# Guidelines for Dapivirine Ring Pilot Implementation Studies: Template Language for National-Level Guidance & Protocol Development

**About this Document**

The intent of this document is to provide adaptable guidelines for the design of dapivirine vaginal ring, also known as the PrEP ring, pilot implementation or post-introduction operations studies to help shape national ring guidelines. The contents here align a set of study objectives and measures to consider for use across multiple contexts to foster building an evidence base on best implementation practices for ring use. The document includes prompts for national-level consideration during the study protocol development process. Areas specifically requiring national input are highlighted in yellow.

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***Countries should use this module as appropriate for their needs and settings; use of PROMISE branding or acknowledgement is optional.***

## Overview and how to use this tool

As new HIV pre-exposure prophylaxis (PrEP) methods become available for use, determining how best to integrate them within the existing health system will be of paramount importance. Implementation studies conducted as part of oral PrEP introduction have revealed opportunities to strengthen health system components, test new approaches to service provision, and improve provider training to optimise oral PrEP delivery and follow-up. These lessons can inform the introduction of new PrEP methods, such as the dapivirine vaginal ring (also known as the PrEP ring and referred to as “the ring” for the remainder of the document), which may have different intended user groups, and thus may require different approaches to service provision than those currently used for oral PrEP.

This template is based on a document originally developed by the dapivirine ring task force within the PrEP Technical Working Group, led by the Ministry of Health of the Government of Zambia. This template is designed for policymakers and government technical specialists to use to apply uniform objectives, study design features, and measures across pilot implementation and other operations research studies for ring introduction, in collaboration with investigator teams. These objectives, measures, and design features are proposed across countries to facilitate the generation of a body of evidence to foster regional learning and programme refinement over time and as additional PrEP methods are introduced.

## Introduction and rationale

The government of [country name], through the Ministry of Health (MOH) [or other health authority], recognises the great burden that HIV has placed on the lives and wellbeing of [nationality] families over the last four decades. The MOH [or other health authority] strives to ensure HIV prevention measures, testing, and treatment are available to and reach all citizens, including provision of oral PrEP to prevent HIV. As new PrEP methods that have the potential to expand the HIV prevention toolbox become available with sound scientific evidence of their safety and efficacy, the MOH [or other health authority] will consider whether introduction of each method in the public sector is feasible and acceptable.

The ring is a flexible silicone ring inserted into the vagina that slowly releases the antiretroviral drug dapivirine over a one month period of continuous use, after which it is replaced with a new ring. The ring protects against HIV acquisition in women only during exposure from receptive vaginal sex. This method is user-initiated and, when used in combination with other interventions to enhance HIV prevention, may present an acceptable option for clients who cannot or do not wish to take oral PrEP. Discrete choice studies (TRIO, Quatro) have been conducted in Kenya, South Africa, and Zimbabwe to determine the best way to deliver PrEP for women, with participants trying several placebo methods and documenting their preferences. The TRIO study compared oral, injectable, and ring methods and found that while injectables were most preferred, ring continuation rates were high among women willing to try the ring compared to those for other PrEP delivery methods.[[1]](#endnote-2) The Quatro study compared four different vaginal methods, including the ring, and found that initial preference for ring was low but increased with trial duration and product crossover with high ring adherence.[[2]](#endnote-3) Table 1 summarises evidence regarding ring efficacy and safety from clinical trials and open-label extension studies.

**Table 1. Summary of dapivirine ring efficacy and safety findings from multi-country trials and open-label extension studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study lead author, name of study; sites; sample size** | **Study design** | **Main safety finding(s)** | **Main effectiveness finding(s)** | **Key limitations reported by authors** |
| Nel *et al*.,[[3]](#endnote-4) The Ring Study; South Africa & Uganda; 1959 women ages 18–45 years  | Placebo-controlled, double-blind randomised controlled trial (RCT) (Phase III) | Serious adverse events were rare but more common in women randomised to ring (2.9% vs. 0.9%), with no detected pattern. Rates of adverse events were similar between groups, and product-related events were rare (0.4% for ring and 0.3% for placebo) and mild. No significant differences were detected in rates of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutation among women with new infections. | Women receiving the ring had a 31% lower incidence of HIV infection (4.1 vs. 6.1 infections/100 person-years [p-y]); there was no significant difference in efficacy for women <21 years compared to those >21 years. | Limitations include the lack of standardised criteria for measuring ring use based on dapivirine concentrations. |
| Baeten *et al*.,[[4]](#endnote-5) ASPIRE trial; Malawi, South Africa, Uganda, & Zimbabwe; 2629 women ages 18–45 years | Placebo-controlled, double-blind RCT (Phase III) | Rates of serious adverse events, adverse events overall, and NNRTI resistance in women with new HIV seroconversions were similar between study arms.  | Overall, women receiving the ring had a 27% lower HIV incidence (3.3 vs. 4.5 infections/100 p-y); women ages >21 years had significantly higher (56%) protection compared to those <21 years (27%), correlated to reduced adherence.  | Ring use as measured by plasma levels and residual drug in used rings may not have perfectly correlated with use patterns based on variability in both measures |
| **Study lead author; name of study; sites; sample size** | **Study design** | **Main safety finding(s)** | **Main effectiveness finding(s)** | **Key limitations reported by authors** |
| Nel *et al.*,[[5]](#endnote-6) DREAM open-label extension (OLE) study; South Africa & Uganda; 941 women who had participated in The Ring Study | OLE observational cohort | Serious adverse events (2.1%) and product-related adverse events (0.6%) were rare. Serious adverse events were not deemed product-related and adverse events related to product use were mild, such as vaginal itching. NNRTI resistance was detected among 29% of those seroconverting. | 18 incident infections (1.8/100 p-y) were detected, with a modelled 62% lower infection rate than the simulated placebo rate.  | Lack of a placebo group and the time lag between parent trial and OLE with differences in background HIV incidence rates may have affected placebo estimates. Another limitation is possible selection bias of having only participants who remained HIV-negative in the parent trial, as they were older and had lower rates of sexually transmitted infection. |
| Baeten *et al*.,[[6]](#endnote-7) HOPE OLE; Malawi, South Africa, Uganda, & Zimbabwe; 1456 women participating in the ASPIRE trial | OLE observational cohort | 22 serious adverse events occurred, with none deemed related to product use. Two adverse events were related to product use (abdominal pain and pelvic pain with ring insertion) and were graded as mild in nature. Seven women seroconverting had NNRTI resistance mutations that differed, suggesting no distinct pattern related to dapivirine. | 35 incident infections (2.7/100 p-y) were detected, with a modelled 39% lower infection rate than predicted mean incidence rate of 4.4/100 p-y from parent trial. 89% of returned rings had dapivirine levels reflecting some degree of use and drug release; 77% of par­ticipants had evidence of use across each 3-month period. Ring acceptance and use rates in the OLE were higher than in the RCT. | Limitations included lack of a placebo group, quarterly follow-up limiting precision of estimates, low inclusion of women ages 18–21 years, and greater participant experience and comfort with ring use or lack of widely available oral PrEP as an alternative, resulting in higher adherence rates.  |

