexts, as well as the QI processes being

used, we anticipate differences in intervention delivery across sites, which will be documented through the process evaluation component described in Section 7.

- Participants who acquire HIV during the study or who are found to have had undiagnosed HIV infection while using any PrEP product will be asked to provide an additional biological specimen to allow for HIVDR testing and PrEP drug level testing. The additional blood draw will occur at the visit when HIV infection is identified. However, if for some reason procedures are not completed on that day, participants will be asked to return to the clinic to complete the procedure. If a participant reports receiving an HIV diagnosis at a non-CATALYST clinic, the participant will be asked to return to the CALALYST site to provide the test results (if available) or to undergo retesting for HIV to confirm the diagnosis for study purposes. Participants may be asked for the additional blood specimen at this time for HIVDR testing. Regardless of whether the participant agrees to provide a biological specimen or not, they will be referred to HIV care and treatment. Participants will receive the results of the HIVDR testing but will be counseled that they are to be used for informational purposes rather than clinical decision-making. If feasible, participants who acquire HIV on PrEP ring will have their most recently used ring collected for residual drug level testing to monitor adherence.
- Providers will be instructed to test participants for pregnancy using a urine pregnancy test at all study visits, except in cases where the need for such testing is clinically implausible, as noted in the study-specific procedures manual.
- Cohort participants who initiate CAB PrEP will also receive additional HIV testing as described in Section 5.

4.3.5 Measures for the cohort

Participant characteristics

- Pregnancy and breastfeeding status
- Sociodemographics collected during the enrollment survey
- Contraceptive use throughout the study and whether family planning services were obtained concurrently with PrEP services

Implementation outcomes

- Acceptability of enhanced service delivery
- Satisfaction (including questions on stigma/discrimination encountered during visit)

Patterns of PrEP use and use effectiveness in the context of PrEP choice

- PrEP uptake (individual, facility, and community levels)
- Rates of and experiences with continuation/switching/discontinuation among PrEP methods
- Product acceptability
- Reported frequency of potential HIV exposure within the last month (i.e., condomless sex)
- Reported frequency of PrEP use within the last month (for oral PrEP and PrEP ring users

Clinically relevant outcomes

- HIV infection, seroconversion, HIV-1 RNA levels, and prevalence of HIVDR among individuals who acquired HIV infection
- Pregnancy outcomes among PBFP
- Participant-reported side effects

4.3.6 Laboratory methods

This study component of the study involves the collection of two biospecimens:

- A sample of blood will be taken by venipuncture for HIV drug resistance testing among participants who acquire HIV.

- A point of care urine pregnancy sample will be collected by the participant, and test results [will be read by a healthcare worker at the time of service. Specimens will be discarded per site standard procedures after results are documented.

Additional blood obtained for HIV tests is described in Section 5.

Biospecimens will be taken by trained health care providers in designated areas at study sites using locally appropriate personal protection and biohazard containment procedures. Samples will be stored under appropriate environmental conditions in designated areas of study sites until they can be transported to the testing laboratory (either within the study site or externally). Details of handling, storing, transporting, analyzing, documenting, and disposing of biospecimens will be clearly outlined in standardized operating procedures prior to study start, and a log will be used to ensure accountability for specimens.

As part of the standard of care for all PrEP clients, cohort participants will also receive:

- Standard HIV testing at clinic visits (schedule of testing may differ among PrEP methods and across countries)

- Standard safety laboratory measures depending on PrEP method, performed per local standard of care (e.g., creatinine testing for oral PrEP) and national guidelines

5 STUDY COMPONENT 1A: CAB PREP HIV TESTING ALGORITHMS

5.1 Overview

Many current HIV testing algorithms utilize a series of 3rd generation antibody (Ab) rapid tests to diagnose HIV infection. However, individuals who start CAB PrEP during acute infection or who acquire HIV on CAB may have delayed seroconversion and delayed detection of HIV infection by current methods, which increases risk of resistance to the INSTI class of antiretrovirals for HIV treatment. The U.S. FDA guidance for HIV testing for CAB PrEP includes the use of 4th generation antigen/antibody (Ag/Ab) tests and HIV RNA tests to detect acute infection but monitoring for HIV infection with CAB PrEP using these tests could pose major implementation challenges.

This nested study will address a key implementation question for CAB PrEP by evaluating national HIV testing algorithms against alternative combinations of antibody, antigen, and nucleic-acid-based HIV tests to determine if the current U.S. FDA-recommended CAB PrEP testing requirements can be simplified. The additional sample collection and testing will also help diagnose HIV infection in ambiguous cases and allow for future drug resistance testing to estimate the delay in diagnosis of HIV and the development of drug resistance in individuals who are HIV infected on CAB PrEP. This study will contribute important real-world data for developing guidance for HIV testing with CAB PrEP.

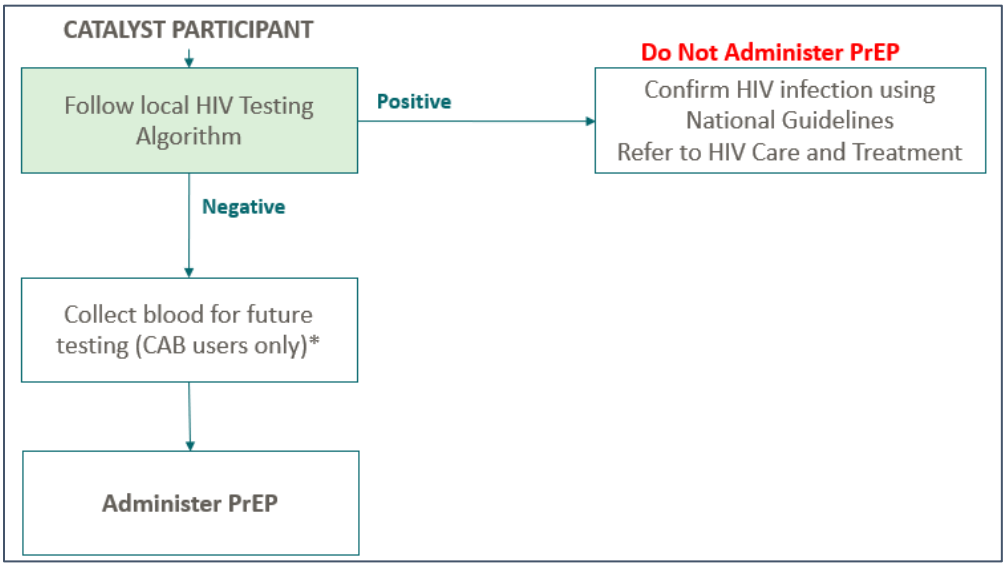
Cohort members who select CAB PrEP will undergo routine HIV screening per the standard of care at their local site. Individuals who test HIV negative per standard of care will have blood collected and stored by trained health facility staff for future ethylenediaminetetraacetic acid (EDTA) testing, and then will proceed to CAB PrEP administration (Figure 5). The blood will be sent to a local laboratory and processed to plasma, dried blood spots, and/or cell pellet remnants for use in evaluating alternative HIV diagnostic tests that are available in-country, which could include nucleic acid testing, antibody testing, and/or antibody/antigen testing. Additional quality control testing may be performed at the discretion of the MOSAIC LC. The MOSAIC LC is a team of laboratory scientists and administrative staff that will provide support for CATALYST laboratory considerations.

Prior to CAB initiation, plasma will be drawn for an HIV RNA test which will be resulted back to the clinician. In the countries that require RNA testing as part of their national guidelines for CAB initiation and have publicly available RNA testing for HIV negative individuals, RNA testing will be performed and returned to the site within local turnaround times In countries that do not require RNA testing as part of national guidelines, testing will be done at study-contracted laboratories and may be batched.

Individuals with detectable HIV RNA or any positive HIV result at any visit may need further HIV confirmatory testing and/or referral to clinical care. These cases will be investigated in real time.

Plasma for HIV additional HIV testing will be collected at all PrEP-related clinical visits in which standard of care HIV testing is performed among all CAB PrEP users. The purpose of this testing is to see if this additional test can identify participants who have acquired HIV during CAB PrEP use but but was not detected by local standard of care testingThe post-initiation HIV testing will be done retrospectively in batched intervals and will not be returned to the site unless clinically indicated or for quality control.

Figure 5. Testing procedures for participants initiating and using CAB PrEP



*For CAB PrEP initiation, the results from HIV RNA done as part of additional testing after CAB PrEP administration will be returned to the participant within standard turnaround times in the local lab in countries that require RNA;. all other HIV RNA testing will be batched and performed retrospectively at periodic intervals. Return of results may not follow standard local lab turnaround times. In some countries, clinics may need to wait for HIV RNA result before administering CAB PrEP, depending on NMRA guidance.

5.2 Selection of study population

All cohort participants who are initiating CAB PrEP will be included in this component. Consent for receiving the additional HIV assays will be provided in the informed consent form for the main study.

5.2.1 Inclusion and exclusion criteria

Participants must be enrolled in CATALYST study and will be included if they are initiating CAB PrEP and have no contraindications for starting CAB PrEP per national regulatory guidance.

5.2.2 Sampling and recruitment

Participants in the nested study will follow the recruitment steps outlined in Section 4.2.2. The main informed consent form for the study cohort in Stage II will explain the additional HIV testing that will occur if the participant chooses to initiate CAB. However, the participant is free to decline any study procedures, including the additional blood draw, unless country guidelines require HIV RNA testing prior to CAB initiation.

5.2.3 Sample size for the CAB PrEP HIV testing algorithm nested study

As noted in Section 4.2.3, we anticipate there will be approximately 845 CAB PrEP initiators per country during Stage II, with an estimated total sample size for the testing component of 4,225 (845 CAB initiations within each of the five CATALYST countries).

5.3 Study procedures for the CAB PrEP HIV testing algorithm nested study

Participants will receive an assessment for PrEP readiness from site providers and/or counselors, including the standard 3rd generation rapid diagnostic test (RDT) (as per the national testing algorithm), assessment of potential HIV exposure in the past 72 hours (in case PEP is indicated) and clinical screening for AHI — all of which are standard of care. Those with a nonreactive RDT, not in need of PEP, and a negative screen for AHI will proceed to have blood drawn (through venipuncture) for additional testing, which may include:

- Third generation antibody-only tests (including a different brand of 3rd generation RDT than was used for the first 3rd generation RDT)
- Fourth generation antigen/antibody tests (could include RDT or centralized enzyme immunoassays); 4th generation enzyme immunoassay that will be conducted at the laboratory
- Nucleic acid tests (could include HIV RNA polymerase chain reaction [PCR] test, HIV DNA PCR test, or qualitative diagnostic tests to detect HIV nucleic acids)

The blood drawn for the additional testing will be stored and analyzed separately in cases of HIV seroconversion for PrEP drug levels, HIV drug resistance, and potentially other testing if needed. Additional quality control testing and pharmacokinetic testing may be performed at the discretion of the Laboratory Center.

Results from the initial HIV RNA test will be returned to participants, when available, and in instances when the results suggest the participant might have HIV infection. If participants are confirmed to have HIV infection following the additional HIV testing, participants will be counseled and referred to HIV care and treatment. At this time, an additional blood specimen will be collected, with the participant's permission, for HIVDR testing. Collection of this blood

specimen will be outlined in the main informed consent form for cohort participants in stages I and II.

5.3.1 Procedures at enrollment

The same procedures that take place for the main cohort apply to this subpopulation as well. If enrollment coincides with the desire to initiate CAB PrEP, the additional testing described above will occur at that time, and then subsequently for each CAB-related study visit. If the participant has already been enrolled in the cohort but would like to switch to CAB PrEP, the additional testing will be conducted at the first clinic visit during which the participant expresses desire to start CAB. Consent for the additional testing will be integrated into the main study cohort informed consent document. Quantitative and qualitative data collection related to the nested study will include the following:

Data collection for the HIV testing algorithm nested study includes:

- **HIV testing results**, including those entered in the participant's medical charts and the laboratory results (These results might be received as paper-based or electronic forms, depending on the site and country.)
- **Feasibility data**, including results from quantitative surveys and IDIs among a subset of providers involved in the testing processes to understand the acceptability/feasibility of conducting the additional blood draw and returning results to participants (See Section 7 for more details.)
- **Process data,** including tracking the length of time it takes to return results to providers and to participants for the initial HIV RNA test among participants in countries that require a pre-CAB PrEP HIV RNA test, and the proportion of participants who receive the results, if applicable.

5.3.2 Measures for CAB PrEP HIV testing algorithms nested study

- Frequency of AHI cases identified with each testing algorithm
- Overall sensitivity and specificity of the testing algorithms (will be descriptive if the sample size is too low)
- Feasibility determined through a combination of provider quantitative surveys, qualitative interviews, and logistical data (i.e., time for returning HIV RNA results to participants if applicable)

Importantly, use of these additional tests might require a strategy to confirm HIV infection that differs from typical confirmations outlined in the national HIV testing strategy. For example, if someone has a detectable HIV RNA result and nonreactive results from antibody tests, additional testing may be needed to confirm infection.

5.3.3 Laboratory methods

Testing performed at study sites and local laboratories will be performed per local standard of care using locally available SOP's and methods. The MOSAIC Laboratory Center will provide technical assistance and guidance as needed. Samples from participants who have consented may need to be sent to a laboratory in the United States for more sensitive testing or advanced diagnostics on a case-by-case basis.

