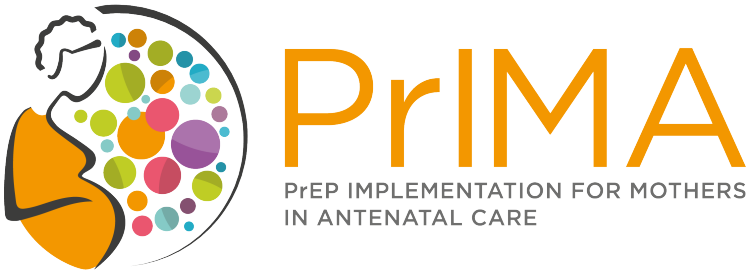

PrEP Implementation for Mothers in Antenatal Care (PrIMA)

A Clinic-Level Cluster-Randomized Trial of Universal Availability Versus Targeted Offer of Oral, Daily Pre-Exposure Prophylaxis (PrEP) among Women Attending Antenatal Care Centers in Kenya

Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

PrEP Implementation for Mothers in Antenatal Care (PrIMA).

1. STUDY SUMMARY AND AIMS

Study Purpose: The broad objective of this study is to determine the best approach to PrEP delivery in pregnancy using existing MCH systems as a platform for efficiently delivering PrEP to pregnant women.

Study Design: This is a cluster randomized clinical trial with 20 ANC clinics in Western Kenya (Siaya and Homa Bay) counties comparing Universal and Targeted PrEP administration. The facility-level cluster randomization will be conducted using a restricted randomization approach based on new antenatal care clinic (ANC) volume, and County. County will be used as a proxy for County differences in HIV prevalence in the restricted randomization approach. In the Universal PrEP arm, PrEP is offered to all and women select whether they want to take it. In the Targeted PrEP arm PrEP is offered to women identified as high risk through a standardized risk assessment and partner self-testing.

Study Population and Sites: Twenty ANC clinics in Western Kenya (Siaya and Homa Bay) counties will be randomized, 10 Universal and 10 Targeted PrEP administration. At each clinic women attending antenatal care will be enrolled in the study. Eligibility for enrollment will include age ≥15 years, pregnancy with the gestational age up to 36 weeks by last menstrual period (LMP) or best available estimate, and tuberculosis negative, plans to reside in area for at least one year postpartum, plans to receive postnatal and infant care at the study facility, and are not currently enrolled in any other studies.

Study Size: At least 200 women per clinic (2,000 per ARM)

Study Duration: At each clinic, enrollment will occur over an approximately 10-month period (~20 HIV negative women enrolled per month) with a ~1-year period of follow-up to 9 months postpartum (time of routine measles immunizations).

Treatment Regimen: PrEP medication and dosing will follow the 2016 Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infections in Kenya using the preferred oral TDF/FTC (300mg/200mg) once per day

Primary Aims:

AIM 1a: To compare Universal PrEP to Targeted PrEP for outcomes reflecting the balance of PrEP effectiveness and safety:

1. HIV incidence at 9 months postpartum
2. Proportion of women who accepted PrEP

Sub-Aim 1a. To compare infant outcomes (growth, birth outcomes, HIV status) between PrEP users and nonusers in combined trial arms.

AIM 1b: To compare trial arms for:

1. Proportion of women 'appropriately' on PrEP (based on risk factors)
2. PrEP adherence (DBS) and duration
3. Partners with known HIV status, on ART

AIM 2: Health economic evaluation of targeted vs. universal PrEP

AIM 3: Assessment of barriers and facilitators of PrEP delivery strategies at the individual patient, healthcare facility, and organizational level

This analysis plan will focus on Aim 1 except for sub-aim 1a which is in a separate SAP for birth/infant outcomes.

2. STUDY ENDPOINTS

Primary Outcome:

HIV infection - a new positive HIV ELISA test after a documented negative HIV test (HIV tests will be the tests recommended and used by Kenya MOH during the course of the study)

Appropriately on PrEP –

a. Initiated (swallowed) PrEP and meeting the risk criterion cutoff

b. Did not initiate PrEP and low risk

Secondary Outcomes:

PrEP Uptake - ever accepted a PrEP prescription from the MCH clinic

PrEP adherence by DBS - any tenofovir-DP detected, tenofovir-DP detected above specific levels (to be defined; analyses are ongoing to better characterize optimal levels in women in general and pregnant women specifically)

Partner HIV status known by end of follow up- by maternal-report when available. Because partners in both trial arms can access HIV testing at the clinic, this data will be captured from maternal MCH cards as available

Infant outcomes – preterm birth, birthweight, 9-month growth (weight, height)