The trials found higher HIV prevention efficacy of the ring among women who had greater drug release from their rings, reflecting more consistent use.[[7]](#endnote-8) The open-label extension studies added data to support the association between consistent, correct ring use and lower HIV acquisition.5,6 All studies noted no product-related severe adverse events. Less than 5 percent of women experienced side effects related to ring use, which were mainly urinary tract infections, pelvic pain, and vaginal discharge or itching and resolved within a few weeks.

In light of these data, the European Medicines Agency provided a positive scientific opinion in July 2020 supporting ring use for women at significant risk of HIV infection. In January 2021, the World Health Organization (WHO) recommended that the ring be offered as an additional prevention choice for women at substantial risk of HIV infection as part of combination prevention approaches, and the ring was included in the revised WHO Consolidated HIV Guidelines for Prevention, Treatment, Service Delivery & Monitoring released in July 2021.

The ring is currently approved for women 18 years and older because younger adolescents were not included in the original trials. The available data regarding safety in pregnant and breastfeeding women are sparse yet reassuring: among 169 trial participants who became pregnant, no congenital, maternal, or infant adverse outcomes were observed among those exposed to dapivirine.[[8]](#endnote-9) Studies assessing the safety and acceptability of ring use among adolescent girls and young women ages 16–21 years (REACH), pregnant women (DELIVER), and breastfeeding women (B-PROTECTED) are ongoing, with the potential for changes in product labelling consistent with study results. Interim results from the REACH study, being conducted at four clinical research sites in Uganda, South Africa, and Zimbabwe, demonstrated that the vast majority (97 percent) of the study’s 247 participants used the ring and daily oral PrEP some or all of the time. Fewer than 3 percent of participants used neither of the products, according to laboratory tests for adherence.[[9]](#endnote-10)

At this time, ring use data are largely based on clinical trials rather than “real world” implementation. Moreover, discrete choice experiments measuring interest in use can inform our understanding of feasibility but not our understanding of acceptability because they do not capture user experience with the actual product. These studies also may not measure or anticipate the impact of specific barriers and facilitators to method access and use, such as partner perceptions or provider counselling and attitudes, that can be measured in implementation evaluations.

[Please add paragraph reflecting ring use or experience within specific country. For example, ring Phase III and OLE trials were conducted in Kenya, Malawi, South Africa, Uganda, and Zimbabwe, so these countries have documented acceptability and safety data within their contexts, which should be featured in this paragraph. For countries not included in these trials or in the Quatro study (which included South Africa and Zimbabwe), here is some example text from the Zambia ring pilot implementation guidelines: “The ring has not been previously used or tested in Zambia, and further information is needed regarding the feasibility and acceptability of this method among clients, providers, and administrators in the public sector health system. Furthermore, MOH administrators will require data regarding ring safety with any pilot use of the ring in Zambia. Prior to considering introduction of the ring as part of the PrEP method mix within Zambia, the MOH requires evidence regarding ring acceptability among key end-user groups and health care providers, the feasibility of ring service provision in a variety of clinical and community-level settings, and anticipated barriers and facilitators to ring introduction and implementation from the perspective of health system infrastructure, cost, and community and provider-level demand.”]

The MOH [or other health authority] has requested pilot ring implementation studies to address this need for data to shape ring decisions. The MOH [or other health authority] mandates that the pilot studies include a set of common features as well as conform to guidelines regarding geographic and end-user group distribution to ensure the resultant data are comparable, robust, and provide sufficient detail to guide decisions about adding the ring to the PrEP method mix and any associated policy, strategy, and guideline development.

