Official Title: Optimizing Pre-exposure prophylaxis (PrEP) implementation and effectiveness among women at high risk for HIV acquisition in South Africa

Brief Title: Le Kip Kip: A Multi-Layered Cluster Randomized Trial to Change Social Norms and Build Sustainable Demand for PrEP among Women in South Africa

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Research Protocol & Statistical Analysis Plan

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1. KEY ROLES:

The NIH/NIMH-funded research study is to be conducted by Johns Hopkins University School of Public Health (JHU) and TB HIV Care (THC) in South Africa. TB HIV Care will lead the data collection in the provinces of KwaZulu-Natal, Mpumalanga, Eastern Cape and North West Province, South Africa. TB HIV Care has extensive experience working with female sex workers (FSW) and adolescent girls and young women (AGYW) through service delivery programmes funded by the Centers for Disease Control (CDC) and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Human subjects research oversight and approvals will be provided by the Faculty of Health Sciences Research Ethics Committee at the University of Pretoria and the Johns Hopkins School of Public Health Institutional Review Board. All investigators and study staff involved with the data collection and analysis will be trained in the protection of human subjects in research and good clinical practice. Interviewers will receive training on the questionnaire, interviewing techniques, and working with FSW and AGYW.

The principal investigators (PIs) and Co-Investigators will make regular site visits during implementation to provide training, review study progress, support ongoing research activities, and provide technical assistance. The Project Coordinator employed by TB HIV Care will ensure that the study team follows the protocol and that all data collection materials and forms are completed and stored in accordance with the protocol and standard operating procedures. These activities will be monitored by the local PI, JHU PI, and other investigators on site visits.

2. BACKGROUND AND RATIONALE:

The HIV epidemic in South Africa is characterized by extremely high HIV incidence rates among marginalized adolescent girls and young women (AGYW) aged 15-24 and female sex workers (FSW).[1-4] Given intersections of biological, behavioral, and structural risks, high HIV incidence has been sustained despite HIV testing and condom promotion programmes. Pre-exposure prophylaxis (PrEP), currently formulated as a once daily pill taken to prevent HIV acquisition, represents an HIV prevention tool with great promise to finally achieve an AIDS-Free generation in the country most burdened by HIV. While PrEP has been effective at preventing HIV among women with high perceived HIV risk in supportive partnerships (e.g., disclosed, HIV serodifferent couples), limited uptake and early discontinuation has limited the HIV prevention effectiveness for marginalized, young women. Although AGYW and FSW are often perceived as separate groups, data from across Southern and Eastern Africa reinforce overlapping vulnerabilities - with over two times the odds of HIV infection among AGYW engaged in transactional sex compared to other AGYW.[5-7] Moreover, young FSW have often not yet developed sufficient health literacy and self-efficacy to protect themselves from occupational HIV exposure.[8,9] In general, adolescence and early adulthood are times of transition and often volatility, amplifying the risks young women experience.[10-13] Biological, economic and structural factors, including social norms reinforcing gender inequalities and violence, heighten vulnerabilities to HIV acquisition among marginalized young women.[1,14-16]

PrEP has been prioritized by the South African government, yet evidence of how to implement PrEP scale-up and promote both uptake and adherence for marginalized, young women is lacking. Restricted promotion of PrEP outside of population-specific (e.g. either sex workers or men who have sex with men) programming has resulted in low PrEP awareness at the community level, and thus those considering PrEP often experience negative social influence from friends, partners, family and even health care providers about PrEP use.[17-22] Furthermore, among those taking up PrEP, persistence among women halves by 1 month and continues a sharp decline during the first 3-6 months; effective strategies to target uptake and persistence during these critical periods are needed. Several barriers to PrEP adherence have been identified, ranging from individual level health literacy, self-efficacy and side effects, to limited social support for PrEP use and PrEP-related stigma at the community level. PrEP programmes in South Africa are implementing many approaches to try and improve PrEP uptake and continuation in South Africa; however, there is a lack of evidence behind these strategies and to what extent these programme implementation strategies are effective for women at the highest risk.

Currently TB HIV Care is implementing large scale PrEP programmes for FSW and AGYW across four provinces (KwaZulu-Natal, Mpumalanga, Eastern Cape and North West Province) in South Africa. PrEP is provided by professional nurses at drop-in centres and mobile vans – implemented largely within communities. As such, TB HIV Care will lead the cluster randomized trial and data collection within the existing programme sites. TB HIV Care has extensive experience working with FSW and AGYW, as they have been providing HIV prevention services, including HIV testing and counseling, sexually transmitted infection screening and treatment, and condom provision to marginalized young women since 2012 through the mobile van health clinics and drop-in centre wellness clinics. PrEP service delivery for FSW across TB HIV Care supported sites in South Africa began in 2016, expanding in line with DOH priorities to AGYW in 2018 (mobile teams, community outreach, staff placement at DOH clinics). The TB HIV Care programme is funded through 2024 and had already initiated >20,000 women on PrEP in 2020. As the programme evolves, so do the interventions to support sustained PrEP uptake. The services for women are provided through both the FSW and AGYW programmes which have substantial areas of overlap. Programmatic data from TB HIV Care reinforce earlier results from South Africa that PrEP uptake among young women is relatively low, and PrEP use falls by nearly half at 1-month, continuing a steep decline until 7-months. Challenges in PrEP uptake and persistence are similar across sites. These data highlight the potential impact of this research to rigorously evaluate PrEP implementation strategies to initiate and maintain young women on PrEP during periods of heightened HIV risk as the programme continues to expand in coming years.