3. SAMPLE SIZE CONSIDERATIONS

Restricted randomization will be used to balance the two arms of the trial in terms of prevalence of HIV, ANC volume, and rates of partner disclosure at included clinics (based on data from our prior CHIME evaluation of 141 MCH clinics). Assuming a coefficient of variation (k) of 0.2, the study has 80% power to detect a 2-fold difference in HIV incidence (between 4% and 2%) with 10 clinics per cluster and 200 women per cluster (Table 1). If targeted PrEP resulted in much better performance (67% decrease rather than 50%), 6 clinics per cluster would be sufficient. Deriving our sample size from HIV incidence difference is conservative and will enable ample statistical power to detect effects on other outcomes (such as proportion on PrEP and partner characteristics). Table 2 outlines implications of potential RCT outcomes illustrating the value of data regarding the two PrEP delivery models in scenarios with or without a significant difference in HIV incidence. We anticipate that the targeted arm may have 20% of women receiving PrEP (based on MSS risk score estimates) while the universal PrEP arm may have 5-25% of women requesting PrEP, however, these are speculative estimates. The study may not detect a difference in HIV incidence between PrEP delivery models because of appropriate PrEP uptake and use in both. However, as outlined in the contingency table (Table 2), for all scenarios the RCT would yield important data on viable approaches for delivering PrEP in pregnancy and likely

reveal a superior model in terms of the balance of effectiveness, safety, acceptability, feasibility, and cost-effectiveness.

Table 1: Sample size power calculations

k	HIV incidence universal	HIV incidence targeted	# women per clinic	#clinics per arm	Total # women
0.2	4%	2%	50	27	2700
0.2	4%	2%	100	15	3000
0.2	4%	2%	150	12	3600
0.2	4%	2%	200	10	4000
0.2	4%	2%	250	9	4500
0.2	4%	2%	300	8	4800
0.2	4%	1.3%	200	6	2400

Table 2: Contingency Table Demonstrating Implications of Potential RCT Outcomes

	Potential HIV incidence outcome	Other potential results	Impact on programs policy in high HIV prevalence regions	Programmatically relevant data from study
Hypothesis Proved	Targeted better	Fewer women on PrEP, cost-effective, safe	Implement targeted PrEP	Data to model and compare impact on HIV transmission, cost, and scale up. HIV incidence/CI, cost-effectiveness, safety, feasibility, process
Hypothesis opposed	Universal better	Fewer women on PrEP, cost-effective, safe	Implement universal PrEP	
Mixed benefits	Universal better	Universal too many women on PrEP not cost effective	Refine universal strategy to decrease cost and unnecessary PrEP exposure	
Mixed findings	Incidence low in both, no difference	Targeted more cost-effective results in few on PrEP	Implement targeted PrEP	HIV incidence estimate/CI, cost-effectiveness, safety, process
		University more cost-effective and fewer women on PrEP	Implement universal PrEP	

4. ANALYSIS SETS

Primary RCT analyses will be intent-to-treat.

5. STATISTICAL ANALYSES AND DESCRIPTION OF MAIN TABLES

AIM 1a: The proportion of all women enrolled in the study who use PrEP (proportion of women exposed to PrEP) will be compared between trial arms using GEE with a binomial link.

AIM 1b: The proportion with 'appropriate' use will be compared between arms using GEE with a binomial link. PrEP adherence will be measured among women on PrEP using DBS TFV drug levels. All women receiving PrEP will have 3-monthly DBS samples available. For each trial arm (10 clinic-cluster) a random subset of 220 DBS will be assessed. TFV drug levels will be compared by trial arm using GEE with a Gaussian link. PrEP duration will be computed for each woman based on self-report and pharmacy records and average duration compared between arms using GEE with a Gaussian link. Reported and confirmed partner with HIV status, proportions of partner HIV positive, unknown and HIV negative status, and reported and confirmed partner ART use will be compared between arms using GEE with a binomial link.

Infant outcomes: mean birthweight and serial weight-for-age z-scores (WAZ), height-for-age z-scores (HAZ), and weight-for-height z-scores (WHZ) will be compared between trial arms using GEE with a Gaussian link. A separate analysis will assess birth and infant outcomes by PrEP exposure in the combined arms.

AIMS 2-4 will conducted after the primary analysis and will not be reviewed by the EAC.

Randomization scheme text for a randomized, unblinded study

The facility-level cluster randomization will be conducted using a restricted randomization approach based on new antenatal care clinic (ANC) volume, and county. County will be used as a proxy for HIV prevalence.