**Study objectives**

1. To measure the feasibility, including cost projections, of adding the ring to available PrEP methods in [country name] among clients and service providers. [For countries that have already conducted ring feasibility assessments but desire costing analyses, please reword this objective to measure cost projections and move it to the final position in the list of objectives, as it will be informed by measures from those feasibility studies as well as from existing health systems data.]

2. To measure the acceptability of ring use among clients and service providers through PrEP method selection/uptake and continuation (ring vs. oral PrEP).

2a. To measure product safety through described side effects and adverse events with either the ring or oral PrEP.

2b. To measure and explore responsive actions by service providers for social harms attributed to PrEP use.

3. To measure the fidelity of ring and oral PrEP service delivery against minimum service standards, including service quality, and document adaptations and the rationale for these changes.

**Study design considerations**

[These design considerations are illustrative from Zambia’s experience; each country can adapt the considerations based on its specific priorities. For example, in countries for which feasibility and safety data already exist, health authorities and investigator groups may agree that having a single dissemination event that reports uptake, acceptability, and safety measures is preferable to the two-prong approach described below.]

The MOH [or other health authority] requests that all investigator teams include these design features in their protocols:

* Study sites should include those currently either directly providing oral PrEP or linked to oral PrEP provision (e.g., primary care sites providing family planning and sexual and reproductive health services) with representation of urban, peri-urban, rural, and remote settings, as possible. Each investigator team will complete a mapping matrix to specify the site and primary end-user group for the proposed study to maximise coverage and prevent duplication (Annex 1).
* The MOH [or other health authority] requests that studies include and identify clients who have used and discontinued oral PrEP as a separate arm/group from PrEP-naïve participants in the sample. The rationale for this differentiation is that users who have tried and discontinued oral PrEP (inclusive of periods of resuming use) may have different perspectives on the tolerability of side effects or product access/use, and those perspectives may influence ring continuation or switching. Because the ring is indicated predominantly for women who cannot or do not wish to use oral PrEP, it is important to capture the perspectives of experienced users who have discontinued oral PrEP as a primary client group for the ring. This number may be limited relative to new PrEP clients and can be considered an exploratory analysis.
* The MOH [or other health authority] recommends inclusion of broad community-level ring sensitisation sessions prior to and during study implementation, with qualitative assessment of planned materials to guide national adaptation. Sensitisation sessions shall feature the nature of the study (i.e., implementation assessment rather than safety/efficacy trial) and plans for inclusion of community oversight within the study’s Advisory Committee.
* The MOH [or other health authority] recommends developing/adapting and testing draft provider training packages with minimum service delivery standards and coaching of providers on offering ring users instruction on and motivation for self-insertion at initial use and subsequent visits. Training and coaching should be provided prior to and during study implementation, with qualitative assessment of planned materials to guide national adaptation. Illustrative questions to aid in refining these packages are provided in Tables 3 and 4.
* For acceptability outcomes, the MOH [or other health authority] requests that all studies measure whether clients opt for either oral PrEP or the ring in addition to other HIV prevention measures (e.g., condom use) at study entry and include PrEP method discontinuation/switching and reported use of other HIV prevention methods as part of required acceptability outcome measures (please see Table 3). Although this differentiation may present statistical power concerns for an individual study if conducted as a pilot, we anticipate that a pooled analysis will be possible in scenarios where there are multiple studies or a multisite study, permitting greater power to detect true differences in initial and longer-term acceptability for each PrEP method.
* To contextualise acceptability outcomes, the MOH [or other health authority] requests that studies conduct qualitative interviews with a subsample of clients to explore the acceptability of ring use, including reasons for selecting or switching to the ring and reasons for continuing or discontinuing its use. These interviews should also address disclosure of ring use and discussions about ring use with partners and peers. Interviews would ideally include representatives across the age span and by group, such as sex workers. Interviews may also include key influencers, such as male partners to whom partners have chosen to disclose their ring use, other family members, or community leaders. These interviews may focus on exploring communication and demand creation strategies and adherence support strategies.
* To contextualise acceptability outcomes, the MOH [or other health authority] requests that studies include qualitative interviews with a subsample of health care providers to explore ease of ring counselling and provision, including preferences for ring insertion by providers vs. teaching self-insertion at initial and follow-up visits, perceived time investment, utility of draft provider training materials/job aids, and factors motivating or dissuading providers from counselling or providing the ring. Interviews may also explore provider-targeted strategies for communication, demand creation, and adherence support. Interviews will ideally include providers representing different cadres, sexes, years in practice, and service areas (e.g., HIV service sites vs. family planning clinics vs. mobile/community/DREAMS services).
* The MOH [or other health authority] requests inclusion of measures to inform ring cost modelling across studies (Table 5); these measures are germane to feasibility outcomes and centre on supply side considerations.
* Study duration should be at least six months of follow-up overall with a proposed two-phase analysis of results: at one to three months (at the end of cohort recruitment) to focus on feasibility and early acceptability (e.g., uptake) and at six months to focus on acceptability outcomes.
* A member of the subnational-level health authority in the area of pilot implementation should be included in the implementation as a co-investigator with funding for routine oversight visits to the study site.
* The MOH requests the inclusion of an MOH [or other health authority]-convened Advisory Committee to include inputs from potential end-user groups (e.g., adolescent girls and young women, sex workers, and gender-diverse individuals) and their communities in the design (upon investigator or MOH request) and oversight of research (please see Advisory Committee section). Please ensure that study budgets include costs for monthly site visits by one member of the Advisory Committee.