6 STUDY COMPONENT 1B: PREVENTION EFFECTIVE USE NESTED STUDY

6.1 Overview

The prevention effective use nested study is a two-stage descriptive study to assess the feasibility and validity of collecting PEU data among CATALYST participants early in the study (henceforth referred to as the validation phase), and then to measure PEU by PrEP method and compare cost of preventive use for each PrEP method later in the study (henceforth referred to as the measurement phase). Results from this study will inform the conceptualization of PrEP coverage as a function of temporal adherence and risk, which will inform the design of service delivery approaches to optimize PEU.

Specific PEU nested study objectives for the validation phase are:

1. To measure completeness of self-reported data on PrEP use and sexual behavior gathered via a digital tool accessed by participants through short message service (SMS) on their phones
2. To assess the validity of self-reported PrEP use
3. To understand user experiences with the digital self-report tool
4. To measure PEU among oral PrEP and PrEP ring users by computing the proportion of days with condomless sex that were covered by effective PrEP method use

Specific PEU nested study objectives for the measurement phase are:

5. To measure prevention effective use among PrEP users over time
6. To describe variations in PEU among populations of interest
7. To compare the costs of enhanced service delivery per protected risk-day between PrEP methods

6.2 Population, sampling, and recruitment for PEU study

The PEU nested study will enroll new and existing PrEP users who are in the study cohort and follow them over time to capture how PEU might change over time. In the validation phase, the PEU nested study will be conducted only in two countries so that feasibility and validity can be assessed on a smaller scale; we will include Kenya and South Africa because their high mobile phone penetration will enable faster recruitment. Additionally, the validation phase will be restricted to oral PrEP and PrEP ring users. In the measurement phase, the PEU nested study will be conducted in all five CATALYST countries: Kenya, South Africa, Lesotho, Uganda, and Zimbabwe, and will include all three PrEP products

6.2.1 Validation phase population, sampling, and recruitment

In the validation phase, the PEU nested study will be conducted at four study sites (two in South Africa and two in Kenya). These sites will be selected by the study team purposively for serving

a range of client populations (including AGYW ages 15–25 years and FSWs), based on recent service statistics.

To be eligible for the PEU nested study, participants must:

- Be enrolled in the CATALYST study at a PEU-selected study site
- Obtain oral PrEP or PrEP ring on enrollment visit
- Have a mobile phone they do not share with anybody[d]
- Able to receive mobile money

All enrolled CATALYST participants meeting the PEU eligibility criteria at a PEU site will be recruited for the PEU sample. After seeing the PrEP provider at their enrollment visit, an interviewer will screen CATALYST participants at PEU sites for the PEU nested study and, if eligible, will read them the PEU consent form. Those who agree will be shown what the self-report tool will look like and how to respond to it. We will recruit participants consecutively at PEU sites until the sample size is achieved in each site. However, if study participants choose oral PrEP at substantially higher rates than the PrEP ring, we will cap the number of oral PrEP users in the PEU nested study at 60 per site and subsequently target only ring users for the nested study to ensure we get sufficient data on ring use.

6.2.2 Measurement phase population, sampling & recruitment

The measurement phase will include all five countries. We will purposively sample two study sites in each country to participate in the PEU nested study. Site selection will be based on having large numbers of clients on all methods in Stage I; the exact sites will be chosen prior to the implementation of Stage II. Like the validation phase, eligibility criteria for the measurement phase include being enrolled in CATALYST at a PEU-selected study site, having obtained PrEP on enrollment, and having a phone and be able to receive mobile money; however, during the measurement phase, our sample will include CAB PrEP users in addition to PrEP ring and oral PrEP users. While daily action is not needed for CAB PrEP users to be protected, gathering data on their HIV exposures while on PrEP, as well as exposures and PrEP use upon discontinuation, will be valuable to understanding PEU and making comparisons between methods.

6.2.3 Sample size

In the validation phase our primary outcome is completeness of data. The target sample size is 400 PrEP users, approximately split evenly between selected sites in Kenya and South Africa (n=100 per site). With this sample size, we will be able to estimate the probability of having complete data with excellent precision; the half-width of 95% confidence intervals for the outcome will be no more than 5% (conservatively assuming a base proportion of 50%).

[d] Daily access to an unshared phone will be an eligibility criterion to reduce the likelihood of unintended disclosure of PrEP use for those who share a phone with others.

Furthermore, assuming half of the PEU sample chooses oral PrEP, the method-specific completeness probability will have a half-width of no more than 7.1%.

In the measurement phase, approximately 1,000 cohort members will be enrolled in the PEU nested study across all five countries. If at least 200 participants per PrEP method have evaluable (complete) PEU data, then we will have a minimum of 85% power to detect a 15% difference in the proportion of risk-days covered between any two methods based on chi-squared tests conducted at the two-sided 0.05 significance level (where minimum power is obtained when the average PEU rate is 50%).

6.3 Study procedures for PEU study

This is a descriptive study embedded in the CATALYST study. In the validation phase, the PEU feasibility assessment will capture data from a subset of study cohort participants who use oral PrEP or the PrEP ring and will follow them for approximately four months. In addition to study procedures for the larger CATALYST study, PEU participants will be asked to respond to daily SMS messages over a period of six weeks starting at study enrollment (weeks 1–6) and again approximately 10 weeks post-enrollment (weeks 10-16). Those who consent to participate in the PEU nested study will be oriented to this digital self-report tool at enrollment by nonclinical staff. This system will send a daily message to participants over periods of six weeks to inquire:

1. What did you use for PrEP yesterday?
2. Did you have sex yesterday?
3. If yes, did you use a condom?

After six weeks, daily messaging will pause. Messaging will resume at 10 weeks post-enrollment and continue for an additional six weeks. This second period of messaging will overlap with the participant's first quarterly PrEP follow-up visit to the study site. During that visit, all PEU participants will be asked to respond to a short survey about their experience with the digital tool. In addition, those on oral PrEP will be asked for a blood draw to prepare a dried blood spot (DBS) sample in the validation phase. A tenofovir concentration level and a tenofovir-diphoshate assay will be run from the DBS to verify self-reported data regarding oral PrEP use within the last 48 hours and the average over the last 3 months. Ring users will also contribute validity data; however, rings will be collected at their 1-month return visit (per standard of care for ring users) rather than their 3-month visit. Residual ring levels will be assessed.

The digital self-report tool will be incentivized to encourage responses. Every day that a participant responds they will be credited mobile money (or similar), regardless of what responses they give. Whether they use PrEP or not; whether they use a condom during sex or not, they will receive the incentive. Incentives will be greater for those who respond more consistently. In addition to financial compensation, responses will be encouraged through brief messages sent via the digital tool designed to leverage behavioral economics concepts such as loss aversion.

Honest responses will be encouraged through careful orientation to the tool at recruitment (describing anonymity, that we will not share responses with providers, and that honest results will most benefit future PrEP users) and reminders of these themes sent via the digital tool.

If the results of the PEU analysis from the validation phase suggest value in measuring in the measurement phase, we will expand the measurement of PEU to all five countries. In the measurement phase, the frequency of obtaining information via the digital tool is expected to involve several cycles of six-week data capture, roughly at baseline, the first quarterly PrEP follow-up visit, the second quarterly PrEP follow-up visit, and the third quarterly PrEP follow-up visit to evaluate changes in effective use over time and with increasing familiarity with the product. During the measurement phase, we will report cost of each method per PrEP-protected risk day in Uganda and Lesotho by utilizing data from a costing nested study (separate from the PEU nested study) in the two countries.

6.3.1 Procedures at enrollment

In PEU nested study sites, eligible participants will be consented for the PEU nested study at the CATALYST study enrollment visit. A waiver of parental consent will be requested for CATALYST participants ages 15–17 for this part of the study, due to the potential harm to the participant if a parent/guardian intercepted the phone messages. Potential participants will be informed that they will receive messages on their phones daily regarding sensitive issues and that these messages will continue for the designated period even if they no longer wish to take PrEP. At consent, participants will be told how they can stop receiving the messages if they wish. They will also be asked to inform the study team if their phone number changes over the course of the study so they can continue participation.

Their contact information (including phone number) will be indicated in the confidential CATALYST participant tracking database. From this database, anonymized lists of phone numbers will be shared via secure transmission with the SMS system operators. The PrEP method chosen at baseline and the scheduled date of the participant's PrEP follow-up visits will also be shared with the operators to enable them to send messages regarding the correct PrEP method and to send them on time.

Recruitment for the PEU nested study will be conducted by study personnel who have no clinical role in the health facility, to help assuage participant fears (and the potential for dishonest responses) that responses to PEU questions will be shared with providers. Participants who consent will be oriented to the self-report tool and the incentive structure.

6.3.2 Quantitative data collection for PEU study

This nested study involves some PEU-specific data collection tools and will also be linked to data being collected under the larger CATALYST cohort study.

PEU specific data collection tools include the following:

1. *PEU self-report tool:* During all periods of follow-up, information on daily PrEP use and sexual behavior recorded electronically by participants via SMS will be compiled by a subcontractor into a follow-up database. In addition to data on the three follow-up questions, data on the time of day the participant responded will be captured from the backend of the SMS systems.
2. *PEU module in Cohort follow-up survey:* At their clinic visit approximately 3 months post-enrollment, PEU participants will be asked about factors related to missing data; understanding of period of risk; opinions about the utility and ease of tracking PrEP use and sexual activity over time; and feelings of pressure to over-report PrEP use or underreport sexual activity.
3. *Drug concentration results during the validation phase only:* Results of drug concentration levels from oral PrEP users and ring users will be compiled into a secure database and linked to the PEU follow-up database using anonymous participant ID numbers. The lab data will also include the date the sample was taken.

The PEU study will also utilize data collected on the following CATALYST data collection tools:
1. *CATALYST enrollment questionnaire:* Data on age, gender, membership in specific groups of interest (FSWs, serodifferent relationship), and prior oral PrEP use
2. *CATALYST register data:* Dates of PrEP refill pickup, CAB injection, or PrEP clinic visits will be combined with PEU data
3. *CATALYST cost data:* Costs for enhanced service delivery of each PrEP method will be used to measure cost per protected risk-day by each method

6.3.3 Measures for nested PEU study

The primary outcome for measuring feasibility (validation phase) will be the percentage of complete data for each six-week period. Each day's data are considered complete if there is a response to each question asked, and the response options will include "no response" and "do not remember" to help differentiate from missing data that may occur due to issues with the technology or failure to respond at all. Comparisons will be made to understand variations in data completeness by PrEP method and groups of interest (e.g., AGYW and FSWs).

Other outcomes of interest for the validation phase include:

- Positive and negative predictive values of self-reported PrEP use in the last 48 hours and detectable parent tenofovir levels
- Positive and negative predictive values of self-reported ring use over the last month and residual ring concentration (<0.9 mg less than initial concentration for that lot representing non-use, 0.9-4 mg for some use, ≥ 4 mg for consistent use)
- Percent who say that the digital self-report tool helped them take PrEP
- Description of factors related to missing data and responses of "do not remember" or "no response"

The primary outcome for measuring PEU (measurement phase) will be the percent of exposure-days (days with condomless sex) in a month that participants were protected from HIV acquisition by taking PrEP for enough days before and after the exposure(s). This measure will be descriptively compared between oral PrEP and PrEP ring users; oral PrEP and CAB PrEP

users, and other groups of interest (e.g., AGYW vs. “older” women, FSWs vs. non-sex workers, Kenya vs. South Africa). For those who miss a reinjection of CAB, we will describe PEU in the post-CAB tail to characterize ongoing risk and effective PrEP use in the period of drug resistance risk. Additional PEU measures of interest include those listed below; these will be described and analyzed in the same way as the primary outcome.

- Percent of risk-days not protected due to non-use
- Percent of risk-days not protected due to use that was insufficient preceding sex
- Percent of risk-days not protected due to use that was insufficient after sex

Figure 6. Calculating prevention effective use for a woman on oral PrEP

√ Oral PrEP used
X Condomless sex (protected by effective PrEP use)
X Condomless sex (NOT protected by effective PrEP use

Week	Sun	Mon	Tues	Wed	Thurs	Fri	Sat
1	√	√	√	√	√	√	√
2	√ X	√	√	√ X	√	√	√
3	√		√	√	√		√ X
4	X		√ X	√	√	√	√
% of Risk-days covered = 1/5 = 20%							

For the purposes of this analysis, oral PrEP users will be considered protected if they took PrEP daily for the seven days preceding and seven days following condomless sex. Ring users will be considered protected if they used the ring the day before and the day of condomless sex. People who fail to reinject CAB will be evaluated based on the effective use of whatever PrEP method (if any) they choose to use after the missed injection.

Other outcomes of interest in the measurement phase include:

- Description of variation by method, population, and over time
- Percentage of people with 100% protected exposure-days who would be labeled non-adherent based on refill data
- Cost of enhanced service delivery per protected risk-day

6.3.4 Laboratory methods

To assess validity of self-reported PrEP use, we will measure drug concentrations from oral PrEP user’s blood and residual drug levels from ring user’s used rings among all those participating in the nested PEU study in the validation phase. The blood drawn for oral PrEP will

be taken approximately three months post-enrollment when the participant returns to the study site. It will be taken via venipuncture and used to create dried blood spots, which will then be shipped for analysis at a designated laboratory. Biospecimen collection will be conducted by clinical staff at the study site responsible for blood draws.