3. OBJECTIVES OF THE STUDY:

Overall, the aim of this study is to evaluate implementation and effectiveness of a social media campaign and community engagement activites to promote PrEP uptake among women and to influence community norms around PrEP in South Africa. During a previous, largely completed phase of research within this grant we evaluated implementation and indications of effectiveness of ongoing PrEP uptake and retention strategies being promoted by TB HIV Care as part of their AGYW and FSW PrEP programmes. Based on these findings and in consultation with programme stakeholders, we have are proposing a pragmatic trial which will introduce adaptations to current services to work to further improve programme impact (Phase 2 of the grant research being submitted now).

The goal of the proposed study is thus to evaluate the relative effectiveness of modified PrEP implementation strategies on increasing uptake and sustained PrEP adherence among marginalized young women. This phase is focused on introducing modified and focused strategies to promote PrEP within the TB HIV Care HIV prevention programme. The effect of these modifications on sustained PrEP uptake and adherence will be tested using a short duration cluster randomized trial (CRT).

An important point of clarity is that the proposed CRT will not engage in PrEP provision to individuals. Rather, the CDC funded programme employs a large team to provide service delivery. The CRT merely is testing strategies that may amplify uptake and persistence among the community, leveraging the programme infrastructure to actually provide services as it is already doing. Embedding strategies within the programme ensures that the existing results come from real world contexts and focuses on implementation of support strategies rather than clinical care provision.

4. STUDY DESIGN:

This grant combines evaluation of ongoing PrEP programme implementation (previous work) with modified, programme informed implementation strategies for testing through two short-duration cluster randomized trials (CRTs). Specifically, this study protocol is focused on PrEP programme optimization through modifying the implementation strategies of ongoing programmatic activities by adjusting the delivery modalities and actors promoting PrEP within the community. The effect of these modifications on PrEP uptake (primary outcome) and continuation (secondary outcome) will be tested using an initial CRT. A second CRT focused primarily on PrEP continuation (retention) will be included in a separate, future protocol.

TB HIV Care is a South African non-profit organization that works directly with the Department of Health as the country's largest PrEP provider for AGYW and FSW. TB HIV Care has initiated over 33,000 women at high risk for HIV infection on PrEP, and has 13 active sites as of 2021. Of note, these are two PrEP programmes that are run by TB HIV Care (8 of the 13 active sites are part of the FSW programme and 5 of the 13 active sites are part of the AGYW programme). **The proposed study design leverages a cluster randomized trial design as some intervention components may not be feasibly randomized at the individual-level (e.g. PrEP peer ambassadors operating within venues/community locations, community mobilization and social media ads).** This trial is feasible given the short duration of the outcomes measured (PrEP uptake and 1- and 4-month PrEP persistence) and utilization of routine programme data for primary outcome ascertainment, and the testing is an adaptation of existing interventions. Based on the programme team's experience and PrEP barriers literature, this first CRT will focus on generating sustained PrEP demand, but also destigmatizing PrEP within young women's social environments (e.g. family, friends, partners). **CRT1 is described within this application.** The second CRT will likely optimize peer support mechanisms during the early days of PrEP use, but this will be refined in late 2022 based on the programme's input and a separate protocol will be submitted surrounding CRT2.

PrEP Social Influence Campaign CRT:

The CRT under current consideration will compare the existing standardized community engagement model (i.e. PrEP sensitization/promotion) to an ehanced PrEP social influence campaign using different delivery mechanisms. **The primary outcome will be the proportion of FSW/AGYW clients within the TB HIV Care PrEP programme who initiate PrEP among all eligible marginalized young women to whom it is offered.** Secondary outcomes will be differences in knowledge, attitudes and peer influence across arms (described in sections below)

and 1 and 4-month sustained PrEP use among PrEP initiators. The enhanced social media campaign will be implemented for 12-months while the PrEP champion and community mobilization interventions will be implemented for 6-months and will target young women, parents, teachers, peers, and partners. 5 TB HIV Care district sites within the four provinces will be randomized to each arm (10 districts randomized in total).

There will be two main study arms which will be randomized 1:1 at the district level across the 10 sites which span four provinces. **Arm 1** will receive PrEP sensitization per the ongoing programmatic Standard of Care. **Arm 2** will receive the standard of care through the programme per normal, as well as an enhanced social media intervention that will be targeted to the intervention districts. This is feasible because through social media platforms like Facebook, advertisements can be geographically targeted to specific areas. The primary outcome of PrEP uptake will be powered to assess the difference in PrEP initiations across the 10 sites, comparing PrEP uptake numbers in Arms 1 and 2. Additionally, a second layer of enhancement will be layered onto the intervention arms (Arm 2). Thus in addition to the social media campaign, wards from the five intervention districts will be randomly selected to implement: a) Nothing additional; b) Training and support for venue-based PrEP champions; c) PrEP community mobilization teams; d) Training and support for venue-based PrEP champions AND PrEP community mobilization teams. Details are further highglihted in Table 1 below:

Table 1: Intervention activities and CRT plan

Arm	**Name**	**Description**
Arm 1*	Standard of care	Full-time peer educators employed by the programme to engage women, layer PrEP promotion across prevention programs, and implement “refer a friend” strategies, information, education and communication (IEC) materials, service user testimonials, risk reduction posters to increase young women’s perception of risk, working after hours/weekends to reach young women, working with school governing bodies, and door-to-door outreach.
Arm 2*	Enhanced social media campaign	PrEP social influence campaign, which will use online approaches to promote PrEP within communities in addition to the standard of care actvities. Messaging crafted with community input will be geographically targeted to women, parents/mentors, and male partners on Facebook and/or Instagram (final platforms to be determined based on marketing research conducted by Community Health Trust who will contracted to manage the campaign), all with the intention to promote PrEP for women at high risk of HIV infection and change community norms and influence around PrEP. A combination of static imagery and brief videos will be used to engage these groups via social media platforms. High profile social influencers may be engaged as faces of the campaign, including for ads and video creation. A Facebook page will be created and maintained that can be accessed by anyone anywhere, but will only be advertised/promoted in the intervention districts.
Arm 2a**	Nothing additional	Wards in Arm 2a will not receive any additional strategies. They will still receive (as will all arms) the standard of care, as well as the enhanced social media campaign received by all wards in Arm 2.

Arm 2b**	PrEP champions	Within venues served by the FSW and AGYW programs, we will identify and train 1 venue-based PrEP champion per venue who will (a) have completed a 2 day group-based (cross-venue) health information training related to PrEP knowledge, with pre and post testing knowledge assessments to identify knowledge gaps; (b) receive supplies (e.g. a hat, pin and posters, flyers, IEC material) to wear to promote PrEP; (c) facilitate linkage between women interested in PrEP and the TB HIV Care PrEP programme; and (d) receive bi-weekly follow-up support from TB HIV Care to discuss challenges, progress and referrals. A partial day refresher training will be held at 3-months. PrEP champions will be either peers with experience taking PrEP, venue managers or local influencers (e.g. women running shops next to the mobile serving AGYW) that have repeated contact with the women the programme is intended to serve. The final selection of PrEP champions will be made in consultation with the Community Advisory Groups, venues and by the programme who works closely with each of the sites. The PrEP champions will receive a small airtime stipend (R150 per month) to follow-up and provide support to women engaging in PrEP.
Arm 2c**	PrEP community mobilization	A PrEP community mobilization team (2 peers, including one woman and one man) will be recruited within each ward to promote PrEP. The team will present information about PrEP and the PrEP programme at the ward councilors meeting, at Learning Support Agent meetings with parents/guardians, at local events/fairs, community meetings and through engaging men, women and parents across the community through informal conversations. Teams will be wearing branded material and will focus on presenting factual information and decreasing PrEP stigma, and will have received 3 days of training in HIV, PrEP, and health communication and persuasion to promote positive PrEP norms and attitudes within the community, with a 1-day refresher training at 3-months. Each team will focus on promoting PrEP within their own ward over the 6-month period.
Arm 2d**	PrEP champions + PrEP community mobilization	Wards in Arm 2d will receive both of the two additional strategies described above (2b & 2c).
*10 districts randomized 1:1 across Arms 1 and 2. ** Each of the wards (~216) across the 5 districts will be randomized to receive additional layered activities intended to change social norms around PrEP and amplify the social media campaign		

5. STUDY POPULATION:

The study population includes female sex workers (FSW) and adolescent girls and young women (AGYW) who will participate in the TB HIV Care programme over a one year period (12-months) across multiple sites starting at the launch of the campaign. Overall, since programme inception, TB

HIV Care has implemented PrEP services for women in 17 sites aross 6 provinces. Currently 13 sites are actively implementing PrEP programming in 10 districts across 4 provinces and will contribute to the CRT aggregate level data: OR Tambo, Eastern Cape (AGYW & FSW); Zululand, KZN (AGYW); uThukela, KZN (AGYW); uMgungundlovu, KZN (AGYW & FSW); eThekwini, KZN (AGYW & FSW); Ehlanzeni, Mpumalanga (FSW); Gert Sibande, Mpumalanga (FSW); Nkangala, Mpumalanga (FSW), Dr. Kenneth Kaunda, North West Province (FSW); and Ngaka Modiri Molema, North West Province (FSW). Here, participation is defined as receiving ≥1 of the following HIV prevention services offered to FSW and AGYW by TB HIV Care: STI screening and/or treatment, pregnancy testing, HIV testing, or any other service that would result in having a health screening form on file. All clients seen by TB HIV Care are assigned to HIV acquisition risk groups (FSW, AGYW, or others) the first time they are seen based on risks reported on a standardized intake form. Women screening positive for HIV on their first encounter with the programme during the study period will be excluded.

The time period of interest will be 12-months. We anticipate the social media campaign to launch in February 2022, in which case the study period would be February 1, 2022-January 31, 2023. The one year of follow-up will begin at the time of campaign launch.