**Inclusion and exclusion criteria**

**Facility or care site features**

All study sites should meet the following criteria:

* Have experience providing oral PrEP counselling and/or services
* Have links to the public sector supply chain and service quality oversight to ensure minimum service standards are met for oral PrEP
* Have authorisation from local authorities to expand service delivery to include oral PrEP provision (e.g., reproductive health care sites)

**End-user participants**

All studies should have the following inclusion criteria for end-user participants:

* At least 18 years of age [Can consider revising this if and when data on ring product safety among adolescents older than 15 years become available and international guidelines are adapted accordingly]
* Assigned female sex at birth — eligibility questions will need to ask potential participants about their sex assigned at birth and gender identity and to help those who are unfamiliar with these terms to answer easily
* Sexually active and wishing to prevent HIV acquisition during receptive vaginal sex
* Able to provide informed consent
* Member of priority groups for HIV prevention: sexually active adolescent girls and young women; sex workers or other women engaged in transactional sexual partnerships; clients with a partner of unknown or positive HIV status; or any client who meets other eligibility criteria and requests access to PrEP
* Using a modern contraceptive method (e.g., hormonal contraceptives, male or female condoms, intrauterine contraceptive device, standard days method) [Can consider revising this requirement if and when data on product safety during pregnancy and breastfeeding become available and international guidelines are adapted accordingly.]
* Able to return to the same health facility or care site during a six-month period

All studies should have the following exclusion criteria for end-user participants:

* Younger than 18 years [Please see above.]
* Currently pregnant or breastfeeding or planning to become pregnant or breastfeed within the next nine to 12 months — The rationale for this criterion is that data for ring safety in pregnancy and during lactation, while reassuring, are relatively sparse. Ongoing studies (DELIVER, B-PROTECTED) are investigating this issue, but these pilot studies will adhere to current ring prescribing guidelines, which stipulate that the ring should not be used by pregnant or lactating women. Women using the ring who become pregnant during the study period should be counselled based on the evidence available at that time and offered the opportunity to switch to oral PrEP. [Please see above.]
* Have documented HIV infection, signs or symptoms of acute HIV infection, or suspected HIV exposure in the last 72 hours (i.e., candidate for post-exposure prophylaxis), or have declined HIV testing
* Unable or unwilling to be contacted for follow-up appointments

**Healthcare providers**

[Please adapt based on current/intended PrEP service site features in your context.]

All studies should have the following inclusion criteria for health care provider participants:

* Experience with providing oral PrEP services
* Currently providing social harm screening and care services at the selected facility/site
* Able to provide informed consent
* Have participated in the draft provider ring counselling, provision, and management training course
* Have recent experience screening for and treating sexually transmitted and other reproductive tract infections
* Have recent experience providing HIV counselling and testing

All studies should have the following exclusion criteria for health care providers:

* Unwilling to provide the ring
* No experience providing HIV, PrEP, or sexual and reproductive health services

**Public health sector administrators and key informants**

[This participant group is optional but recommended for additional insights into feasibility, fidelity, and cost measures.]

Studies may consider inclusion of the following groups for insights into ring feasibility, fidelity of implementation and adaptations, and perceived costs:

* Provincial/county/district-level health administrators
* Government or implementing partner technical advisers for HIV service delivery
* Community leaders
* Members of HIV advocacy groups

*All studies should record the number of potential participants deemed ineligible, the reason for ineligibility, and, separately, the number who are eligible but declined study participation.*

Visit schedule and outcome measures and indicators

The MOH [or health authority] asks that all investigator teams include the following required measures/indicators for feasibility and acceptability analyses and safety and also proposes a number of additional indicators for inclusion for each objective. The rationale for this mandate is to ensure comparability across studies and consistent data quality to sufficiently power analyses.

We have mapped a minimum visit schedule, location, and interview type within presumed routine care visits to capture the “real world” nature of implementation studies as well as respect cost and time constraints within study operations (Table 2). This table is illustrative and should be adjusted based on the oral PrEP minimum service package and, where available, draft ring minimum service package schedules unique to each implementing country.

**Table 2. Illustrative study data collection mapped to service engagement points**

|  |  |  |
| --- | --- | --- |
| **Service delivery point** | **Participant group; outcome** | **Interview type** |
| Pre-service: Initial service site engagement following provider training | Provider; feasibility | Provider interview with quantitative questions for all; for subsample, qualitative interviews on how to improve in-service training, factors contributing to perceived service readiness, and appropriateness  |
| Initial patient consultation with HIV testing services (HTS) and HIV prevention counselling (including PrEP) | End-user; feasibility, acceptability (service and method uptake), and fidelity (HIV prevention & PrEP counselling conducted with main points included)  | Enrolment visit conducted as exit interview; for subsample, qualitative interview regarding perceived service quality and reasons for PrEP choice/non-use |
| Initial patient consultation with HTS and HIV prevention counselling (including PrEP) | Provider; fidelity | Relevant clinical (e.g., HIV test completed) or validation (e.g., PrEP method selected and dispensed) inputs from chart review and end-user exit interview |
| Phone consultation at one month (or ring visit if reflective of patients preferring provider removal/insertion or service guidelines) | End-user; acceptability | We note that phone follow-up at one month may be limited to study activities but have built in this time point for monitoring use patterns. |
| Phone consultation at one month (or ring visit if reflective of patients preferring provider removal/insertion or service guidelines) | Provider; fidelity | For ring: to capture provider counselling, pregnancy (as indicated) testing, and offering/teaching self-insertion/removal |
| Quarterly PrEP follow-up visits | End-user; acceptability, fidelity, and clinical measures | Quarterly resupply visits with relevant quantitative acceptability (e.g., continuation, satisfaction, risk perception), fidelity (e.g., received ongoing counselling and adherence support), and clinical outcomes |
| Quarterly PrEP follow-up visits | Provider; fidelity | Quarterly resupply visits with quantitative provider interview for fidelity (e.g., services offered with accompanying chart audit) |
| **Service delivery point** | **Participant group; outcome** | **Interview type** |
| Ad hoc PrEP method issue management, switching, or discontinuation visit | End-user; acceptability, fidelity, and clinical measures | Quantitative interview with acceptability (including reasons for switch/discontinuing), fidelity (e.g., did provider support continuation/ discontinuation decision or counsel on other options), and clinical measures (e.g., serum creatinine for oral PrEP); subsample for qualitative interviews on change in PrEP method use |
| Ad hoc PrEP method issue management, switching, or discontinuation visit | Provider; fidelity | Quantitative interview with chart audit; subsample with qualitative interviews regarding perceived reasons patients change PrEP methods and altered perspectives on how to provide different PrEP methods |