Rings will be collected approximately one-month post-enrollment when the participant returns to the study site. If the ring is still in use, the provider or participant will remove it during the visit and the participant can get a new ring. The used ring will be packaged by site staff and sent by study staff to the designated laboratory for residual dapivirine testing. Lot number will be included with the ring to assist with analysis.

The rationale for measuring ring residual drug levels at 1 month is to avoid the potential of removing a ring that has not been used for a full month. Since the provider is likely to have inserted (or assisted with inserting) the ring at enrollment, the 1-month visit is our best chance to capture the potential for a full month's use. In contrast, oral PrEP users may not return to the site 1-month post-enrollment and their drug concentrations will be more stable if measured at month 3. Furthermore, measuring at month 3 allows for us to capture more typical use than that we might observe in the first month.

At the laboratory, all testing materials (e.g., the DBS card, any remaining blood, rings), will be disposed of according to the laboratory's waste management procedures once analyses of the PEU validity outcome are completed.

Results of this analysis will not be communicated back to the facility or the participant because they have no bearing on clinical treatment. Results will be compiled by staff at the testing laboratory using a secure data entry system.

7 STUDY COMPONENT 2: PROCESS EVALUATION

7.1 Overview

The process evaluation will document implementation of the enhanced service delivery package (including quality improvement adaptations), assess ongoing perceptions of enhanced service delivery (i.e., acceptability and feasibility, barriers and facilitators) among providers and key stakeholders, and document other important implementation considerations (e.g., opportunities for PrEP and FP integration). This component, which will address the first study objective, involves gathering information on multiple implementation outcomes, such as acceptability, feasibility, and cost of enhanced service delivery. All sites will define the details of intended service provision through the development of SOPs. Operational feasibility will be assessed through baseline and periodic site assessments, service statistics, and review of existing quality improvement reports (developed as a part of the CATALYST QI Collaborative described in Section 1.3). Costs of implementation and ongoing operations will be captured through the costing nested studies in Lesotho and Uganda (described in Section 8). Furthermore, a quantitative provider questionnaire and pre-training attitude assessment will gather information about provider knowledge, practices, and attitudes around the delivery of PrEP choice. These will be complemented by qualitative interviews with a subset of providers. System-level barriers to and facilitators of enhanced service delivery will be obtained through qualitative interviews with key stakeholders at the national, subnational, site, and community levels. The qualitative data collection will be conducted at up to three time points during the study. Quantitative provider surveys and site assessments will occur every 6-months.

7.2 Selection of study population for process evaluation

7.2.1 Inclusion and exclusion criteria

All participants in this study component must be at least 18 years of age.

All providers who participate in clinical training at a site participating in the study on the ring or CAB through CATALYST will be eligible for the pre-training attitude self-assessment.

To be eligible for the provider questionnaire, individuals must currently provide some aspect of PrEP service delivery at a site participating in the study, including but not limited to PrEP clinicians, nurses, and counselors.

To be eligible for the site staff IDIs, individuals must currently be involved in providing or documenting PrEP services at a site participating in the study, including but not limited to PrEP clinicians, nurses, counselors, pharmacy staff, M&E staff, site supply chain managers, and laboratory staff.

Key stakeholders who meet the following criteria will be eligible to participate in stakeholder IDIs:

- Key Informants: Serve in an official capacity (such as MOH official, district health management team representative) in the Ministry of Health or serve as a manager at a study site.
- Community stakeholders: Represent a population, community, or other group interested in PrEP delivery.

Of note, it is possible that some providers who participate in the provider questionnaire will also participate in the site staff IDIs.

7.2.2 Sampling, recruitment, and sample size

7.2.2.1 Quantitative

All study sites across all five countries implementing CATALYST will participate in the site assessment, provision of service statistics, and QI reporting. The selection of specific site staff contributing information for the site assessments will vary, based on availability and requisite knowledge of the information needed (e.g., commodity stock status).

All providers participating in the clinical ring training (Stage I) or the clinical CAB training (Stage II) will be asked to complete a pre-training attitude questionnaire.

Approximately three randomly selected service providers from each CATALYST site will be selected every six months during implementation, with the first assessment occurring approximately 3-months into the study period. To randomly select providers, the study staff members will write the names of all eligible providers on the day of data collection on slips of paper and will put the slips in a box or similar container. In the presence of clinic staff and the research staff, three names will be selected from the box. Over the study's duration, we anticipate interviewing approximately 600 providers, assuming quantitative data collection

occurs every 6-months for up to three years, with three providers at approximately seven sites per country interviewed per data collection point. The sample size is based on both feasibility and ensuring equitable representation across staff cadres and study sites.

7.2.2.2 Qualitative

For the qualitative component, study staff will purposively select approximately two sites per country (10 sites selected in total per data collection period), with selection driven by performance, which will be gauged qualitatively by reviewing site-specific PrEP uptake, provider acceptability, and the success of enhanced service delivery adaptations provided in the QI briefs. Sites will be selected to represent both high and low performance levels, with input provided from the local research teams, to allow for comparison across high and low performing sites in analysis. Once sites are selected, research staff will contact the In-Charge of selected sites to explain the additional data collection and schedule dates for data collection (see section on study procedures for more details). We anticipate conducting three rounds of qualitative data collection for the process evaluation, including one round in Stage I, another round occurring within the transition from Stage I and Stage II, and one final round in Stage II. Of note, the second round of qualitative data collection will depend on the length of Stage I. If Stage I is relatively short in duration (i.e., a few months), depending on the timing of the approval of CAB PrEP per country, the second round of qualitative data for the process evaluation may be omitted or abbreviated given logistical constraints.

Within the sample of qualitative sites, we will sample approximately three staff members per site for round of site staff IDIs (anticipated to be two rounds in Stage I and one round in Stage II). Providers will be selected purposively to capture perspectives from different cadres and will be based on staff availability; efforts will not be to interview the same providers longitudinally, although this might happen. The Study Coordinator, or another trained study staff member, will approach service delivery staff within the selected study sites and invite them to participate. If more than three eligible staff are present and available on the day of data collection, selection will be purposive to include staff most frequently engaged in PrEP service delivery. If possible, study staff will be interviewed on the same day as to the invitation to participate in a qualitative interview. If the interview needs to occur on a subsequent day, study staff will make an appointment with the provider and will contact the provider a few days ahead of the scheduled interview time as a reminder. If the provider does not show-up for the interview, or is otherwise unavailable, interviews will be rescheduled as needed, and if necessary, another provider will be selected. The sample size per country is presented below in Table 9.

For the key informant interviews (KIIs), the Study Coordinator will invite individuals affiliated with the Ministry of Health, including representation from HIV, reproductive health, and/or maternal child health programs at national and subnational levels (including members of the DHMT or their equivalent); facility in-charges responsible for PrEP to respond to questions regarding the organization of PrEP services as well as challenges and facilitators to its implementation; and possibly supply chain managers and laboratory directors. Selection of these participants will be purposive; we seek to interview the policymakers and decision-makers most engaged in PrEP

service delivery in the study areas. Site in-charges for each of the two sites selected for qualitative interviews will be prioritized. Approximately five KIIs will be conducted per country for a total of 25 per round of qualitative data collection.

Community stakeholder interviews will be conducted to provide insight into community attitudes and social norms regarding PrEP use in the facility's catchment area. Community stakeholders may include community leaders, youth advocates, religious leaders, members of civil society organizations, learning institutions, and other community-based organizations (see Section 11 for more detail). Study team members will recruit key informants purposefully based on 1) their lived experiences and how they relate to the study/its outcomes, and 2) vicinity to HIV prevention work both nationally and in their personal lives. Recruitment and interviews may be conducted virtually or face-to-face. Approximately five community members per country (approximately 2–3 per selected site) will be recruited for IDIs for a total of 25 interviews per round of data collection.

To recruit both the key informants and community stakeholders, site staff will purposefully reach out to individuals in official capacities (e.g., members of the DHMT, local community organizations) by phone, by visiting their office in person, or by approaching them at a study-related event, such as a stakeholder meeting. In a private location or where auditory privacy can be maintained, the study staff member will explain the study to potential key informants and community stakeholders, and if the participant shows interest, the study staff member will schedule an interview. The study staff member will call the participant a few days prior to the scheduled interview to confirm the appointment. Interviews will take place at a location of the participant's choosing, such as the participant's office, where privacy can be maintained. Interviews may also happen virtually. Missed interviews will be rescheduled as needed. If the participant changes their mind about participation or can longer participate in the interview due to a change in circumstance, another participant will be selected.

At each of the three time points in which qualitative data will be collected, a comparative case study approach will be used to inform the qualitative component of the process evaluation,[59,60] with each site selected serving as a "case," and key informants providing both site-specific and country-level insights. Data gathered from policy makers, community leaders, and other key informants that is relevant to a site will be treated within the bounds of the "case". Choosing two sites per country will allow for both within country and cross-country comparisons of high and low performing sites. Additional country-specific analyses might be carried out if warranted by the data, such as by conducting a cross-country comparison of key informant interviews to better understand policy- and structural-level barriers and facilitators to implementation from this perspective. Interviewing approximately three staff members per site, in addition to interviewing several local community stakeholders, will allow for triangulation between site interviews to derive a more complete, nuanced case description. Although no set sample size exists for case study research, choosing 10 sites falls within recognized rules of thumb for this methodology.[61] Additionally, the standalone sample sizes for each type of population (e.g., clinic staff, community stakeholders, and key informants), as outlined in Table 9 below, should be sufficient to identify key, population-specific themes.[57]

Table 9. Sample size for qualitative components of the process evaluation by stage

Country	Site Staff IDIs		Key Informants Interviews		Community Stakeholder Interviews		Total
	Stage I	Stage II	Stage I	Stage II	Stage I	Stage II	
Lesotho	12	6	10	5	10	5	48
Kenya	12	6	10	5	10	5	48
South Africa	12	6	10	5	10	5	48
Uganda	12	6	10	5	10	5	48
Zimbabwe	12	6	10	5	10	5	48
TOTAL	60	30	50	25	50	25	240

7.3 Data collection procedures for the process evaluation

Quantitative and qualitative interviewers for the process evaluation will be trained in research ethics and study procedures prior to initiating any data collection in trainings similar to those described in Section 4.3 for the prospective cohort. All data collection with facility staff and policymakers will be conducted in English. Community stakeholder interview guides will be translated into the appropriate local languages, and that translation will be checked by a translator as well as data collection teams during training activities. Interviewers will be fluent in English and the local language so that community participants can choose their preferred language for the interview. All data collection tools will be pretested with volunteers during data collection training to assess question clarity, flow, translation (if needed), correct consent procedures, secure storage and transfer, and interviewer performance.

7.3.1 Study procedures for the process evaluation

Prior to study implementation, members of the study team will first seek a meeting with all site in-charges to introduce the study and the process evaluation. The facility in-charge will also be notified prior to conducting facility surveys, provider surveys, and provider IDIs. Written informed consent will be obtained for the provider and staff surveys and qualitative IDIs in which participants are being asked about their knowledge and opinions. For data collection involving questions on operations within the facility, such as for the facility surveys, verbal permission from the in-charge will be sought prior to data collection.

7.3.1.1 Quantitative data collection tools

Quantitative data will be captured in an electronic data collection system. See data management section for more details.

Site assessment: Structured questionnaires, captured electronically in the CATALYST study database, completed close to baseline and every six months thereafter will document how PrEP services are being provided and any challenges to intended service delivery; client flow; how PrEP stock and laboratory samples are managed; facility hours of operation and staff capacity; and infrastructure. These will be completed by a research assistant in collaboration with a variety of site staff responsible for different aspects of service delivery (e.g., triage nurse, HIV testing counselors, pharmacy staff, laboratory staff, and community health workers) during facility visits. Verbal permission from the facility in-charge will be sought prior to data collection. The site assessment will also involve a review of relevant site standard operating procedures (SOPs). At a site assessment conducted towards the end of the study, study staff will also invite available site staff complete an anonymous questionnaire (either paper-based or electronic, depending on the site) related to assessing project sustainability using a validated tool[62].

Pre-training provider attitude assessment: As part of the requirements prior to attending CATALYST's clinical training for PrEP ring provision (Stage I) and CAB PrEP (Stage II), providers will be asked to conduct an anonymous, quantitative self-assessment of their attitudes toward existing and novel PrEP methods and providing them to specific populations such as AGYW.

Provider questionnaire: Research assistants will administer a structured questionnaire to a cross-section of providers as close to the start of study implementation as possible and every six months to ascertain the knowledge, acceptability, appropriateness, and feasibility of enhanced service delivery (the package, offering choice, and the products) using validated measures.[63] In addition, when applicable, providers will provide feedback on the acceptability and feasibility of receiving and reporting back to clients the results from the additional HIV testing for CAB PrEP (discussed in Section 5). Written informed consent will be obtained prior to administration of the questionnaire.

Service statistics: De-identified aggregate data on PrEP service provision (such as number of PrEP visits by client type and quantity of PrEP dispensed) will be obtained monthly from the site and, when possible, up to six months prior to study implementation. These data will aid understanding of changes in PrEP uptake during the intervention period. These data will comprise both study participants and non-study participants.

7.3.1.2 Qualitative data collection procedures

All qualitative interviews will take approximately 60 minutes. The interviews related to the process evaluation will occur at up to three time. Semi-structured interview guides will be used**.** All interviews will be audio-recorded, pending permission from the participants, and the audio recordings will be stored in a secure, password-protected online folder, only accessible to key study staff, until transcription has been verified. At that point, audio recordings will be destroyed from recording devices and online files. Interviews will be transcribed and translated by trained research staff.