A. Inclusion Criteria

For active enrollment for cross-sectional survey: Participants will be recruited during programmatic activities led by TB HIV Care. Cisgender women and adolescent girls (15+ years) who are eligible for PrEP per TB HIV Care programmatic criteria: HIV negative; AND engaged in sex work (18+ years) OR transactional sex OR sex with multiple partners OR who have a partner who has multiple partners OR have a partner who is known or suspected to be HIV positive); AND individuals must also be current TB HIV Care HIV prevention programme users (including HIV prevention messaging, condoms, HIV/STI testing and/or PrEP).

For passive enrollment using programme data: Analyses using de-identified, aggregate programmatic data will utilize data from cisgender adolescent girls and young women (15-24 years) engaged in the AGYW programme and cisgender FSW women (18+ years), who are eligible for PrEP per TB HIV Care programmatic criteria (HIV negative, engaged in sex work or transactional sex or sex with multiple partners or who have a partner who has multiple partners or is known or suspected to be HIV positive); individuals must also be current TB HIV Care HIV prevention programme users (including HIV prevention messaging, condoms, HIV/STI testing and/or PrEP). Programmatic data will be utilized in an aggregate, de-identified manner, similar to what is reported to the Department of Health and program donors (PEPFAR/CDC).

B. Exclusion Criteria:

For active enrollment for cross-sectional survey: Not eligible for PrEP (no risk factors identified in programmatic screening.

For passive enrollment using programme data: Not eligible for PrEP (no risk factors identified in programmatic screening).

C. *Selection of the Study Population:*

For active enrollment for cross-sectional survey: A sample of TB HIV Care HIV prevention program users (individuals the HIV prevention team engages with, including but not limited to offering PrEP, independent of uptake) will be approached by research assistants with quantitative interviewing experience independently hired through the study.

Pre-intervention launch: First, we will randomly sample 6 programme districts (3 in Arm 1 – standard of care areas, and 3 in Arm 2 intervention areas). Next, within each selected district, we will work closely with the programme site(s). Each programme site has one or more HIV prevention/PrEP programme team which operates at drop-in centres or at mobile vans operating at various community-based venues. Each programme site has a schedule of venues that they visit each day. During the one-month active enrollment period, these schedules will be used to randomly select two implementation teams to accompany each work-day (each day we will sample one team without replacement and then sample a second team; the next day all teams will be eligible for sampling again). One research assistant will accompany each team (in the event that there is only one programme team, both research assistants will accompany that team). Based on the programme teams randomly selected on a given day, we will accompany the team in their programmatic activities. During these visits, the research assistant will consecutively approach women at the site (starting with the order of arrival), explaining the study, screening for eligibility and offering a brief 20-30 minute survey to eligible women and adolescent girls engaging with the service. We will recruit up to 4 women and girls per day per site (8 if there is only one team for both research assistants to accompany). This will ensure a wider representation of women and girls from sites across the district. Recruitment will last an estimated 4 weeks (~25 women and girls per week per site will be recruited, which across two research assistants is roughly 2-3 interviews per day, with a maximum of 4 allowed). Each site will conduct 100 cross-sectional interviews during this one-month period; enrollment in some cases may be slightly faster or slower than one-month, but we anticipate one-month will be on average how long it will take.

Post-intervention: Using the previously sampled districts, we will repeat the approach of randomly selecting teams to accompany after 1-year of intervention activities. This post-intervention survey will be identifical in approach to the first survey (n=100 participants per site), although a few additional questions will be added to the post-intervention to assess exposure to the intervention. Participants who completed the first survey will not be intentionally recruited for the follow-on post-intervention survey, but if present and systematically approached on the day of enrollment, individuals will not be excluded if they participated in the prior round of research.

Pre and post-intervention survey: The survey will collect minimal individual behavior data, and is mainly intended to assess PrEP knowledge and attitudes, exposure to PrEP promotion events and the social media campaign, as well as the woman or adolescent girl's views on partner, family and peer perceptions of PrEP. Interviews will be conducted cross-sectionally at two time points (serial cross-sectional interviews with programme users). Following screening and the informed consent/assent process, the trained research assistants will administer the survey to study participants on a tablet, reading each question aloud and recording all participant responses. Overall, 600 women and adolescent girls (300 in the standard of care and 300 in the intervention sites) will be enrolled pre-intervention and 600 women and adolescent girls (300 in the standard of care and 300 in the intervention sites) will be enrolled post-intervention, totaling 1,200 participants across the sites and the two time periods.

For passive enrollment using programme data: No individual human subjects will be recruited for this element of the study. Rather than individually target programme users with the enhancements to understand their impact, these are strategies that are attempting to change the

norms around PrEP within communities and social spaces which cannot be individually randomized. Thus, we are randomizing clusters (sites) to receive the package and it will be offered routinely throughout. Women engaging with the TB HIV Care programme may or may not notice or be impacted by the intervention, however each has the potential to be reached by it if they are in the programme area. Routinely collected, aggregate programme data will be used to assess the proportion of FSW and AGYW programme users within the TB HIV Care PrEP programme who initiated PrEP among all eligible women to whom it was offered per programme logs during the 12-month period of the PrEP social influence campaign (CRT).