Table 3 includes questions required to achieve the study objectives, along with visit type and application of information. Table 4 provides suggested measures, with some additional entry points listed that correlate with an alternative time point for a required or suggested measure.

**Table 3. Required study outcome measures**

|  |  |  |  |
| --- | --- | --- | --- |
| Required outcome measures | How measured? | When measured? | Role in analysis? |
| **Feasibility Measures: End-Users** |
| Interest in ring as a PrEP method | Please see Annex 3. | Enrolment visit with questionnaire following counselling and HIV prevention method selection | Primary feasibility outcome measure for end-users  |
| Required outcome measures | How measured? | When measured? | Role in analysis? |
| **Feasibility Measures: Providers**  |
| Perceived readiness to offer the ring following training session | Please see Annex 3 for quantitative questions.Probe service readiness in qualitative interviews for context. | Post-training interview | To inform pre/post-test as part of provider training package and help refine package |
| Ring knowledge score | Composite score for 5–7 quantitative knowledge questions with answers presented in training materials (questions and answers in Annex 3) | Questions as part of pretest and post-test for ring training package | Primary outcome for feasibility of training package; can add questions on provider’s attitude about time/ability to include ring services within existing duties |
| **Acceptability Measures: End-Users** |
| Uptake: Participants initiating specific PrEP method | # consented eligible participants counselled who receive oral PrEP pills or the ring (placed by provider); enrolment interview questions (Annex 3) verified with clinic or pharmacy record | Enrolment visit (assume done as exit interview) | Primary outcome measure for specific method uptake; denominator for continuation/ acceptability measures |
| Uptake: Reason for method selection | Please see Annex 3 for quantitative questions.In qualitative subsample, ask about why participants selected their specific method or decided not to start PrEP.  | Enrolment visit [assume done as exit interview] | To provide context for method uptake and set baseline for determining acceptable features that are sustained over time |
| Continuation: Participants using PrEP method selected at study entry through cohort period  | # participants reporting use of initial PrEP method at follow-up visits with pharmacy record verification/total # initiating that method | All follow-up visits | Primary outcome measure for acceptability; disaggregate by method, target group, prior oral PrEP use, and province  |
| Required outcome measures | How measured? | When measured? | Role in analysis? |
| **Acceptability Measures: End-Users (continued)** |
| Use patterns as part of continuation: Participants modifying PrEP use based on perceived risk or opportunity cost | Please see Annex 3 for quantitative questions. Include qualitative subset to probe reasons for intermittent use. | All follow-up visits | To characterise use patterns as part of acceptability and to inform adherence support; exploratory analyses of barriers to continuation  |
| Switching: Participants changing from one PrEP method to another  | # participants requesting and changed from PrEP method initiated at enrolment to new method with pharmacy record verification/# total new PrEP usersPlease see Annex 3 for quantitativequestions; probe reasons for switching in qualitative subsample.  | All scheduled and ad hoc follow-up visits | Acceptability outcome; disaggregate by method, target group, and province |
| Acceptability: Participant perceived acceptability, partner acceptance, and would recommend to friend | Proposed quantitative questions are in Annex 3.Please see Annex 2 for alternative question structure if you anticipate following end-users who decline PrEP use or having high discontinuation rates.  | All follow-up visits | Mean/median scores; disaggregate by method, age, target group, prior oral PrEP use, and province  |
| Acceptability: Discontinuation and reasons for discontinuing PrEP | Please see Annex 3 for quantitative questions. Probe reasons for discontinuation in in-depth interviews among a subsample of those discontinuing PrEP and those switching methods. | Visit where discontinuation requested/ reported | Comparison by original method; self-reported length of use; disaggregate by age and target group, prior oral PrEP use, and province; reasons for discontinuing (clinical, use challenges, provider-initiated, partner-related, etc.) |
| Required outcome measures | How measured? | When measured? | Role in analysis? |
| **Acceptability Measures: Providers** |
| Frequency offering oral PrEP and the ring  | Quantitative measure in interview [# times counselled/week; see Annex 3]; check facility pharmacy records for # new oral PrEP or ring clients receiving product in designated time period; probe in qualitative interviews to determine provider confidence vs. changes in service readiness (e.g., stock-outs) | Provider questionnaire at end of enrolment period; pharmacy record check at follow-up visits | Overall proportions; disaggregate by cadre and province |
| Acceptability of counselling on the ring/oral PrEP together and offering choice | Please see Annex 3 for quantitative and qualitative questions.  | After training  | For quality assurance and improvement; observational checklist findings and reported qualitatively in aggregate only |
| **Additional content areas relevant to PrEP effectiveness/safety measurable within pilot studies and for inclusion in minimum service packages** |
| HIV acquisition | HIV testing per national guidelines/minimum service package | 1 month and quarterly/routine follow-up visits | Effectiveness outcome (though note studies are not powered for this outcome); plan aggregate across sites |
| Incident pregnancy\* | Pregnancy testing  | 1 month and quarterly/routine follow-up visits | Safety outcome; plan aggregate across sitesRing to be discontinued in event of incident pregnancy. |
| Required outcome measures | How measured? | When measured? | Role in analysis? |
| **Additional content areas relevant to PrEP effectiveness/safety measurable within pilot studies and for inclusion in minimum service packages** |
| Adverse drug reaction reporting per national guidelines | # of participants reporting adverse drug reactions | All follow-up and ad hoc visits  | Safety outcome; relatedness to PrEP method use; plan aggregate across sites |
| Social harms† reported by participant or recorded at study site  | # of participants reporting social harms and sub-portion attributed to PrEP use | All follow-up and ad hoc visits  | Safety outcome; relatedness to PrEP method use; plan aggregate across sites |