Qualitative site staff interviews: Trained interviewers will conduct IDIs with consenting site staff, using semi-structured interview guides constructed based on CFIR domains, to better understand the drivers of implementation success or challenges. Participants will also be asked questions regarding their perceptions of community acceptance of HIV prevention, PrEP, and PrEP choice, as well as how community norms affect their motivation to prescribe PrEP.

Qualitative key informant interviews: To understand facilitators of and barriers to delivering PrEP choice from decision-makers' perspectives, face-to-face or virtual semi-structured interviews will be conducted with key informants, including managers and policymakers at the facility, subnational, and national levels. Managers and policymakers will be selected based on their technical oversight and leadership in the project implementation.

Qualitative community stakeholder interviews: Using semi-structured in-depth-interview guides, trained interviewers will ask community leaders about their perspectives on the new PrEP methods and their provision in both Stage I and Stage II. Community leaders will also be asked about their perceptions of community acceptance of HIV prevention, PrEP, and PrEP choice. Interviews will be conducted in person, if possible, or virtually, as needed.

Quality improvement knowledge briefs: QI briefs will be completed quarterly by QI coaches (described in Section 1.3) at each site using a standardized template. These qualitative reports will describe bottlenecks in service provision identified through the QI process, adaptations made to address the bottlenecks, and the impact of the changes on QI indicators. These reports will serve as a data source for the qualitative case study analysis.

7.3.2 Measures for the process evaluation

- Community and policy-level outcomes include:
    - Community acceptance of PrEP and PrEP choice
    - Perceptions of barriers and facilitators to implementation of PrEP choice at the community, subnational, and/or national level
- Site-level outcomes include:
    - Feasibility of offering informed PrEP choice
    - Feasibility of laboratory services for offering informed PrEP choice
    - Number of providers who are trained on and offer PrEP choice (obtained through the site assessments)
    - Proportion of PrEP clients in the study cohort who are offered PrEP choice and receive quality counseling (obtained through cohort participant questionnaires)
    - Overall changes to the provision of PrEP during the course of study implementation (obtained through service statistics)
- Provider-level outcomes include:
    - Acceptability, feasibility, and appropriateness of providing the enhanced service delivery package and offering PrEP choice
        - Barriers to and facilitators of implementing the enhanced service delivery package and PrEP choice (Qualitative interview guides will be developed using CFIR domains.)

8 STUDY COMPONENT 2A: COSTING COMPONENT (LESOTHO AND UGANDA ONLY)

8.1 Overview

The objective for this study component is to determine the average and incremental unit costs of providing oral PrEP, the PrEP ring, and CAB PrEP for women seeking health services (e.g., HIV prevention and family planning), in Lesotho and Uganda. All study sites in the two countries will participate in the costing analysis.

Data collection for the nested costing studies includes:

- **Qualitative data** from staff interviews at each facility to determine the resources used, e.g., personnel involved, salaries, supplies, equipment and furniture, overhead costs, etc.
- **Study procurement or national source data** for items that are obtained centrally (e.g., HIV test kits)
- **Time-motion data** from observations of client movement through study sites to capture the time spent at each step of PrEP service provision

8.2 Sample size determination

The cost data will be collected from all participating study sites in Lesotho and Uganda. Cost data will be collected from program managers at sites in Lesotho and Uganda when all three forms of PrEP are being offered. To validate cost information and to identify variations in the use of staff time and actual resource use, up to 40 participants will be followed at each study site as part of a time-motion study, identifying the time required and the resources used in the delivery of oral PrEP, the PrEP ring, and CAB PrEP.

8.2.1 Sampling procedures

Cost data will be collected from all sites offering the three forms of PrEP to determine the average and incremental unit cost of each service. In addition to the facility-based cost data, time-motion data will utilize a convenience sample based on client visits that occur during the week of data collection. Data collectors will ensure they obtain time-motion data from a minimum of five participants for each PrEP method at each site, with a goal of collecting time-motion data from approximately 40 participants across all methods at a site. The time-motion data should include the different types of visits (initiation, refill, etc.) for each method.

8.2.2 Study subject recruitment

Site staff will be informed about the study and the study procedures. Research assistants will work with site staff to identify potential clients for the time-motion study. Study participants seeking services at the study sites during the days of data collection will be approached consecutively about participating in the time-motion study. Recruitment will cease once approximately 40 participants have been enrolled per site. Following check-in at the site, study

staff will briefly explain the time-motion study to potential participants using an approved recruitment script. Potential participants will first be approached in the waiting area and if audio privacy cannot be maintained, study staff will ask the potential participant to move to a place within the facility where auditory privacy can be maintained while they explain the study and seek consent. Those who consent to being followed will participate in the time-motion study. To help maintain privacy, study staff accompanying consenting participants for the time-motion study will not enter the room where participants interact with providers but will wait outside the room to maintain an accurate time assessment. Participants in the time-motion study will be study cohort members, but participation in the time-motion study will require separate informed consent.

8.3 Data collection methods

8.3.1 Recruitment and training of data collection team

A senior health economist will lead the costing team in each country and will oversee all cost data collection and training of the data collection team. The senior economist will lead the collection of costing data at each of the study sites. As study lead, they will supervise the rest of the team, including approximately two research assistants per country who will be responsible for collecting the time-motion data and interviewing program managers for the facility-based costing element. These research assistants will have prior experience collecting data for costing studies and will undergo specific study training, including in research ethics, prior to implementation.

8.3.2 Pre-testing of data collection processes

Pretesting of the time-motion instrument will occur at a pre-selected site in one of the countries. This pretesting will be performed after the training and after IRB approval has been received. After pretesting is completed, the forms will be modified based on the feedback from the pretesting and finalized. The facility-based costing form will be in English only since it is expected that the research assistants completing these forms will be fluent in English.

8.3.3 Data collection procedures

Prior to the arrival of the data collection team, the facility-in-charge (or managers, as appropriate) will be contacted and informed about the costing nested study aims and the data collection methods that will take place. In addition, they will be consulted about scheduling to arrange dates that are convenient for both the team and the facility. Finally, the in-charge will be asked to designate one or more staff who can assist with the completion of the facility-based costing form.

The study lead will travel to all sites for the costing component to avoid any inconsistencies in data collection. They will work with the staff who have been designated to help collect the programmatic and financial data and/or documents and records needed to complete the facility-based costing form. It is expected that completing this form will take approximately one to two days per site.

For the time-motion component, research assistants will be assigned to all sites in Lesotho and Uganda. Upon arrival, the site's facility-in-charge will introduce them to staff and inform staff about the study and study procedures. Once eligible participants are recruited, they will be given the opportunity to provide informed consent, and those consenting will be followed for the time-motion study. Research assistants will identify the activities at each visit that are study-related and not part of routine service delivery, so that study-related costs can be excluded from the analysis. It is anticipated that research assistants will spend approximately one week at each study site, with one research assistant being responsible for the time-motion study and the other responsible for the facility-based costing analysis.

Data collected from each site will include costs related to personnel, materials/supplies (including commodities), equipment/furniture, and overhead (utilities, rental value of the facility, etc.). Shared costs used by different forms of PrEP services will be allocated based on numbers of client visits and staff time spent per visit for each method.

9 STUDY COMPONENT 2B: COMMUNITY ACCEPTABILITY

9.1 Overview of community acceptability nested study

The goal of this component is to understand community acceptability of informed PrEP choice, especially among primary PrEP influencers within communities (parents/caregivers and partners of both existing and potential PrEP users). More specifically, the two subobjectives are to: 1) understand how these primary PrEP influencers describe their role in support of PrEP choice; and 2) understand the behavioral and social drivers behind their support (or lack of support) of PrEP choice. The objectives will be accomplished by leveraging the qualitative IDIs being conducted among community members and leaders as part of the process evaluation (Study Component 2) and IDIs among PrEP users conducted as part of the cohort (Study Component 1) and conducting IDIs and FGDs with parents/caregivers and partners of existing and potential PrEP users, which are unique to this component. The methods described below focus on the study population of PrEP influencers, as other study populations have been described elsewhere.

9.2 Selection of study population

To understand community acceptability of PrEP choice, we plan to conduct IDIs and FGDs among community members who serve as primary influencers of AGYW PrEP users, including parents/caregivers and partners of existing and potential AGYW PrEP users. Partners and parents/caregivers of existing PrEP users will be identified directly from the cohort of PrEP users (i.e., during the IDI and/or clinic visit questionnaire while recruiting for this study component, cohort members will be asked whether partners and/or parents know about their PrEP use and how supportive they are; further description provided in section 9.2.2).. Therefore, this population will represent positive deviance, i.e., primary influencers who are aware of and are supportive of their partner's or child's PrEP use. This perspective will provide critical information on potential factors that cultivate support for PrEP use and PrEP choice, the desired role in encouraging and supporting PrEP use and choice, and the perceived role of the community-based PrEP demand generation activities in fostering influencer support. We will also collect data from parents/caregivers and partners of potential PrEP users (i.e., those who are not currently aware of any PrEP use by partners/parents) because these populations will represent more typical community norms around the acceptability of PrEP and PrEP choice compared with the supportive partners/parents of existing users.

9.2.1 Inclusion and exclusion criteria

Inclusion criteria for primary PrEP influencers of existing PrEP users:

- Currently has an adolescent or serves as a caregiver for an adolescent (AGYW ages 15–24 years) who is currently using PrEP or has recently used PrEP as part of the CATALYST study OR is a partner of an AGYW who is currently using PrEP or has recently used PrEP as part of the CATALYST study (oral, ring, or CAB)

- Resides within the catchment area of a clinic involved with the CATALYST study
- Is 18 years of age or older (For partners, both partners must be 18 years or older)

Inclusion criteria for primary PrEP influencers of potential PrEP users:

- *For partners:* Currently has a sexual partner (AGYW ages 18–24 years) who is not currently known to be using PrEP and has an HIV status that is negative or unknown (to the best knowledge of the partner)
- *For parents/caregivers:* Currently has and resides with a child or acts as a primary caregiver for a child (AGYW ages 15–24 years), who is not currently known to be using PrEP and has an HIV status that is negative or unknown (to the best knowledge of the parent)
- Resides within the catchment area of a clinic involved with the CATALYST study
- Is aged 18 years or older (For partners, both partners must be 18 years or older)

Exclusion criteria for primary PrEP influencers of existing or potential PrEP users:

- Unable or unwilling to provide written informed consent
- Unwilling to have the interview or focus group discussion audio-recorded

9.2.2 Sampling and recruitment for nested community acceptance study

Primary PrEP influencers of existing PrEP users will be identified through snowball sampling of cohort members. In Stage II, cohort members will be asked whether they have a partner and/or parent who currently knows about their PrEP use during the brief follow-up structured questionnaire administered during PrEP clinic visits. If AGYW cohort members respond affirmatively, participants will be asked at the end of the interview during periods of recruitment for the community acceptance nested study whether they would be willing to have study staff interview their parent and/or partner. If a participant reports disclosing PrEP use to a partner or parent/caregiver during a qualitative IDI, similarly the data collector may ask the participant at the end of the interview if they would be willing for the study to talk to their parent and/or partner. If the participant is willing, study staff will provide a card containing contact information for study staff that cohort participants can provide to their parents and/or partners. When partners or parents are contacted, study team members will explain the study and schedule IDIs with interested partners and/or parents.

Primary PrEP influencers of potential PrEP users will be identified using purposive sampling, with an emphasis on identifying “typical” community members who fit one of two profiles: parents/caregivers of AGYW (ages 15–24 years) or men who have sexual partners who are AGYW ages 18–24 years, with no current knowledge of PrEP use among children or partners, respectively. For partners, we will employ age-stratified purposive sampling to ensure a representative sample of younger partners (defined as partners ages 18–24 years) and older partners (defined as ages 25 years and older). Members of this population will be identified by advertising the nested study at community meetings and posting flyers or other recruitment materials within the community and through community leaders. Interested participants will be provided the contact information of study staff for further information, screening, and scheduling.

9.2.3 Sample size

Primary influencers of PrEP users in the CATALYST study will provide critical information on supportive factors, and thus will be scheduled for IDIs to allow for deeper exploration. For primary influencers of potential PrEP users, FGDs will be scheduled to allow for discussion and debate between community members.

For PrEP influencers of existing PrEP users, we will conduct IDIs with approximately 30 partners, seeking maximum variation in terms of age, and with 30 parents/caregivers. For parents/caregivers, although cohabitation with the PrEP user is not a requirement for study participants, potential parents/caregivers who are cohabitating with the PrEP user will be prioritized for IDIs. Although research shows that thematic saturation can mostly be achieved through 16 IDIs,[57] we plan to conduct approximately 30 IDIs with parents/caregivers and 30 IDIs with partners of existing PrEP users, based on country-specific considerations. More specifically, interviewing six parents/caregivers and partners per country will most likely ensure that main country-specific themes will be identified as there is general acceptance that main themes can be identified within 4-6 IDIs.

For PrEP influencers or potential PrEP users, we will conduct approximately 30 FGDs, including 10 focus groups with young partners, 10 focus groups with older partners, and 10 focus groups with parents/caregivers. Approximately 6–10 participants will take part in each FGD, although fewer or more may participate depending on the total number of eligible participants who are interested and available. The FGD will proceed with a minimum of 4 participants. We will aim to conduct approximately three FGDs per country, including two FGDs with young partners, two FGDs with older partners, and two FGDs with parents/caregivers, depending on feasibility and thematic saturation. Evidence suggests that most themes are found within the first focus group and that all themes are identified within three FGDs,[58] suggesting this sample size will likely ensure we will identify both country-specific and more general themes within each population.