For passive enrollment using social media metrics: Through Facebook Ad Manager (and Instagram or other platforms if relevant), we will receive analytic data to assess our our ad metrics, including: # times each ad was viewed overall and by an individual, # times someone clicked on each ad, and the click-through rate metric which tells you the percentage of people who click an ad out of all the people who saw the ad; we will also assess the number of website/Facebook page visits, video views and appointments made. Quotes may be collected from posts in the study's public facing Facebook group to be used anonymously in analyses. This will be made clear in the study's Facebook group description, and no names will be linked to quotes. No quotes will be collected from any users' posts outside of the study public Facebook group; for example private messages sent through Facebook messenger will be categorized based on their general content as process indicators (e.g. informational questions, access questions, questions pertaining to personal risk, etc.), but any direct quotes will be excluded from analysis.

6. STUDY PROCEDURES:

Social influence campaign: Individuals living in the 5 intervention arm districts will potentially be exposed to the enhanced social influence strategies. This will include both static ads and video content which will be posted on social media platforms during the duration of the 12-month CRT. The second layer of the campaign will include additional interventions including PrEP champions who will be based at venues where FSW/AGYW work or socialize. Given that randomization is occurring at the programme site and ward levels, service users and their families, peers, and partners will not all be exposed to the campaign given we are not randomizing at the individual level.

Cross-sectional survey: Recruitment details are described above. Following completion of the informed consent process, all eligible and enrolled cross-sectional study participants will be asked to participate in a brief 20-30 minute survey. The survey will collect very minimal information related to individual behavior, but will assess PrEP knowledge and attitudes, exposure to PrEP promotion events and the social media campaign, as well as the young woman's views on partner, family and peer perceptions of PrEP. No biological assessments will be performed and no identifying information will be collected from the participants. The trained research assistants will administer the survey on a tablet, reading each question aloud and recording all participant responses. The age of the young woman and the location that the survey was conducted at will be collected.

Assessment of PrEP programme data: Participants will not undergo any procedures and no individuals will be recruited for this element. Programme monitoring and evaluation staff will support with providing routinely collected, de-identified programme data for assessment of PrEP initiations and follow-ups completed during the 12-month CRT period.

Social media metrics: Participants will not undergo any procedures and no individuals will be recruited for this activity. Aggregate and anonomized data will be collected through social media

metrics in line with each platform's respective privacy policy. Additional data shared through comments or posts onto the website will be categorized and if publicly shared may be used for analysis; privately sent messages, information and information identifying individuals will not be used.

Table 2. Number and type of study visits and/or contacts			
	Number and type of study visits	**Length of each study visit**	**Where they will take place**
Social influence campaign	N/A	N/A	N/A
Cross-sectional survey	1 visit (cross-sectional assessment)	20-30 minutes	Private room at the TB HIV Care offices or in a private room at the mobile van or venue where women are accessing services if that is the preference of the participant and confidentiality can be secured
Assessment of PrEP programme data	N/A	N/A	N/A
Social media metrics	N/A	N/A	N/A

Reimbursement of 100 ZAR (~7 USD) for time associated with completing the cross sectional survey will be provided to each survey participant. Each survey with TB HIV Care service users is estimated to last 20-30 minutes and compensation will be given immediately after completion of the survey.

7. STATISTICAL CONSIDERATIONS

Statistical considerations, specifically around sample size and participant recruitment, will ensure the study is able to detect important differences in the outcomes. Moreover, the statistical analysis plan will outline the analyses that will be conducted to address the main aims of the study.

A. Randomization

The 10 districts /sites in which THC provides PrEP will be taken as unit of randomization for the first layer of comparison. Five of the sites will be randomized to the standard of care PrEP promotion arm, and five to the PrEP promotion+enhanced social media campaign arm. Constrained covariate randomization will be applied taking into account the baseline number of annual PrEP initiations, the number of subdistricts within a site, the number of rural subdistricts, mean district HIV prevalence, and program type (AGYW or FSW or a combination of the two).

Within the PrEP promotion+enhanced social media campaign arm, wards will be randomized to 4 sub-arms receiving different combinations of the enhancements described in Table 1. The

randomization will be stratified by site and effort will be made to reduce potential contamination between wards.

All randomization activites will be completed by the team biostatistician who specializes in cluster randomized trials, Dr. Aletta Bareng Nonyane (Co-Investigator).

B. Sample Size Considerations

Social influence campaign (CRT): The primary outcome for this study will be PrEP uptake within the TB HIV Care programme. Each of the 10 cities in which TB HIV Care provides PrEP will be included as clusters. Assuming between 500 and 1000 PrEP-eligible women reached by the TB HIV Care PrEP programme per geographic region annually, we considered a coefficient of variation (CV) ranging from 0.25 to 0.4, and a minimum improvement in uptake of 10 percentage points (5% to 15%).With a conservative CV of 0.4, 5 clusters per arm will provide 87% power to detect this difference at an α=0.05 level of significance. For the second layer of randomization for enhanced social influence activities, a total of 216 wards (a smaller unit of subdivision used in South Africa to divide regions for political and administrative purposes) exist across the 5 intervention sites, which will be randomized across four sub-arms. There will be roughly 54 wards per sub-arm each with at least 10 PrEP-eligible women. Overall, arm 2 is hypothesized to have PrEP initiations of 15% where the least effective sub-arm [no additional enhancement] has an uptake rate of ~10% and the most effective sub-arm [2d which combines PrEP champions and PrEP community mobilization will have] will have an uptake rate of up to ~20%. Having at least 30 venues per sub-arm would provide 84% power, at a 5% level of significance, assuming a conservatively high CV of 0.4, to detect this difference. As this will be an exploratory investigation, the emphasis will be on the additional yield by the enhancements and thus no correction for the multi-arm hypothesis testing will be conducted.[23]