\*Change pending emerging evidence of safety in pregnancy

† Social harms should use the most appropriate national definition. A suggested definition is: “Social harms are events that cause physical, emotional, or financial but nonmedical adverse consequences due to PrEP use.”

**Table 4. Suggested outcome measures and questions for investigator consideration**

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| --- | --- | --- | --- |
| Outcome measures | How measured? | When measured? | Role in analysis? |
| **Suggested Feasibility Measures: End-Users** |
| PrEP method planned to use at time of facility visit (enrolment) | Please see Annex 3 for suggested quantitative questions. | End-user interview following sensitisation session and before provider visit, if feasible | Comparison of client perceptions prior to and following provider counselling |
| Perceived effort to access/use the ring | Please see Annex 3 for suggested quantitative questions. | Interviews following community or waiting room sensitisation sessions | Context-specific client preferences to shape demand creation and service provision |
| Outcome measures | How measured? | When measured? | Role in analysis? |
| **Suggested Feasibility Measures: End-Users (continued)** |
| Perceived “opportunity costs” associated with ring use | Please see Annex 3 for suggested quantitative questions. | Interviews following community or waiting room sensitisation sessions | Context-specific client preferences to shape demand creation and service provision |
| Perceived effectiveness of ring compared to oral PrEP or other HIV prevention methods | Please see Annex 3 for suggested quantitative questions. Probe role of perceived effectiveness in decision-making about the two methods in qualitative interview subset. | Key informant interviews of representative end-user participants | Context-specific client preferences to shape demand creation and service provision |
| Perceived self-efficacy to use ring as PrEP | Please see Annex 3 for suggested quantitative questions. | Interviews following community or waiting room sensitisation sessions | Context-specific client preferences to shape demand creation and service provision |
| Perceived most reliable source for PrEP information/ recommendation | Please see Annex 3 for suggested quantitative and qualitative questions. | Interviews following community or waiting room sensitisation sessions | Context-specific client preferences to shape demand creation and service provision |
| Preferred site and provider for general PrEP provision and specifically for the ring | Please see Annex 3 for suggested quantitative questions. | Interviews following community or waiting room sensitisation sessions | Context-specific client preferences to shape demand creation and service provision |
| Perceived facilitators/barriers to ring access and use | Please see Annex 3 for suggested quantitative and qualitative questions. | Interviews following community or waiting room sensitisation sessions | Context-specific client preferences to shape demand creation and service provision |
| **Suggested Feasibility Measures: Providers** |
| Perceived demand for ring vs. oral PrEP by clients | Please see Annex 3 for suggested quantitative and qualitative questions. | Qualitative semi-structured in-depth interviews of sub­sample of providers at selected follow-up visit where providers have experience with both PrEP methods | Provider attitude inventory to determine need and content for values clarification as part of training package |
| Outcome measures | How measured? | When measured? | Role in analysis? |
| **Suggested Acceptability Measures: End-Users** |
| Participants reporting ring self-insertion after initiation [ring users only] | Please see Annex 3 for suggested quantitative questions. | First follow-up visit where self-insertion is reported | Proportions: disaggregate by age and target group, prior oral PrEP use, and subnational level |
| Participants disclosing PrEP use to at least one person | Please see Annex 3 for suggested quantitative questions. | Enrolment visit [See partner disclosure questions in required questions for follow-up visits] | Proportions: disaggregate by type of person (e.g., male partner, family member), participant age, PrEP method and target group, prior oral PrEP use, and subnational level |
| **Suggested Acceptability Measures: Providers** |
| What is/is not working for providers and how can the tools/job aids/training provided to them be improved upon to better support their role? | Please see Annex 3 for suggested quantitative and qualitative questions. | One month and end line | Overall proportions: disaggregate by cadre and subnational level |

Costing analyses content

The [MOH or national authority] also requests that the following required and suggested measures be added to permit costing analysis across studies, which will provide essential information to guide ring introduction decisions. Table 5 provides these measures, which will be combined with health system costs in analysis. Should interest and funding be available, willingness-to-pay substudies could be considered in contexts where user fees are part of PrEP service costs.