IDIs and FGDs may be conducted within only one or two sites within each country for reasons pertaining to feasibility and logistics. Table 10 provides a summary of the various study groups and the associated target numbers of IDIs and FGDs to be completed with each.

Table 10. Summary of study groups and associated target numbers of FGDs

Population	Subgroups	Data collection method	Target sample size per country	Target sample size (total)	Type of sampling
Primary influencers of existing PrEP users	Partners (maximum variation in terms of age) Parents/caregivers	In-depth interviews	6 IDIs per country, per subgroup	60 IDIs (30 per sub-group)	Snowball sampling
Primary influencers of potential PrEP users	Younger partners Older partners Parents/caregivers	Focus group discussions	2 FGDs per country, per subgroup	30 FGDs	Purposive sampling (age stratified for partners)

9.3 Community acceptance nested study procedures

9.3.1 Procedures at enrollment

IDIs will take place either in person or virtually, at a location of the participant's choosing. The interviewer will ensure that audio privacy can be maintained at the location selected for the interview. A few days prior to the interview, study staff will contact the participant to remind them of the appointment. Interviews for participants who do not show up for the initial appointment will be rescheduled. If the participant does not come to the rescheduled appointment, the participant will be replaced.

FGDs will be conducted in a central location within the community. Study staff will contact participants a few days before the scheduled FGD to remind them of the appointment. The FGD will proceed with a minimum of 4 participants, and a maximum of 12. Study staff doing the recruitment will confirm availability at the specified time for the FGD to ensure adequate participation. If fewer than four participants are present at the specified time, the FGD will be rescheduled.

All FGD and IDI participants will provide written informed consent prior to the start of an FGD or IDI. FGDs and IDIs will be conducted using the approved data collection guides while allowing some flexibility to explore relevant topics. Basic demographic questions will be asked for each participant prior to the start of the FGD (individually and privately). All FGDs will be audio-recorded. Participants who do not agree for the IDI or FGD to be audio-recorded will not be eligible. FGDs will take place in a central location within the community, such as a school or community center, where auditory privacy can be maintained for the duration of the FGD.

9.3.2 Qualitative data collection

As is common in qualitative research, questions may be modified, added to, or deleted in an iterative process as new information is learned during ongoing IDIs and FGDs to guide a detailed exploration of emerging themes. Topic guides may also be modified following staff training or pretesting. Such modifications will be made after original ethical approval is obtained and will not be submitted for approval; however, they will be limited to probes relevant to the overall topics described in this protocol. Any changes beyond these topics will be submitted for ethics review and approval prior to use. Each FGD is expected to last approximately 90 minutes. Each IDI is expected to last approximately 60 minutes. IDIs and FGDs will be audio-recorded.

10 DATA MANAGEMENT

Primary qualitative and quantitative data gathered as part of this study will be entered into electronic database repositories owned by FHI 360 and accessible to CATALYST country teams. Secondary data used for this study, including service statistics, will be handled per local regulations defined in a separate data management plan. Data cleaning and verification will be performed by in-country data managers prior to transferring to FHI 360. FHI 360 will further perform data verification and resolve any issues with local partners. Analysis will be led by FHI 360 with support from MOSAIC partners.

The primary database for the study, referred to as the CATALYST study database, will consist of datasets captured in Open Data Kit (ODK), or similar software. It will be hosted on a cloud-based server managed by FHI 360 and stored in the cloud until downloaded to an access-restricted FHI 360 SharePoint file. In this section, we describe different datasets and whether or not they are stored in this database.

10.1 Data management procedures for specific datasets

Cohort contact database: A secure cohort contact information database will be developed to facilitate cohort follow-up. This database will contain the study ID number and personal information, preferences for method of contact, dates of PrEP-related health facility visits, and participation in nested studies. The personal information to be collected is participant name, phone number (personal or of somebody participant chooses for study contact), community of residence and name of affiliated community health worker (in case of difficulty contacting the participant for follow-up), and birthdate.

Each participant's information will be entered at enrollment and updated throughout the study by study staff who already have access to these identifiable data. This database will be accessible only to those responsible for entering data, the local (in-country) CATALYST staff responsible for contacting study participants for follow-up and the data managers responsible for oversight.

To assist in tracking study participants over time, we may employ a variety of techniques including providing each cohort member with a card indicating their unique study ID number, taking fingerprints to identify them as study participants, and/or adding an inconspicuous mark to the client register/client files next to study participants' names. These approaches may vary by country and will be described in study SOPs.

- The unique study ID number will be unrelated to any medical record number. If an ID card is used, it will not include any indication that it is for a PrEP study or any text or images that might result in deductive disclosure of study participation.
- Sites that use sensors to scan fingerprints will use them only for people who identify themselves as a study participant and agree to fingerprinting. Participants would provide a fingerprint at enrollment, which would be stored in a secure file either within or linked

to the cohort contact database. When a participant returns to the site for a PrEP visit, they could be fingerprinted in confirm their identity as a study participant. Fingerprints will only be accessible to those who have access to the cohort contact database, and will be deleted at the end of the study.

- Some sites may choose to add a small asterisk or mark next to participant names in client records to facilitate data abstraction.

The cohort contact database will be specific to each country. These data will be securely stored on a cloud-based server with restricted access. It will be stored separately from study questionnaire data and not in the CATALYST study database. To access the password-protected cohort contact database, those with access will need to use an approved, password-protected device. This database will be deleted from all devices (if downloaded) and all servers one year after the end of CATAYST; this timeframe was selected because participants will be able to indicate their preference for being contacted for other (non-CATALYST) studies in the next year. FHI 360 will vet those requests and work through in-country MOSAIC partners to provide consenting participant contact information to external researchers.

Periodically, select de-identified data will be exported from this database to enable implementation of other aspects of the study. For example, monthly accrual information for CATALYST and the nested studies will be summarized, pulled from this database, and shared with the study team. In addition, dates of upcoming facility visits and phone numbers by participant ID number, will be exported from this database and shared with the PEU nested study data manager; this step is essential to implementing the SMS-based components of the PEU nested study and to understand the timing of implementation of the PEU SMS campaigns.

Quantitative client enrollment questionnaire, client follow-up surveys, facility assessment, and provider questionnaires: These quantitative data will be collected electronically by designated study staff on tablets via a secure data collection software, such as ODK. Questionnaire data will contain a participant's unique ID; names will not be collected on the survey form itself (see Section 14 for more detail). To ensure confidentiality, data collection devices will be password protected, and when they are not in use, they will be stored in a secure, locked room or cabinet. Uses of the devices unrelated to the study will not be allowed during the implementation period. Procedures will be put in place to minimize errors in data entry. These include, but are not limited to, restricting value ranges, establishing logic checks, and preventing form submission if data fields are incomplete for any required question. Programming of tablets will be tested and validated prior to deployment by study data mangers and/or analytic staff at FHI 360 and each country partner.

Data will be uploaded to the CATALYST study database daily. If internet connectivity is not available, data will be saved on tablets and uploaded at first opportunity. De-identified data will be routinely accessed on the server or securely exported for further monitoring and data cleaning. Any open-ended responses to survey questions that are collected in local languages will be translated by local country teams into English prior to analysis. Final datasets will include both the original language and English translations.

Questionnaire data will undergo a quality assurance check. Each country will have a data manager who is responsible for ensuring that data are collected in accordance with the protocol, to troubleshoot challenges in real-time, and to verify that the data have been uploaded to the appropriate location. Quality assurance procedures will be jointly developed and outlined in a data management plan that is agreed upon by the CATALYST country teams and FHI 360.

Serious Adverse Event Report and Social Harm Report forms: These forms will either be completed directly in an electronic data collection form, or completed on paper with data transcribed into the electronic data collection form. This form will be based in ODK or similar software but will have additional access restrictions compared to the primary CATALYST study database. Access to the SAE and social harm forms will be restricted to study staff and providers responsible for collection, follow-up, analysis, and reporting of relevant events. Reports will be extracted for reporting to product developers and ethics committees as required. Although client names will not be present in the dataset, other personally identifiable information, such as date of event, will be included. Reports that include these identifiers will be sent via a secure transmission system.

Chart/register review: Study staff will be responsible for obtaining CATALYST participants' data from clinical health records (registers, medical records) and entering them into the CATALYST study database. In sites with paper-based records, processes will be defined to ensure that data abstractors know which individuals in the register are CATALYST participants whose records should be gathered (e.g., sticker or written symbol next to name in register). Abstracters will have access to the cohort contact database and will use it to link individuals on the register (identified by name) with CATALYST participant ID numbers. Once they have found the participant ID number in the cohort contact database, they will open the separate chart review data collection form on their electronic data collection device and enter the participant ID number, along with the requested data from the medical charts.

In facilities with electronic medical records, we will work with facility data managers to develop a system to obtain electronic records only for study participants; this process will be defined in country-specific SOPs and designed to ensure minimal use of and confidential transfer and storage of personally identifiable information.

PEU self-reported digital data: These data will be gathered via SMS and exported to an Excel file by the PEU data manager. Prior to sharing that file with the analysis team, the PEU data manager will merge the participant ID number onto the data file using the associated phone number; subsequently, they will remove the phone number and upload the now deidentified dataset into the CATALYST study database for merging with other study datasets.

Qualitative data: All IDIs and FGDs will be digitally recorded. All interviews will be transcribed and translated into English, if conducted in a language other than English. When possible, recorded interviews will be simultaneously transcribed and translated from the original language to English by research assistants trained in transcription and research ethics. The local co-investigator or designated representatives (such as team supervisors) will check transcripts for completeness and quality. Once transcripts have been checked, audio recordings will be

deleted from all locations, including recording devices and computer files. Transcripts will be password protected and stored in a Microsoft SharePoint folder that is accessible only to those engaged in qualitative data analysis or its oversight. In transcripts, potentially identifying information such as proper names of people or places will be redacted from transcripts prior to analysis. Qualitative analysis will be done collaboratively between FHI 360 and in-country research partners. Completed transcripts will be uploaded into a qualitative software data package such as NVivo for coding and analysis. Qualitative data is not part of the CATALYST study database.

10.2 Data storage and access

Upon study completion, data will be cleared from all data collection devices, such as tablets and audio recorders, and all stored materials will be destroyed at the sites after permissions has been received from the investigators. Final survey datasets, IDI and KII transcripts, and electronic field logs documenting response rates will be kept in password-protected electronic project files at FHI 360 for three years, per FHI 360 policy. Hard copies of relevant documents, such as signed consent forms, compensation logs, or participant logs will be kept in a locked filing cabinet at the in-country MOSAIC partner's office. Access will be restricted to approved study staff only.

In accordance with the USAID Automated Directives System (ADS) 579, after acceptance of any knowledge product presenting study findings and after being cleaned of any information that could be used to personally identify participants, the quantitative survey datasets and their relevant documentation will be made available publicly in an open data repository, to the extent permissible by each country's data privacy regulations. Qualitative transcripts will not be made publicly available because even after removing directly identifiable information such as names and addresses, participant identity may be difficult to fully conceal. Qualitative interview guides will be shared in an open data repository.

10.3 Biospecimens data

Data from tests conducted as part of study procedures will be captured in various locations. Results obtained at the study site (e.g. urine pregnancy test results) will be captured in the CATALYST study database through the Cohort Visit Form. Results from tests conducted at laboratories external to the study sites (e.g. HIVDR testing, HIV RNA testing, drug concentrations) will be captured through secure laboratory information systems and then securely transferred to access-restricted Sharepoint files. Details of this data capture will be stipulated in country-specific SOPs and the data management plan. Results will be merged with other study results for analysis using participant ID. Biospecimens will be handled and disposed of as indicated in the study procedures manual and according to laboratory waste disposal guidelines. For people who consent to it, leftover blood samples may be stored for use in future studies. Locations and details of this storage will be defined in the study specific procedures manual.

11 COMMUNITY AND STAKEHOLDER ENGAGEMENT PLAN

Stakeholder engagement in research is critical to ensuring that research responds to the needs of those most affected, aligns with local community and government priorities, and builds durable partnerships for country ownership of the research and use of the study results. Involving stakeholders in a research study is a critical step toward the translation of research into practice. It is also integral to Good Participatory Practice guidelines[64] and foundational to ethically conducted research that reflects community stakeholders' needs, priorities, and interests. MOSAIC is committed to ensuring stakeholder engagement throughout CATALYST — from protocol development through study implementation and dissemination and use of results — to optimize the impact of the study on HIV prevention product introduction policy and practice.

The term stakeholders in this context refers to individuals, groups, organizations, government bodies, or any other individuals or collection of individuals who are affected by the conduct and outcome of HIV prevention product introduction studies and/or have the power or influence to apply study findings and recommendations to programs or policies. These include a broad range of local, provincial, national, and regional stakeholders such as (but not limited to) ministry of health officials, health care providers, faith leaders and faith-based organizations, HIV prevention and treatment advocates, implementing partners, civil society organizations, and current or potential PrEP users, including AGYW, FSWs, transgender women, transgender men, nonbinary people assigned female at birth, and PBFP.