Cross-sectional survey: In order to assess the penetration of exposure to the intervention and thus yield insights into the mechanism of intervention effect (or lack thereof), we are assessing changes in PrEP knowledge and community attitudes over time. Given that awareness to PrEP and attitudes may change over time independent of the intervention, we have included both intervention and control sites pre- and post- intervention in order to compare differences in awareness and atttidues over time between the intervention and control sites. Cross-sectional surveys will be administered across 3 intervention and 3 control sites pre- and post-CRT implementation. With 100 surveys being conducted per site per timepoint, we will collect a total of 1200 survey responses across the 6 selected sites (600 pre-intervention and 600 post-intervention). When selecting the 6 sites for survey implementation, programme type (FSW vs. AGYW vs. both) will be accounted for and from there a random sample will be drawn. With 100 women included per site, there will be a sufficient number of women to account for heterogeneity across sites and will ensure sufficient representation across both intervention and control sites, but will also allow for 300 combined FSW/AGYW before and 300 combined FSW/AGYW after intervention in the intervention arms, which will allow for further assessment of the impact of the additional layered strategies (PrEP champions and community mobilization) on modifying the effect of the social media campaign on PrEP uptake.

Social media metrics: No sampling plan needed; these will be process indicators used to evaluate engagement with the social media campaign (intervention activities).

C. Statistical Analysis Plan

Results will be synthesized across the data sources and implementation outcomes, and utilized to assess the reach and effectiveness of social influence campaign strategies. Findings from the review of programme logs, social media metrics, and cross-sectional surveys will be reported. Costing data and ranges of intervention fidelity and penetration parameters will be used to inform programme activities. A comparison of the social influence campaign intervention vs standard of care at achieving PrEP uptake (primary), 1-month PrEP persistence (secondary) and 4-month PrEP persistence (secondary) will be key outcomes. Cluster level proportions of clients within the TB HIV Care PrEP programme who initiate PrEP will be compared between the main study arms using the unpaired t-test after a log-transformation if necessary. A secondary analysis will adjust for residual confounding by age and other individual characteristics through a two-stage logistic regression residuals approach.[24] A similar approach will be used for the secondary outcomes and the comparison between sub-arms within the intervention main arm. Changes in PrEP knowledge, attitudes and social support across intervention and control areas over the two time periods (pre- and post-intervention) will be estimated using a difference in differences approach[25].Prevalence of PrEP knowledge, attitudes and social support across intervention and control areas over the two time periods (pre- and post-intervention) will be summarized by questions/item. Multivariate analysis will be conducted to generate patterns of responses by theme (e.g. perceptions of PrEP). Changes over time will be analysed using the difference in differences approach[25] that uses suitable regression models (e.g. logistic, linear) to study the effect of time period and study arm, as well as their interaction, on the responses.

Analysis of data will be conducted using STATA Version 15.0.

D. Analysis Plan for Implementation Outcomes

Process and implementation outcomes will be summarized using descriptive statistics across sites. Further, analyses of the primary outcome (PrEP uptake) and secondary outcomes (persistence/retention on PrEP at 1-month and 4-months within the programme) will be evaluated in conjunction with the implementation outcomes to determine the extent to which process outcomes moderate (effect measure modification) the impact of the intervention.

Table 4. Implementation measures to be assessed and the respective data sources

Implementation Outcomes	**Salience**	**Data Sources and analysis**
Acceptability	Satisfaction with social influence campaign components	**Cross-sectional survey**: descriptive statistics related to acceptability of the social media campaign (captured in post-intervention cross-sectional survey only).
Adoption	Service user uptake and engagement with campaign	**Social media metrics:** # times each ad was viewed overall and by an individual, # times someone clicked on each ad, and the click-through rate metric which tells you the percentage of people who click an ad out of all the people who saw the ad; we will also assess the number of website/Facebook

		page visits, video views and appointments made.
Costs	Cost-effectiveness and affordability	Costs associated with planning, designing, and implementing the social influence campaign will be assessed
Penetration	Extent to which the social influence campaign reached FSW/AGYW and their families/peers/partners	**Cross-sectional survey:** descriptive statistics from survey questions on campaign exposure and perceptions among FSW/AGYW and their social support networks
Fidelity	Extent to which the social influence campaign was carried out according to plan	**Social media metrics:** Social media metrics will be used to assess whether static and video content were shared across platforms as planned; **Programme logs:** trainings, logs of communication with PrEP champions and community mobilization logs/quality assessments will be assessed to determine the degree to which implementation activities were carried out as planned.