We will select 20 clinics from Western Kenya. Ten clinics will be randomized to universal PrEP and ten to targeted PrEP (Table 2). To ensure balance between study arms in terms of key site characteristics, sites will be categorized on HIV prevalence and ANC volume, and restricted randomization will be used for site (cluster) allocation to intervention and control arms (67). Specifically, all possible randomizations that evenly distribute sites on these two specified factors (HIV prevalence, ANC volume) into 2 study arms will be generated, and one combination will be selected using a random number generator. Randomization and allocation will be performed by Dr. Richardson, who has no knowledge of sites other than the variables included in the restricted randomization process.

In order to build excitement for the study among study staff and facility representatives, we aim to conduct the final randomization activities as part of the study training. Prior to the training, each facility was ranked by county and ANC volume and assigned to one of six groups. The ANC volume and county for each group are summarized in Table 1.

Table 1: Summary of facility group assignments for PrIMA randomization activities

Group	County	Number of Facilities	Mean ANC Volume (SD)
1	Homa Bay	2	173 (60.8)
2	Homa Bay	4	59.8 (1.3)
3	Homa Bay	4	53.8 (3.3)
4	Siaya	2	140 (26.9)
5	Siaya	4	54.8 (6.4)
6	Siaya	4	38 (5.5)

One representative from each facility will be identified to represent their facility during the randomization event. Representatives from facilities in each group will be asked to select a select a ball from a bag during the PrIMA training. The bag will contain one ball per facility, and half of the balls will be blue (universal arm) and half of the balls will be orange (targeted arm). The final facility randomization will be determined by what color ping pong ball the facility representative selects. Facility group assignments are including in Table 2.

6. INTERIM ANALYSIS PLAN

Prior to RCT initiation, we will convene an external advisory panel (EAP) to review study aims and protocol. At annual EAP meetings enrollment, retention, and pooled outcomes will be reviewed. Because of the short RCT timeline and potentially imbalanced follow-up time between sites, we do not plan to conduct an interim comparison of outcomes.

7. REFERENCES

8. PROPOSED TIMELINE

	2016	2017		2018		2019		2020		2021
Activity	**June-Dec**	**Jan-Jun**	**Jul-Dec**	**Jan-Jun**	**Jul-Dec**	**Jan-Jun**	**Jul-Dec**	**Jan-Jun**	**Jul-Dec**	**Jan-Mar**
Study Protocol Developed										
Consent forms developed										
Kiswahili translated consent										
CRFs development										
IRB/ERC Applications										
SOPs developed										
SOP and CRF Training										
IDI Guides developed										
FGD guides developed										
Facility Eligibility Criteria data collected										
Facilities Randomized										
Data Collection- Aims 1 and 2										
Data collection- Aim 3										
Data analysis										
Manuscript writing										
Final Close-Out										
Dissemination of results										