CATALYST has multiple opportunities for local, national, and regional stakeholder engagement built into the study design and implementation process, including but not limited to the study's QI collaborative procedures. Each CATALYST country study team will develop stakeholder engagement plans that guide working with country stakeholders to ensure the research is locally relevant and tests scalable interventions; leverages existing service delivery infrastructure; generates early buy-in among potential evidence users; and is accountable to the communities in which it is conducted. The study teams will leverage existing mechanisms, such as national technical working groups and existing community advisory structures, for stakeholder engagement where possible. The study teams will build new structures, such as the NextGen Squad youth advisory mechanism, to support stakeholder engagement as needed.

The study's QI collaborative will provide additional mechanisms for regular engagement with national and subnational decisionmakers, site managers, health care providers, youth and community advisory group representatives, and civil society representatives involved in CATALYST through regular learning sessions. In addition, through the regional PrEP Exchange, MOSAIC will convene members of each country's QI collaborative for cross-country dialogue, knowledge sharing, and learning. As detailed below, engagement of AGYW and members of the communities in which the study is being implemented will be a cornerstone of stakeholder engagement early and throughout the study.

11.1 Community advisory mechanisms

Developing sustained relationships and communication with stakeholders in the communities where the study is taking place is the responsibility of the implementing site, clinic, or partner with support from the MOSAIC country team. Each CATALYST country study team will develop and implement plans for stakeholder engagement throughout the study, including strategies for engaging stakeholders from the communities where the study sites are located. These plans will be tailored to the local context and needs of each country's study sites and informed by early input from civil society stakeholders on CATALYST and the study teams' extensive experience with community engagement.

As appropriate for their context, the teams will establish or leverage existing stakeholder advisory mechanisms (i.e., community advisory boards, community advisory groups, clinic committees, district committees, or other similar mechanisms) with diverse and inclusive representation to act as a conduit between implementing study sites or clinics, surrounding community stakeholders, and the broader CATALYST study teams. These country-specific community advisory structures will advise on planning, development, and implementation of the CATALYST study; assess community impact and ensure community concerns are considered; amplify the voices and feedback of community and study participants; and help convey updates to and triage questions, concerns, and other feedback from the implementing site communities to the research teams.

The CATALYST study teams will determine the best way to convene community stakeholders and/or work with existing community advisory structures on a regular basis to ensure their insights, concerns, and other feedback are addressed by the study teams and reach other CATALYST stakeholders at district and national levels. Community stakeholders will be included in the national QI collaborative learning sessions, and country teams will also elect a community representative(s) to participate in the regional PrEP Exchange cross-country knowledge exchange sessions. Through the various engagement mechanisms, community stakeholders will have opportunities to advise on study design in relation to stakeholder and volunteer concerns; keep local community advisory boards and/or local advisory mechanisms apprised of CATALYST activities nationally; foster maturation of community involvement and stakeholder engagement at a national level; provide information on national stakeholder issues to the CATALYST country teams; and build collaboration with other PrEP awareness campaigns. The CATALYST teams will also collaborate with community stakeholders to provide knowledge building and/or skills strengthening as needed to enhance engagement with the study (e.g., detailed product information, how to read the protocol, etc.).

11.2 Youth advisory mechanism

MOSAIC has created a youth advisory mechanism — called the NextGen Squad — that will provide input on the CATALYST protocol development, study implementation, results dissemination, and research utilization phases to strengthen gender integration and meaningful youth engagement. In addition, the NextGen Squad will provide support to research teams in

soliciting feedback from youth groups on protocol development, engaging youth members of community advisory groups, national youth stakeholder engagement, and specific elements of implementation when requested. The NextGen Squad consists of one young person (under the age of 30) from each MOSAIC core country, including those where CATALYST will be implemented. Each young person has been hired by the local implementing partner (FHI 360, Jhpiego, LVCT, PZAT, or Wits RHI) in the country and is mentored and supported by that local partner. NextGen Squad members will be able to provide mentorship to youth who serve on local community advisory boards, as needed. They will convene youth representatives on community advisory boards regularly to understand how their participation is going, how their participation could be bolstered, and how they can best provide feedback to the research teams. The study teams will provide regular study updates to the NextGen Squad and will work with their country teams to disseminate updates to youth groups locally. Representatives from the NextGen Squad will also be included in national engagements of the QI collaborative and the regional PrEP Exchange to highlight the insights and recommendations from the youth groups with whom they engage.

We will ensure community voices are heard throughout CATALYST by; prioritizing the establishment of and/or collaborating with existing community advisory structures and mechanisms; developing several mechanisms for engagement with youth advisors across the study; ensuring there are mechanisms to support young people to better engage with research; and ensuring that community stakeholders and NextGen Squad representatives are included in national and regional advisory and implementation structures.

12 DATA ANALYSIS PLAN SUMMARY

Details of the planned analyses to address study objectives will be provided in a separate statistical analysis plan, developed in a collaboration between FHI 360 and CATALYST country teams. The following is a summary of the planned analyses. Of note, countries/sites that do not progress to Stage II due to delays in regulatory approval of injectable cabotegravir will not be included in the Stage II analysis of data but will be included in the Stage I analysis.

12.1 Quantitative data

Accrual metrics will be captured by site throughout enrollment and follow-up. Once data entry has been completed, data will be cleaned and checked for consistency locally. These data will be uploaded onto a shared online repository for analysis. FHI 360 staff will develop and provide an approved, detailed analysis plan to local partners prior to initiation of the data analysis. In collaboration with MOSAIC in-country partners, FHI 360 staff will perform data analysis using Stata, SAS, or other validated statistical software programs.

12.1.1 Analysis of Objective 1

We will conduct descriptive statistics to summarize data gathered from the site-based surveys, as well as use the data to create individual site profiles. Quantitative data from the provider structured questionnaires, which will assess the acceptability of delivery of PrEP products, offering PrEP choice, and the enhanced service delivery package, will be analyzed using time-series analysis to assess changes within sites and across sites over time, accounting for repeated measures (e.g., on provider or site) as appropriate. The service statistics (monthly disaggregated facility-level data on PrEP use) will be further analyzed using interrupted time series methods to assess change in PrEP uptake over the course of intervention implementation, including the shift from Stage I to Stage II.

Using an explanatory mixed-methods design, the qualitative data will be collected yearly following interim analysis of the quantitative data. More specifically, the interim quantitative analyses (as described above) will be used to identify sites with high and low performance, with input from local research teams, considering factors such as changes in PrEP uptake, provider levels of acceptability and feasibility, and intervention adaptations as assessed in the QI briefs. The interviews with providers and key informants, using domains from the CFIR framework, will seek to explain and delve deeper into findings from the quantitative components. Data triangulation and joint presentation of data will be employed to synthesize findings and provide a complete picture of implementation of PrEP choice through CATALYST.

Analysis approach for costing component (Study Component 2a)

Standard activity-based costing methods (including an analysis of costs via a time-motion study) will be used to collect and analyze the site-level and above-site-level cost data, including the costs of demand creation. Different types of visits (e.g., initiation, refill, restart, and method switch) will be determined, and the full and incremental cost for each method for each type of

visit will be determined from the service provider perspective using economic (as opposed to financial) costing. An ingredients-based approach to costing PrEP service delivery will be followed, whereby all the inputs will be listed and their contributions to the overall cost tallied. Costs specific to each PrEP method will include personnel, supplies, commodities, and overhead. The direct and indirect costs for each site providing services will be computed separately. A step-down approach will be used to allocate overhead costs (maintenance and utility, transport, equipment and furniture, support staff, and management and supervision costs) to the PrEP service and then to each PrEP method based on the number of visits for each PrEP method. Unit costs will be expressed in terms of cost per visit (by method and visit type), cost per client initiated (for each method), cost per person-year on PrEP, and cost per PrEP-protected condomless sex act (for each method). The cost per PrEP-protected condomless sex act will leverage the data collected on prevention-effective use in Lesotho and Uganda. The unit costs will be disaggregated into fixed costs (costs that do not vary with the number of clients) and variable costs (costs that do vary with the number of clients).

12.1.2 Analysis of Objective 2

What follows is an outline of planned quantitative analyses of Stage I and Stage II cohort data with respect to Objective 2: Patterns of PrEP use and use effectiveness in the context of PrEP choice. More details will be provided in a separate statistical analysis and modeling plan.

12.1.2.1 Stage I baseline data

The frequency and percentage (with 95% CI) of participants selecting the PrEP ring and oral PrEP will be summarized by population subgroup, facility, country, and other factors (e.g., previous experience with oral PrEP) identified by the protocol team. The association of these factors with the odds of selecting the PrEP ring versus oral PrEP will be assessed using logistic regression; the results of an adjusted (multivariable) model will also be reported. Differences in uptake rates between methods will be compared among new PrEP adopters using chi-squared goodness of fits tests conducted at the 0.05 level of significance, overall and stratified by country. Reasons for choosing not to enroll, including continued use of oral PrEP outside of the study, will also be tabulated with 95% Cis for proportions refusing.

12.1.2.2 Stage I method continuation

The cumulative incidence of method discontinuation, together with 95% Cis at regular intervals, will be reported by discontinuation reason, including method switching, medical reasons, personal reasons, and loss to follow-up. Participants who are lost to follow-up will be counted as discontinuing the method on their last clinic visit date, regardless of their PrEP supply at that visit. Participants who complete Stage I without discontinuing will be censored on the date Stage II is initiated but will be included in subsequent analyses of pooled Stage I and Stage II data (see below). Cumulative incidences will be reported separately for participants initiating the PrEP ring and oral PrEP, as well as a pooled analysis that does not consider method switching as discontinuation. The analysis will be repeated based on consistent method use, in

which participants who are more than two weeks late for resupply or who self-report inconsistent use of their method will be included as an additional category of method discontinuation.

In addition to crude rates of method discontinuation, a propensity score model will be developed to allow for more formal (pseudo-randomized) comparisons of method discontinuation between participants who initiate the PrEP ring versus oral PrEP, adjusting for factors related to the choice of method at enrollment. Population subgroup, country, age, and other factors identified by the protocol team prior to implementing the analysis will be considered when developing propensity score weights. Factors associated with method discontinuation will be assessed at the two-sided 0.05 level of significance, without adjustment for multiple comparisons.

12.1.2.3 Stage II baseline and method continuation

The analysis of Stage II data will mirror that of Stage I, except it will include CAB PrEP as a third PrEP method. The Stage II cohort analysis will initially exclude participants continuing from Stage I to directly assess the impact of a third method option (CAB PrEP) on PrEP choice and continuation rates. Although participants receiving CAB injections are inherently using the method for the subsequent two months, subjects in the CAB group who are lost to follow-up will be assumed to have discontinued at their last clinic visit to make consistent comparisons of method continuation across method groups.

12.1.2.4 Stage II prevention effective use

The primary outcome for measuring PEU in Stage II is the percentage of exposure-days when a participant was protected from HIV acquisition by taking PrEP, as detailed in Section 6.3.3. The proportion protected will be summarized over time using 95% Cis and compared between relevant subgroups using generalized estimating equations to account for repeated measures over time.

12.1.2.5 Combined analysis of Stage I and Stage II data

Stage I PrEP continuation rates will also be summarized using cumulative incidence rates, but without censoring participants when Stage II is initiated. Overall patterns of method adoption and switching will be described using frequency tables, by population subgroup and overall. Interrupted time-series analysis will be used to assess whether the introduction of a third PrEP option (CAB PrEP) in Stage II leads to greater uptake of PrEP among people eligible for the study as well as changes in method discontinuation rates. If the independence of irrelevant alternatives assumption appears valid (i.e., if the inclusion of a third PrEP option does not impact the odds of selecting only the PrEP ring versus oral PrEP), then factors associated with selecting ring versus oral PrEP will be explored using pooled Stage I and Stage II data.

12.1.3 Analysis of Objective 3

Rates of HIV infection (events per 100 years of follow-up) will be summarized by PrEP method adopted at enrollment into Stage I or Stage II, as well as the method being used at the time of seroconversion. Because CAB PrEP will not be available in Stage I, primary comparisons of HIV infection rates between methods will be restricted to Stage II data using propensity score analysis to account for differences in factors related to choice of method and risk of HIV. However, analyses that pool Stage I and Stage II data and compare differences in infection rate by stage will also be performed to gather insight on the impact of a third method choice on HIV risk. Rates of HIV drug resistance (HIVDR) will be summarized using exact 95% confidence intervals, by PrEP product, duration of use, and other relevant factors. The number and percentage of participants experiencing side effects, including side effects leading to method discontinuation, will be summarized by PrEP method in frequency tables. Additional details, including method of categorizing side effects, will be described in the separate statistical analysis plan.

The performance of various HIV screening algorithms vis-à-vis eligibility for initiating CAB PrEP will be compared to the FDA recommended algorithm based on sensitivity, specificity, and related measures. Because acute infections (PCR-positive but antigen test negative) are expected to be rare, the denominator for sensitivity calculations will be small (likely no greater than 15) and the precision low. For example, even if the estimated sensitivity is 100%, the lower 95% confidence bound on sensitivity would be 0.78 with n=15 acute infections. Hence, we will rely in large part on mathematical modeling to inform the risk of initiating HIV-infected participants on PrEP and the potential impact on drug resistance, particularly for integrase strand transfer inhibitors among CAB PrEP adopters. Additional details, including model specification and approaches for handling missing data, will be described in separate statistical analysis and modeling plans.