8. ACCESS TO SOURCE DATA / DOCUMENTS:

Study documentation, including but not limited to the research plan, consent form, study tools, standard operating procedures, etc., will be securely shared between the coordinating centre and all partners by means of a preset Dropbox Business folder specifically developed for this study. Access to the Dropbox folder will be by email invitation only. As study documents are changed, official amendment requests will be put through to both the JHU IRB and the IRB at the University of Pretoria.

Source data will be collected, managed and protected using REDCap, a secure, encrypted online platform, and in accordance with a detailed Standard Operating Procedure (SOP) for Data Management. All computers with data will be protected by passwords, data files will be stored in encrypted folders on Johns Hopkins OneDrive, and hard copies of data kept in a secure cabinet or room with limited access by individuals on the study team. All consent forms will be stored separately from other study documents, in a discrete secure cabinet or room. Data from the cross-sectional survey will be anonymous, so no generation of link-logs or other databases with identifying information will be created. All programme data available to JHU or collaborators outside of TB HIV Care will be de-identified. For the cross-sectional survey, tablets and computers will be password protected, returned to the office on a daily basis, synced and stored in a locked cabinet. Hard paper copies will be available as back-ups in the event that the electronic systems are not working and then entered within two business days into the electronic data collection system. Paper copies will be returned to the office on a nightly basis by a designated study staff, trained in data security, and stored securely in a locked cabinet. Paper-based and electronic data will be kept for no longer than

10 years following study completion. Specifically, informed consents will be destroyed 10 years following completion of the study.

9. QUALITY CONTROL AND QUALITY ASSURANCE:

Data quality control and quality assurance is imperative to ensuring that all research results are of high quality and are valid. Moreover, systematic and continuous quality control measures and a detailed quality assurance plan is central to making sure that research activities are conducted as planned and to avoid poor data results, wasted time, effort, and resources. Therefore, the study has enacted a number of quality assurance and control measures.

Furthermore, all study staff will undergo good clinical practice training, focusing on data quality control and quality assurance, and follow daily quality control measures put forth within the protocol, data monitoring plan, and directly by the programme coordinator and investigative team. All study staff will be held accountable for data quality.

Inbuilt measures will help support and ensure quality assurance. Data will be collected, managed and protected using REDCap. Tablets will be disinfected before and after use to prevent possible transmission of Covid-19. The questionnaires will be programmed with built in skip patterns and validation rules. Validation rules (e.g. valid data ranges or logic checks) assist in ensuring that data is captured and recorded in a standardized way. The questions will also be programmed to ensure no question is left blank and/or skipped by ensuring that the data collector indicates some sort of refusal or 'do not know' options to the unanswered question. Electronic data collection will allow for real-time data monitoring and review to ensure that quality assurance and quality control measures are effectively being implemented and possible issues are being appropriately addressed. Paper-based and electronic data will be kept for no longer than 10 years following study completion.

Ongoing internal monitoring will be conducted on a daily basis, led by the study coordinator based in Pietermaritzburg, and presented to the investigative team on a weekly basis. The internal monitoring will ensure quality control by actively identifying and mitigating issues, ensuring proper informed consent documents are in place, eligibility criteria preserved, and data quality. Additionally, a source documentation checklist will be employed to ensure all study related activities are carried out as stipulated in the protocol and in a consistent way.

Development of a structured procedures manual will also act as a data quality control strategy. Study procedures will be presented in an instruction-based format and anticipated unexpected circumstances and potential solutions are presented. Moreover, there will be a specific SOP in place to guide and ensure quality control systems. The team will run daily and weekly quality control reports that will identify and flag potential issues.

10. PROTECTION OF HUMAN SUBJECTS:

This study will take preemptive and ongoing measures to ensure the protection of human subjects before, during and after the research study. The study team will ensure participants' privacy is safeguarded and the confidentiality of their data are protected. Moreover, through the process of informed consent, all individuals participating in the study will be participating voluntarily and with full knowledge of the study procedures, duration, risks, and benefits.

A. Declaration of Helsinki

The ethical principles outlined with the Declaration of Helsinki guide this research. The wellbeing of the participants takes upmost importance and precedence over the proposed research and interest of

science and society. This research is held to ethical standards that promote respect for persons and protect their health and human rights. Moreover, given that this research involves vulnerable populations, specific and special attention has been inbuilt to ensure the protection of these individuals. As a result, the study has is being reviewed and will be approved prior to launch by the ethical review boards at Johns Hopkins Bloomberg School of Public Health and University of Pretoria. Participation in the study is voluntary and all subjects must provide informed consent to enroll.

B. Institutional Review Board

The clinical site will use the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria for this study. Approval will also be ascertained by the JHU IRB, which will collect IRB approvals and renewals from the University of Pretoria.