9. APPENDIX: SHELL TABLES AND FIGURES

Figure 1. Flow diagram of cumulative enrollment for Universal and Targeted Arms

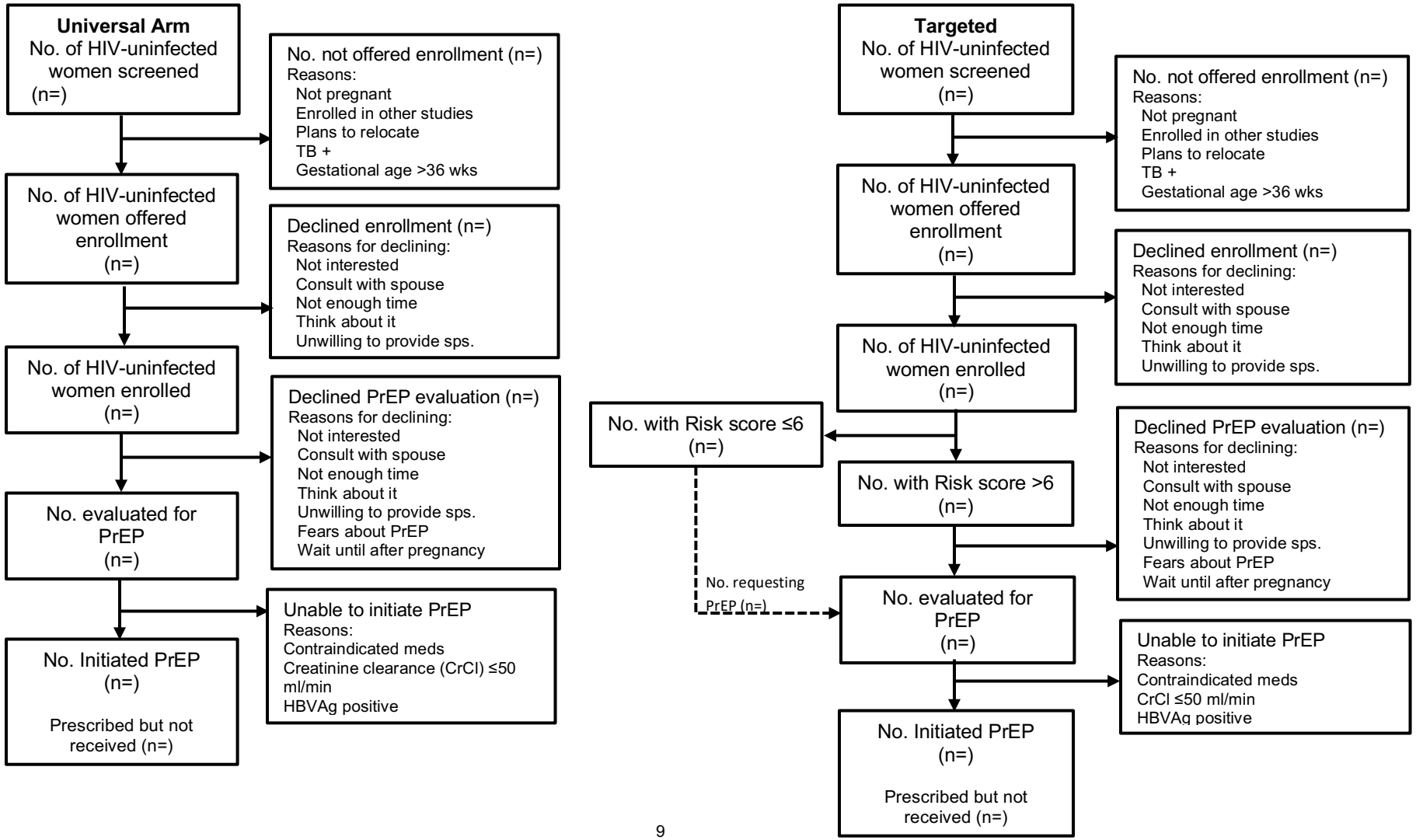

Table 1. Distribution of demographic and clinical characteristics of women by randomization arm

	N (%) or Median (IQR)		
	Overall	Project arm	
		Universal	Targeted
Demographic characteristics			
Age (years)			
Median age			
<25			
25-35			
≥35			
Marital status			
Currently married			
Divorced/separated			
Cohabiting			
Never married			
Widow			
Education (years)			
Regular employment			
People per room			
Risk assessment chacteristics			
No. of lifetime sexual partners			
HIV status of sexual partner(s)			
Positive			
Negative			
Unknown			
No male partner			
RPR reactive			
Pregnancy history			
Gestational age at enrollment (weeks)			
Primigravida			
Previous abortion/miscarriages			
Previous premature birth (<37 weeks)			
Psychosocial scales			
Perceived risk of HIV scale score			
HIV treatment adherence self-efficacy score			
CESD-10 score			
HITS score			

Table 2. Primary and secondary endpoints

	N (%) or incidence/100 py			RR (95% CI), p-value
	All subjects	Trial arm		
		Universal	Targeted	
Primary outcomes				
HIV incidence				
Initiated on PrEP				
Secondary endpoints				
'Appropriately' on PrEP (based on risk score)				
Partner known HIV status by end of follow-up				
Partner on ART if HIV infected				
TFV-DP levels (median on random sample)				

Supplementary Table 1. Distribution of demographic characteristics of women screened and enrolled in the study

	N (%) or Median (IQR)			
	Project arm			
	Universal		Targeted	
	Screened *(n=)*	Enrolled *(n=)*	Screened *(n=)*	Enrolled *(n=)*
Demographic characteristics				
Age (years)				
Median				
<10				
21-34				
≥35				
Gestational age (weeks)				
Plan to receive postnatal care services at this facility				

Table 2. Partner characteristics and self-test results for targeted arm

	N (%) or Median (IQR)			
		Self-test		
	Overall	Accepted *(n=)*	Declined *(n=)*	p-value
Participant Characteristics				
Participants enrolled in targeted arm				
Self-Tests Distributed to Participants				
Self-tests distributed by participants to sexual partners				
Sexual partners who refused a self-test				
Partner characteristics				
Partner HIV status				
Positive				
Negative				
Unknown				
Living together with partner				
Yes				
No				
Married to partner				
Yes				
No				
Partner self-test results				
Positive				
Negative				
Unkown				
No response				

How does the participant know the results of the self test?				
Partner took test with participant present				
Partner told participant the results				
Partner showed participant the test results				
Other				