12.2 Qualitative data

Qualitative data will be used to respond to objectives 1 and 2. Our qualitative data collection methods (interviews and focus group discussions) will generate digital audio files and textual data. We will transcribe the digital audio files verbatim and will implement quality assurance procedures, such as cross-checking the written transcription with the audio file, to ensure accuracy. Any transcripts that are in a local language will be translated into English, if necessary. Once all transcripts have been checked for quality, we will upload them into a qualitative data analysis software program, such as Dedoose or NVivo. A master tracking database will be kept by the study team, noting the date of occurrence and study site of IDIs and FGDs, completion of transcription, completion of translation, completion of initial coding, etc. No personally identifying information will be stored in the tracking database; participants will be identified by their participant identification numbers only.

A multi-country team of study investigators will develop coding schemes for each qualitative data collection component that will be constructed using both *a priori*, deductive codes for key

concepts related to the study objectives and data-driven, emergent codes identified through initial reading of the transcripts. The coding schemes will be refined as data analysis proceeds. Emergent codes/themes will be discussed with the entire coding team during regular debriefing meetings. Approximately 5–10% of transcripts will be double-coded to assess inter-coder reliability and to help ensure quality and consistency. Discrepancies will be resolved through consensus, with all coding teams alerted to any changes or decisions made resulting from the coding resolution.

To the extent possible, qualitative data collection, coding, and analysis will occur in parallel given the iterative nature of qualitative research. Regular debriefing meetings will occur with study investigators, qualitative data analysts, and the field teams conducting the interviews and focus groups to discuss emerging themes and potential adaptation to the IDI and/or FGD guides as needed. Data analysis per objective is described in more detail below; the qualitative team will employ thematic analysis to synthesize results. As the analysis progresses, data reduction techniques will be used to examine codes in detail for subthemes and patterns across the transcripts. The study team will categorize codes and develop themes, with conceptual decisions and thought processes noted through detailed memos.

12.2.1 Qualitative analysis for Objective 1: Intervention implementation

12.2.1.1 Process evaluation

Qualitative analyses for the process evaluation will comprise three primary components:

1. **Overall assessment of barriers to and facilitators of intervention implementation:** Using CFIR as a guide, transcripts from site staff and stakeholder interviews will be coded as described above, with primary barriers to and facilitators of intervention implementation categorized by site, country, and across countries, including factors at the individual-, provider,- facility-, community-, and health system-level. If relevant, barriers to and facilitators of specific aspects of the enhanced service delivery package will be described in addition to barriers and facilitators to implementation more broadly.

2. **Identification of care service delivery components:** QI briefs from all sites will be treated as qualitative data sources and coded as described above. More specifically, adaptations made to the enhanced service delivery package and reasons for adaptation will be coded and categorized. The analysis will involve categorizing intervention components that remained consistent throughout implementation (i.e., core components), in addition to categorizing components that were perceived as being unsuccessful. Results will be triangulated with qualitative findings from the provider interviews.

3. **Comparative case study analyses among selected sites** (one high and one low performing site per country per stage): This analysis will involve triangulating both qualitative data from the provider and stakeholder interviews within sites and quantitative

data gathered through site assessments and provider/cohort questionnaires. The study team will draft in-depth case descriptions integrating findings across data sources showcasing site contexts, general themes identified within sites regarding implementation challenges and successes, and cross-case synthesis identifying similarities and differences across cases and countries, specifically comparing high and low performing sites. Thematic analyses may also be conducted specific to interviews conducted among a particular type of respondent, such as among policymakers, community stakeholders, etc., depending on the richness of data and time/staff availability.

12.2.1.2 Community acceptance

From qualitative data gathered from the nested community acceptance nested study, in addition to specific components of IDIs with cohort members, providers, and stakeholders, we will conduct thematic analysis to understand community perceptions on the acceptability of offering, receiving, and/or supporting PrEP choice from different perspectives (e.g., users, providers, primary PrEP influencers such as parents/caregivers and partners). We will also seek to understand how different types of community members view their role in support or not supporting PrEP choice and understand the behavioral and social drivers behind their support (or lack thereof). We will assess main themes both within and across countries.

12.2.2 Qualitative analysis for Objective 2: PrEP uptake and patterns of use

Qualitative data analysis from cohort participants will be grounded in understanding the user experience of informed PrEP choice across multiple levels, including at the individual level (e.g. product acceptability, perceptions of PrEP), the interpersonal level (e.g., role of peers, partners, and parents in supporting or not supporting PrEP choice), the facility-level (e.g., users experience of receiving the enhanced service delivery package and being offered PrEP choice), and community-level (e.g., impact of social norms and community acceptance of PrEP on PrEP choice). Population-specific experiences from both AGYW and FSW will be included, relying on both data generated from the population-specific FGDs in addition to IDIs. Additionally, barriers and facilitators to PrEP use will be explored, focusing specifically on how having a choice between PrEP products influenced users' ability to persist or not persist with PrEP use. As described above, data will be analyzed using thematic analysis. Additionally, qualitative data will be used to support and explain quantitative findings, such as adding context to the patterns of PrEP use by providing reasons for observed patterns of use and a deeper understanding of facilitators of and barriers to PrEP use.

13 STUDY TRAINING AND MONITORING

The study will have a collaborative management and monitoring approach. Briefly, each country will have an investigative team that includes members from the MOSAIC partner and the national health authority, with technical coordination and management through the overall CATALYST team. The study will seek both national and FHI 360 ethical reviews and approvals.

13.1 Leadership and management

The FHI 360 Coordination and Operations Center to Research and Operations Group (ROG)will monitor the CATALYST study across countries to ensure the appropriate ethical reviews are completed, research is implemented per the approved protocol, findings are effectively communicated and disseminated, and emerging issues are responded to in a timely manner.

The CATALYST study is led by a Protocol Chair, Protocol Co-Chair, and five country principal investigators (PIs). The Protocol Chair and Co-Chair, in collaboration with the country principal investigators and MOH co-investigators, will provide overall strategic and technical vision for the CATALYST study and will work closely with the lead country study coordinators to ensure high-quality study implementation. See Table 11 below for more details on study leadership and management roles and responsibilities.

Study implementation will be guided by the CATALYST Study Specific Procedures (SSP) Manual that provides further instructions and operational guidance on conducting study visits; data collection and processing; specimen collection and testing; safety monitoring, management, and reporting; PrEP product provision and documentation of study product accountability; and other study operations. Study-specific training will be provided to all country study teams by the CATALYST Study Management Team and other designated members of the Protocol Team.

Table 11. Study leadership/management roles and responsibilities

Role and Location	Responsibilities
Protocol Chair, Global	The Protocol Chair will be responsible for providing overall direction, coordination, communication, and oversight of study design, study conduct, data management, data analysis/interpretation, and results dissemination. They will be responsible for submission and maintenance of the protocol with the FHI 360 IRB, as well as submission and maintenance of all USAID and product developer reporting requirements.
Protocol Co-Chair, Regional	The Protocol Co-Chair will contribute to overall direction, coordination, communication, and oversight of study design, study conduct, data management, data analysis/interpretation, and results dissemination. They will be responsible for providing direction and oversight of the approach to service delivery adaptation across study countries and providing regional scientific/technical assistance as needed.
Kenya Principal Investigator Lesotho Principal Investigator South Africa Principal Investigator Uganda Principal Investigator Zimbabwe Principal Investigator	Country PIs will be the primary individuals responsible for study implementation in each country. They will liaise closely with the MOH co-investigators on all aspects of the study. They will lead the country study team and provide oversight for in-country study conduct, data management, data analysis, and results dissemination. They will contribute to overall study design, data analysis/interpretation, and results dissemination. They will also be responsible for managing submission of the study protocol to in-country regulatory bodies, including IRBs, and maintaining appropriate and timely correspondence about the study, including ensuring adverse events are reported.
Kenya Study Coordinator Lesotho Study Coordinator South Africa Study Coordinator Uganda Study Coordinator Zimbabwe Study Coordinator	Study coordinators will be responsible for recruitment and training of field staff for data collection, overseeing all field data collection processes, and ensuring the data collected are of high quality. They will also participate in data management, data analysis, and results dissemination.

14 ETHICS CONSIDERATIONS

14.1 Reviews

This protocol will be submitted for review by the Protection of Human Subjects Committee (PHSC) at FHI 360 and IRB/IECs in Kenya, Lesotho, South Africa, Uganda, and Zimbabwe. Field work within each country will not be initiated until after approval has been received from both the FHI 360 IRB and the country IRB. All study team members will be required to have current training on FHI 360's human subjects research ethics curriculum or another approved ethics training, such as the Collaborative Institutional Training Initiative (CITI Program). Prior to data collection, all data collectors will receive further training on the importance of privacy and confidentiality. All study staff are responsible for monitoring for potential protocol deviations, with leadership from MOSAIC. Country PIs will be responsible for reporting any deviations to the relevant IRBs in a timely manner, as required by the boards.

14.2 Informed consent process

Informed consent, and assent and parental permission for those under the age of legal consent per IRB requirements, will be obtained before a participant is included in the study. The informed consent process will include describing risks, benefits, protection of privacy and confidentiality, adverse events, and compensation. Written consent (and assent from minors and parental permission from their legal guardians if a waiver of consent is not granted) will be obtained by the data collectors from all cohort participants in the study, as well as providers and key stakeholders participating in surveys, IDIs, FGDs, and/or KIIs. During the informed consent process, data collectors will read the consent form aloud in the language of the participant's choice and explain to eligible study participants and stakeholders the basic purpose and conduct of the study — including confidentiality procedures and the risks and benefits of participation — and will give the participant time to ask questions about the study. For illiterate participants, a witness of the participant's choosing (often a care facilitator) will also sign that the consent form was read to the participant and that the participant understood it. Provides and key stakeholders may be given the option to read the consent form themselves, although key information will still be summarized by the data collectors.

For IDI, FGD, and KII participants, we will ask specifically if they agree to be audio-recorded. IDI, FGD, and KII participants who do not consent to audio recording will not be interviewed to ensure accuracy and completeness of study data. Data collectors will then ask participants if they are willing to participate in the study and, if so, to sign their name on the informed consent form. If the stakeholder interview is conducted virtually, the data collector will sign a statement attesting to obtaining verbal consent from the stakeholder prior to beginning the interview. All participants will be offered a paper copy of the form, which includes contact information for the relevant IRB(s). If a participant does not agree to sign the form, the interviewer will discontinue the process, refer the client to other HIV prevention services if appropriate, and move on to the next eligible individual.

The informed consent forms to be used in the CATALYST study are listed in Table 12.

Table 12. Informed consent forms for the CATALYST Study

Component	Consent Form Name	Use	Stage
Cohort	Cohort Participant Stage I	Stage I: All client study cohort	Stage I
	Cohort Participant Assent Stage I	Stage I: All minors in study cohort	Stage I
	Cohort Participant Parent Permission Stage I	Stage I: All parents/guardians of minors in study cohort, if a waiver of parental consent is not granted	Stage I
	Cohort Participant Stage II – New ppts	Stage II: All new clients for stage II	Stage II
	Cohort Participant Stage II – Current ppts	Stage II: All current clients from stage I (reconsent)	Stage II
	Cohort Participant Assent Stage II – New ppts	Stage II: All minors in study cohort new to the study	Stage II
	Cohort Participant Assent Stage II – current ppts	Stage II: All minors who were in stage I cohort (reconsent)	Stage II
	Cohort Participant Parent Permission Stage II – New ppts	Stage II: All parents/guardians of minors new to the cohort, if a waiver of parental consent is not granted	Stage II
	Cohort Participant Parent Permission Stage II – current ppts	Stage II: All parents/guardians of minors who were in stage I cohort (reconsent), if a waiver of parental consent is not granted	Stage II
	Cohort IDI	Stage II: subset of cohort ppts for IDIs	Stage II
	Cohort IDI Assent	Stage II: subset of cohort minor ppts for FGDs; parental permission is imbedded in the main Stage II parental permission consent	Stage II
	Cohort FGD	Stage II: subset of cohort ppts for FGDs	Stage II
	Cohort FGD Assent	Stage II: subset of cohort minor ppts for FGDs; parental permission is imbedded in the main Stage II parental permission consent	Stage II
	PEU cohort - Validation Phase	Nested study: Stage I; cohort subset (SA & KE only)	Study start
	PEU cohort - Measurement Phase	Nested study: Stage II; cohort subset	Later
Other	Decliner Survey Script	Verbal consent from clients who don't join study (either w/ or w/o hearing about the study)	Stage I & II

Component	Consent Form Name	Use	Stage
Process Evaluation	Process Evaluation Provider IDI	All stages: Process eval; providers for IDI	Stage I & II
	Process Evaluation Provider Survey	All stages: Process eval; providers for survey (quant)	Stage I & II
	Process Evaluation Provider Pre-Training Assessment	All stages: Process eval; providers for PrEP pre-training survey	Stage I & II
	Process Evaluation Key Informant IDI	All stages: Process eval; policy makers for qual IDI	Stage I & II
	Process Evaluation Community stakeholder IDIi	All stages: Process eval; Key informants for qual IDI	Stage I & II
	Community Acceptance Partner/Parent IDI	Nested study; parents or partners of existing AGYW on PrEP qual IDI	Stage II
	Community Acceptance Partner/Parent FGD	Nested study; parents or partners of existing AGYW on PrEP qual FGD	Stage II
	Costing client consent	Stage II: to follow client during visit (UG & LE only)	Stage II

14.3 Risk mitigation plan for COVID-19

The study will implement measures to reduce the risk of exposure to COVID-19 for study participants and the study team. As the situation with COVID-19 is dynamic, these measures might change over time and will be updated based on the situation at the time of data collection and other study activities. Some potential measures that might be taken to mitigate the risks of COVID-19 include:

- Research assistants taking part in data collection might be periodically tested for COVID-19 during data collection per national COVID-19 regulations.
- Data collectors may wear face masks when interacting with participants and will have additional face masks for participants to wear (if needed).
- Data collectors will be provided with other personal protective equipment, including disinfectant and microfiber towels (e.g., to clean tablets, wipe down chairs, etc.) and bottles of hand sanitizers.
- When possible, and as necessary given the local COVID-19 incidence rates, data collection will occur outside, in well-ventilated areas, or even virtually in some cases, so long as participant privacy can be maintained.