**Table 5. Required and suggested costing measures**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome measures** | **How measured?** | **When measured?** | **Role in analysis?** |
| **Required Costing Measures** |
| Patterns of PrEP visits (continuation, cycling) | For each client who initiates PrEP, collect data on dates and PrEP method use (continuation, re-initiation, discontinuation, method switching, non-refill visits for other reasons) at subsequent visits | Enrolment, scheduled follow-up, and ad hoc visits | Captured above in required acceptability measures, but repeated here because it has implications for costing |
| Incremental PrEP service delivery costs | Please see Annex 3 for costing data inputs needed. |  | Incremental cost of adding ring service delivery to existing services per visit, per client initiated, per person-year, disaggregated by type of site and type of client |
| **Suggested Costing Measures** |
| Cost to clients for those seeking ring services | Include wealth quintile measures in demographic data and ask about estimated costs borne by clients to access PrEP services. Please see Annex 3.  | Conducted at the pilot testing phase or during early stages of scale-up | Clarifies the cost to clients of seeking ring services and assesses the extent to which these costs represent barriers |
| Ratio of numbers of rings dispensed to used | Data relating numbers of rings dispensed to patterns of use (please see Annex 3). | Track ring insertion and removal via reported use across follow-up visits | Estimating costs of service delivery per person-year of protection |

Study efficiency review

The MOH [or health authority] requests that each investigator group list specific subnational sites, type(s) of service sites, and end-user groups planned for each study prior to submission to the institutional review boards (IRBs). These selections will be reviewed to ensure coordination across investigator groups and to suggest alterations or expansion in target groups or service sites to ensure multiple data sources for key measures. A matrix will be provided to facilitate this process (Annex 1). Each investigator team should include a plan for sustained ring provision for women who participate and wish to continue ring use after the study period.

Ring implementation pilot Advisory Committee

The MOH [or health authority] will convene an advisory committee to provide ongoing guidance and input during protocol development (upon request of the MOH or the investigator team), implementation, initial results presentation (feasibility and uptake data), and final results presentation. We recommend that investigator teams avail themselves of the expertise within the Advisory Committee for the wording of the consents and questionnaires as well as selection of study facilities and engagement with local community-based organisations.

The committee will comprise MOH [or health authority] and stakeholder representatives, including representatives from end-user groups, who are not investigators on the pilot implementation studies (number to be determined by health authority). The committee will also include representation from advocacy groups for sexual and reproductive health and HIV prevention in [country name] and civil society organisations comprised of specific ring end-user groups. Advisory Committee members will be nominated by the MOH, NAC, [or health authorities] and selected members of the PrEP task force [or relevant technical working group] not affiliated with pilot implementation studies. At least one Advisory Committee member will be selected from the provincial health team and one from the health teams of each district where the pilot studies will be conducted.

The Advisory Committee will be available to review study instruments and protocols to provide contextual insights as well as suggest improvements in phrasing or supplemental questions to better achieve the study outcomes. Committee members will also assist investigator teams and the MOH in designing dissemination plans and will provide direct support, as possible, for community updates on study progress and findings, aligned with study and national community sensitisation efforts.

To ensure alignment with MOH [or health authority] guidance, investigator teams should submit the protocols, instruments, and consent documents for MOH [or health authority] review and concurrence prior to IRB submission. The MOH [or health authority] will consult the committee as needed to confirm guideline adherence. The committee will also ensure that study efficiency review (e.g., geographic and end-user representation) has been completed prior to implementation.

The Advisory Committee will meet quarterly to monitor study progress and input from sites and communities in the study areas. The committee may convene ad hoc meetings in the event of reported safety or social harms and ensure mitigation measures proposed by the investigators are sufficient to address the issue, potentially in collaboration with the local IRB. At study end, the investigator team will present the main results to the committee for input on synthesis and interpretation, and the committee will report to the MOH [or health authority] regarding study alignment with MOH [or health authority] guidance and lessons learned to inform product introduction decisions and planning.