14.4 Procedures for protecting participant confidentiality

Interviewers and data collectors will be trained on the importance of privacy and confidentiality and coached on efforts to maintain confidentiality to the best of their ability. All researchers will be bound by confidentiality agreements to fully respect the confidentiality of participants. As the study is likely to include vulnerable populations such as those under 18, FSWs, and/or those in the lowest wealth-quintiles, the importance of confidentiality to these groups will be emphasized. Privacy will be maintained as best as possible for all recruitment and study procedures.

All printed study materials, including signed consent forms, will be kept in a locked cabinet to ensure the confidentiality and privacy of collected data. All study participants will be assigned unique identification numbers, which will be used on study forms and all interview transcripts. The document linking study IDs to participant information will be kept secured in a location separate from other data. ID numbers will not be included on the consent forms. For data collection, all interviews will be conducted in a private setting where auditory privacy can be maintained. No identifiable information will be presented with the study findings.

During qualitative interviews, participants will not be asked to state their name or mention the name of their health facility. Any names that are inadvertently captured on the audio recording will not be transcribed. Direct quotes may be included in the final deliverables but will not be attributable to the individual respondent. Audio recordings will be transferred from the audio device to a password-protected file on a password-protected computer on the day they are collected, and then removed from the device as soon as quality control procedures have ensured that the recording has been successfully saved on the computer. Once transcription is complete and quality control procedures have ensured that the transcription is accurate, the audio files will be removed from the computer as well.

14.4.1 Special consideration for minors

This study may include women ages 15–17. The eligibility of women younger than 18 years will be country specific. If women younger than 18 are included, we will request a waiver of parental consent both for participation in the cohort and in the nested PEU study, for the following reasons:

- Adolescent participants will be enrolled in compliance with US regulation 46.408(c)[e] (requirements for permission by parents or guardians and for assent by children). This regulation states the following: “In addition to the provisions for waiver contained in §46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable

[e] U.S. Department of Health and Human Services Office for Human Research Protections. U.S. Regulation 46.408(c). https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-d/

requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, state or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition."

- As HIV is a sexually transmitted infection, participants ages 15–17 in this study can be considered mature minors. Acquiring parental consent for participation in this study could put study participants in emotionally or socially complicated situations. In addition, as interest in using PrEP — an eligibility criterion for our study — suggests a participant is currently sexually active or is considering becoming sexually active in the near future, obtaining parental consent would disclose the participant's sexual activity to the parent/guardian and could lead to embarrassment, stigma, and/or discrimination. Because adolescents are a priority population for national efforts to improve access to PrEP, minors are an important population to measure in this study.
- For the PEU nested study, there are concerns of participant confidentiality, safety and data quality if parents might intercept SMS messages.

14.5 Risks

We will minimize the physical, psychological, social, or legal risks to clients and stakeholders due to participation in this research. Cohort participants will be recruited from the various service delivery sites, and interviews will be conducted during usual clinic hours to minimize any undue burden or risk of disclosure of being a study participant at the clinic. However, there is a risk of loss of privacy around product use or discovery of belonging to a stigmatized population, such as FSWs. It is possible some client participants may feel uncomfortable answering some of the study questions, such as questions about sexual behavior. Participation is voluntary, and respondents can choose not to answer any of the questions. Participants will be informed via the consent form of the confidentiality measures being implemented, and the team will make every effort to protect confidentiality. Participants will also be assured that their responses will not affect their ability to obtain health services.

In additionally, participants may encounter social harms/stigma (such as intimate partner violence [IPV]) for using PrEP products or for involvement in a study about HIV prevention. To minimize this harm, during provider training we will ensure that providers have guidelines on how to support people who encounter IPV or other retaliation for PrEP use, including local referrals to supportive services.

Participants may also experience minor risks related to blood draws that occur as part of study procedures for selected populations, such as participants initiating CAB and participants who acquire HIV. These risks include potential discomfort and bruising or swelling at the site of where the needle was inserted. Only staff members trained in phlebotomy will collect blood specimens. Participants may also experience anxiety or distress from learning their HIV status.

Participants will receive counseling by a trained counselor before and after testing to minimize this risk.

14.6 Safety monitoring and reporting

The safety of participants in this study is of utmost importance. Adverse events, expected or unexpected, that meet the criteria for serious adverse events (SAEs); social harms related or possibly related to study participation and study-provided PrEP use; safeguarding incidents; and protocol deviations will be documented and reported. An adverse drug reaction (ADR) is defined per ICH E2 definition, as a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis diagnosis or therapy of disease for modification of physiological function. There should also be at least a reasonable possibility of a causal association between the study product and the ADR, i.e. the relationship cannot be ruled out. A serious adverse event (experience) or reaction, per ICH E2 definition, is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing, hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is medically significant (i.e., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above). Loss of pregnancy (i.e. fetal deaths) of cohort participants will also be considered as SAEs. Providers and study staff are to identify and document social harms and SAEs for study reporting. A subgroup of the Protocol Team will be established as the Protocol Safety Review Team (PSRT) responsible for advising on study eligibility and product use management and any potential safety concerns, including SAEs and social harms, as well as pregnancies and pregnancy outcomes of cohort participants.

All social harms and SAEs, spontaneously reported by participants or learned of (e.g., family member or partner of a participant discloses a participant's death or prolonged hospitalization) by a provider or study team member will be documented on a study specific form. Providers are also to document ADRs (of any severity) in client registers, as applicable and reported onwards to national pharmacovigilance programs and product market authorization holders per facility SOPs and country reporting guidelines. SAEs and social harms related or possibly related to study participation or study product use will be reported to ethics committees, and product-related SAEs will be reported to the relevant study product developers. Pregnancy-related exposures and pregnancy-related outcomes will be reported to relevant study product developers. The PRST will be responsible to review all SAEs and pregnancy cases and outcomes before onward reporting to ethics committees and product developers, as relevant. Specific reporting guidelines will be outlined in the CATALYST Study Specific Procedures Manual as well as in respective agreements between the product developers and the study sponsor.

Study staff and providers will be trained on how to identify and respond to any reports of unanticipated events or problems related to the study. This includes making an initial determination about relatedness or possible relatedness of an event to the study and whether the event meets SAE criteria and how to immediately contact the study supervisors. We will

develop country-specific risk mitigation plans and a referral system for responding to any social harms related to product use or study participation reported by participants during the study. Providers will receive clinical training on how to address ADRs related to study product, including product management.

Protocol deviations and safeguarding incidents will be immediately reported to the relevant Country PI and Protocol Chair/Co-Chair, who will be responsible for reporting to the ethics committees and study funders per FHI 360 policies and contractual requirements. Study participants will be given a contact name and telephone number and/or email address to use if they have questions or feel they are encountering problems as a direct result of study participation.

14.7 Benefits

Study participants may benefit from the study by gaining access to certain PrEP products, including PrEP ring and CAB PrEP, that might not be available outside of the study context. There are no other benefits to study participation. The study results are intended to inform rollout or scale-up of new PrEP methods and to strengthen PrEP service delivery for female populations. The study results will be useful for the governments of countries included in this study, implementing partners, and donors, in understanding the optimal delivery of PrEP choice. Ultimately, the study may benefit women who could benefit from PrEP by facilitating PrEP method access and acceptable service delivery platforms to expand PrEP prevention effective use and reduce HIV incidence.

14.8 Compensation

14.8.1 Cohort participants

Participants in the cohort will not be compensated for attending regularly scheduled clinic visits related to PrEP initiation, PrEP use, and PrEP discontinuation. Participants will be compensated for their time and reimbursement for travel/phone costs for additional study procedures and participation in any IDIs or FGDs that occur during follow-up.

Cohort participants who participate in an additional IDI or FGD will receive compensation for their time and reimbursement for travel costs incurred getting to and from the interview (if the interview is held in person and away from where the participant lives). The amount of compensation for time and travel will be based on local rates for compensating research participants (approximately US$5 or US$10 inclusive of travel, depending on the country) and/or be the local equivalent of US$5, with additional travel reimbursement based on public transport rates while taking into consideration travel restrictions on vehicle carrying capacity due to COVID-19. FGD participants will receive this level of compensation, as well as refreshments (e.g., tea and snacks) during the discussion.

Participants in the nested PEU study will receive incentives for responding to the digital self-report tool. The incentives will be small amounts of mobile money that will increase if participants respond multiple days in a row or for longer periods of time. Incentives will range from approximately US$0.25 to US$3, based on airtime and data pricing structures. Bonuses for consistent reporting at three and six weeks will be provided in the amount of approximately US$2 or US$6, respectively. Finally, at the end of each six-week reporting period, participants with consistent reporting records will be entered into a raffle for a phone, valued at approximately US$500. One winner will be chosen per country.

14.8.2 Implementers and stakeholders

National and subnational MOH officials will not be compensated for their time spent during key informant interviews.

Other stakeholders (i.e., facility staff, providers, community representatives, and implementing partner staff) will be compensated per local requirements or at the local equivalent of US$10 for their time to participate in an IDI or KII. No additional reimbursement for travel will be provided.

14.8.3 PrEP influencers

For the nested study on Community Acceptance, PrEP influencers, including partners and parents/caregivers, will participate in either an IDI or FGD. Participants will be provided with compensation for their time and travel (if applicable) according to national regulations or at the equivalent of US$5 plus reimbursement for travel expenses. FGD participants will also be provided with refreshments (e.g., tea and snacks) during the discussion.

15 Dissemination and use of study findings

The CATALYST team intends for the study to result in relevant, persuasive, and actionable evidence. Because the design and implementation of research influences how findings are used, preparing early for future use of evidence is a critical component of the research process. CATALYST study teams will take several steps to ensure the study is designed and implemented to maximize the potential for application of findings, including the potential for scale-up of interventions found to effectively advance product introduction and choice. In addition, the CATALYST team will share interim study results approximately every six months with the MOHs and national HIV drug resistance surveillance studies in each CATALYST country, so that interim data can inform ongoing PrEP implementation planning at the national level.

In line with FHI 360's RU Framework, in the foundational phase the CATALYST study teams will develop stakeholder engagement plans that guide working with country stakeholders, including civil society and members of disproportionately affected communities, to ensure the research is locally relevant, tests scalable interventions, and generates early buy-in among potential evidence users. MOSAIC has conducted stakeholder mapping and analysis related to HIV prevention and PrEP product introduction in countries where CATALYST will be implemented. This mapping will inform the development and implementation of stakeholder engagement plans specific to the study (see Section 11).

In the research implementation phase, each CATALYST country study team will develop an RU plan for the study; routinely discuss study progress, interim results, and their anticipated application with local stakeholders; and, as part of the QI collaborative, document the implementation of the interventions being evaluated to inform future replication. As part of the QI collaborative, MOSAIC will implement national learning sessions with key stakeholders in each CATALYST country and a regional knowledge exchange forum called PrEP Exchange. The PrEP Exchange will bring together key stakeholders at the subnational, site, and community levels across CATALYST countries to share CATALYST implementation experience, results, and lessons and collectively discuss and solve common challenges across countries during study planning and implementation. Insights from these discussions will inform intervention adjustments and modifications during study implementation, as well as guidance and recommendations for sustainability and future scale-up of a PrEP service delivery package that offers choice.

In the translation phase, study teams will synthesize and package study findings for use; consider translating results into programmatic guidance, tools, training curricula, policy briefs, and/or job aids; work with civil society to advocate for changes in policy and practice based on evidence; provide technical assistance to incorporate evidence into national policy/planning; and leverage existing knowledge exchange platforms to promote uptake of evidence. The team will have both global and country-specific dissemination strategies; the latter will be built out in each CATALYST country's RU plan and will include tailored strategies and knowledge products for reaching USAID Missions, government policymakers, PrEP implementing partners, civil

society advocates, and end users. Global products will include peer-reviewed articles, an intervention toolkit for scale-up, and presentations at major international HIV conferences, as well as targeted dissemination to influential global decision-makers, including staff at PEPFAR, WHO, and UNAIDS.

In the institutionalization phase, MOSAIC's local partners will continue to engage local stakeholders to monitor implementation of new evidence, review data, and identify ongoing technical assistance needs to support sustainability in the health system and product rollout.

16 Timeline

Activity	2022												2023												2024												2025												2026											
Month -->	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Protocol development	X	X	X	X	X	X																																																					
Ethical & technical reviews							X	X	X	X	X	X			X	X	X	X	X																																								
Train study teams													X	X	X	X																																										
Recruitment - Stage I															X	X	X	X	X																																							
Recruitment - Stage II (anticipated)																			X	X	X	X	X	X	X	X	X	X	X	X																											
Data collection															X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X													
Data cleaning																X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Analysis																	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Dissemination & reporting																								X					X							X					X					X									X	X	X	X

17 References

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