References

1. 1 van der Straten A, Agot K, Ahmed K, Weinrib R, Browne EN, Manenzhe K, *et al.;* TRIO Study Team. The Tablets, Ring, Injections as Options (TRIO) study: what young African women chose and used for future HIV and pregnancy prevention. *J Int AIDS Soc.* 2018;21(3):e25094. doi: 10.1002/jia2.25094. [↑](#endnote-ref-2)
2. 2 Montgomery ET, Beksinska M, Mgodi N, Schwartz J, Weinrib R, Browne EN, *et al.* End-user preference for and choice of four vaginally delivered HIV prevention methods among young women in South Africa and Zimbabwe: the Quatro Clinical Crossover Study. *J Int AIDS Soc.* 2019;22(5):e25283. doi: 10.1002/jia2.25283. [↑](#endnote-ref-3)
3. Nel A, van Niekerk N, Kapiga S, Bekker L-G, Gama C, Gill K, *et al.;* Ring Study Team. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. *N Engl J Med.* 2016;375(22):2133-2143. doi: 10.1056/NEJMoa1602046. [↑](#endnote-ref-4)
4. Baeten J, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, *et al.;* MTN-020–ASPIRE Study Team. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *N Engl J Med*. 2016;375(22):2121-2132. doi: 10.1056/NEJMoa1506110. [↑](#endnote-ref-5)
5. Baeten JM, Palanee-Phillips T, Mgodi NM, Mayo AJ, Szydlo DW, Ramjee G, *et al;* MTN-025/HOPE Study Team. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. *Lancet HIV.* 2021;8(2):e87-e95. doi: 10.1016/S2352-3018(20)30304-0. [↑](#endnote-ref-6)
6. Nel A, van Niekerk N, van Baelen B, Malherbe M, Mans W, Carter A, *et al*; DREAM Study Team. Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study. *Lancet HIV*. 2021;8(2):e77-e86. doi: 10.1016/S2352-3018(20)30300-3. [↑](#endnote-ref-7)
7. Brown ER, Hendrix CW, van der Straten A, Kiweewa FM, Mgodi NM, Palanee-Phillips T, *et al*.; MTN-020/ASPIRE Study Team. Greater dapivirine release from the dapivirine vaginal ring is correlated with lower risk of HIV-1 acquisition: a secondary analysis from a randomized, placebo-controlled trial. *J Int AIDS Soc*. 2020;23(11):e25634. doi: 10.1002/jia2.25634. [↑](#endnote-ref-8)
8. Makanani B, Balkus JE, Jiao Y, Noguchi LM, Palanee-Phillips T, Mbilizi Y, *et al*. Pregnancy and infant outcomes among women using the dapivirine vaginal ring in early pregnancy. *J Acquir Immune Defic Syndr*. 2018;79(5):566-572. doi: 10.1097/QAI.0000000000001861. [↑](#endnote-ref-9)
9. Nair G, Ngure K, Szydlo D, Brown ER, Akello CA, Macdonald P, Palanee-Phillips T, Siziba B, Hillier SL, Garcia M, Johnson S, Levy L, McClure T, SotoTorres L, Celum C, on behalf of the REACH Protocol Team. Adherence to the Dapivirine Vaginal Ring and Oral PrEP Among Adolescent Girls and Young Women in Africa: Interim Results from the REACH Study. Abstract OALC01LB01, IAS Conference, July 20, 2021.

**Annex 1. Proposed study subnational site and focus population matrix**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Investigator Team** | **[Province or other sub-national level]** | **[District or other sub-national level]** | **Site (facility or civil society organisation community or DREAMS centre name)** | **Focus group** | **Sample size** |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

**Annex 2. Domain considerations for acceptability questions**

**Streamlined approach to assess end-user ring feasibility measures for implementation studies**

[Assuming questions are asked after initial visit with an HIV prevention counsellor or after a PrEP method has been selected]:

**1. Which method would you prefer to use for HIV prevention?**

	1. Dapivirine ring
	2. Oral PrEP
	3. Male condom
	4. Other: [describe]
	5. None of the above**2. [If PrEP method selected as preferred method]:** What influenced your decision about your preferred method for HIV prevention? (*Select all that apply using statements in Column A.*)

**[If non-PrEP method selected as preferred method, or no method selected at all]:** What influenced your decision about why you prefer not to use the ring or oral PrEP? *(Select all that apply using statements in Column B.)*

|  |  |  |
| --- | --- | --- |
| ***Relevant domain***  | **COLUMN A** | **COLUMN B** |
| **Reasons for preferring PrEP method (ring or oral PrEP)** | **Reasons for not selecting either PrEP method for HIV prevention (or selecting no prevention method at all)**  |
| *Cost* | It is affordable (or free). | The PrEP methods are too expensive. |
| *Access* | It is available in my community. | The PrEP methods are not currently available in my community. |
| *Ability to access* | It is available and will be easy for me to get (*e.g., reasonable clinic wait times, no transportation issues*). | The PrEP methods might be available, but they would not be easy to get (*e.g., long clinic wait times, transportation issues*). |
| *Ease of use* | It will be easy for me to use. | I do not believe the PrEP methods will be easy to use. |
| *Side effects* | I will not worry about the side effects. | I think the PrEP methods will cause side effects. |
| *Emotional comfort/discomfort* | It will cause me to feel pleasant feelings like happiness or reassurance. | Either PrEP method would cause me to feel unpleasant feelings like sadness or anger. |
| *Physical comfort/**discomfort* | It will not cause my body discomfort to use. | Either PrEP method would cause my body discomfort.  |
| *Social comfort/**discomfort* | It will not cause me worry related to the reactions of people around me. | Either PrEP method would cause me worry related to the reactions of people around me. |
| *Effects on health and well-being more generally* | It will be good for my well-being. | Either PrEP method would not be good for my well-being. |
| *Perceived effectiveness*  | It will be effective for me in preventing HIV if I use it well. | Either PrEP method would not be effective for me in preventing HIV.  |
| *Support/disclosure* | I will have support from someone close to me to use it well. | I will not have support for using either PrEP method from someone close to me. |
| *Self-efficacy*  | I can use it correctly and consistently.  | I would not be able to use either PrEP method correctly and/or consistently. |
| *Risk perception (only relevant for those who chose no prevention method)*  |  | I am not at risk for getting HIV right now.  |

*[For each option selected, one could go on to ask a more specific question about that particular response similar to or the same as items we have already pulled out from the existing surveys.]*

**3. What most influenced your decision?**

Response option 1: Repeat options from the questions above but have participants rank their top three reasons.

Response option 2: Think about what things are most important to you now in choosing a product that would provide HIV prevention. What is the most important to you? What is the second most important? (Have participant free list and record responses verbatim below:)

a. (Most important): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

b. (Second most important): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

 [↑](#endnote-ref-10)