Johns Hopkins Bloomberg School of Public Health
Institutional Review Board
FWA: FWA0000287
Address: 615 N. Wolfe Street
Suite E1100
Baltimore, Maryland 21205
Telephone number: +1-888-262-3242

University of Pretoria
The Faculty of Health Sciences Research Ethics Committee
FWA: FWA00002567
Address: Tswelopele Building, Level 4, Rooms 4-59 and 4-60
Dr Savage Road, Gezina, Pretoria
Private Bag X323
Arcadia 0007, South Africa
Telephone number: +27 012 356 3084

C. Potential Risk

There are no direct physical risks related to this research. The service user participants could be harmed if individuals outside of the study found out about their participation in the study and discovered that they at risk for acquiring HIV, though given that they will be encountered only during clinical interactions or at FSW/AGYW community sites, we believe this risk to be very low. Other risks include negative impact on social standing with peers and family, loss of relationship with partner, arrest/incarceration/fine (if female sex workers), or discrimination from medical personnel, friends or family members if confidentiality is breached. However, due to strict confidentiality procedures, we do not anticipate disclosure of HIV risk, unless revealed by the participant.

Social influence campaign: As the campaign activities will not be targeted at any specific individuals but rather throughout specific cities, we anticipate limited risks associated with these activities. The campaign activities are meant to promote sexual health and well-being, however it is possible that individuals may interact with the social media campaign (e.g. post publicly onto Facebook) and share details or information that may cause them harm or harm others; we anticipate this risk to be low as we anticipate most of our target population has some experience using social media platforms; we will monitor and delete posts that are

harmful to others (e.g. bullying) and diligently foster a positive social media environment that limits misinformation or malignment.

Cross-sectional surveys: It will be made clear that there are no negative consequences to HIV prevention services for TB HIV Care programme users who choose not to participate in the survey and that data collection will be anonymous; the age of the young woman and the location will be recorded, however only limited information related to her sexual and health-seeking behavior or health will be captured and she will remain anonymous. We will request to use written consent for these brief cross-sectional surveys and participants will indicate their consent to participate by signing the consent form; participants that cannot write or who have privacy concerns may request to sign with an 'X', for which a witness will need to be present and sign in addition to the researcher. . Potential participants will be approached discretely and surveys will be conducted in a private and secure location in order to ensure privacy.

Assessment of PrEP programme data: Since no individual human subjects will actually be recruited, we do not anticipate that there will be any risk to the individual. Data on PrEP initiations and follow-up visits will be assessed at the aggregate level within the program, and no personally identifiable information will be collected for this activity.

Social media metrics: Since no individual human subjects will actually be recruited, we do not anticipate that there will be any risk to the individual. Social media metrics are reported at an aggregate level and only deidentified publicly visible quotes will be used, and therefore no PII information will be collected for this activity.

To minimize the risk that confidentiality is breached, no names will be stored except for signed consent forms which will be kept separate from all study data in a secure and locked cabinet. In addition to all data being reported anonymously, we will ensure that any contextual information that might identify a particular individual will not be reported in publications or reports that result from this study. Participants will be offered a copy of the consent form but will not be required to take it. All participation will be voluntary, and declining participation will not affect access to existing health services available through TB HIV Care.

Additionally psychological and psychosocial referrals will be provided to participants as needed. This research will operate embedded within the existing TB HIV Care program. Therefore, psychological and psychosocial referral systems within the study will be based on existing referral systems within the TB HIV Care program.

D. Potential Benefits

There are no direct personal benefits for participants. Participants may gain indirect benefit from eventual improvement in implementation of PrEP service delivery.

This study aims to improve service delivery for women at high risk and optimize implementation strategies delivered. We hope that through more effective social influence and messaging that PrEP user outcomes (PrEP uptake and retention) will be improved. Additionally, we hope that the positive messaging around PrEP that will be included in the campaign may serve to increase PrEP awareness and reduce stigma among young women and their parents, mentors, partners, and peers.

E. Informed Consent Process

The informed consent and assent process and surveys will be conducted either in a private room at the TB HIV Care offices or in a private room at the mobile van or venue where women are accessing services if that is the preference of the participant and confidentiality can be secured. Although we do briefly ask about sexual history as part of the cross-sectional assessment it is not the primary focus of the questionnaire. Study staff administering the questionnaire will ensure that participants are comfortable with the location prior to administering the survey, and the participant will be able to skip any questions they do not wish to answer. All individuals at recruitment locations are seeking services and are part of the AGYW or FSW community.

Enhanced social influence campaign: A waiver of consent is requested as we are not enrolling at the individual level for this activity, but relying on de-identified programme registers to indicate PrEP uptake and continuation at 1- and 4-months across programme users by age.

Cross-sectional surveys: Trained study staff members will conduct the informed consent process using written information sheets and consent scripts. All staff will be trained in protection of human subjects and good clinical practice. For cross-sectional surveys we will be requiring written informed consent for participants ages 18 and older, and written adolescent assent for participants ages 15-17. Participants will be asked to sign their name on the informed consent document. If a participant is unable to sign their name, they will be allowed to mark an 'X' indicating consent and an additional member of the research or programme team will sign as a witness. At the time of data collection at each of the six selected sites, the consent and assent processes, including the provision of detailed information about the study, will be conducted by a trained study research assistant privately, one-on-one, after confirming eligibility with the service user. Consent and assessments will be conducted either in a private room at the TB HIV Care drop-in centre or in a private room at the mobile van or venue where women are accessing services. We will not attempt to enroll adults lacking capacity to give informed consent. Trained study staff members will use an information sheet and consent or assent form approved by the University of Pretoria Research Ethics Committee and the Johns Hopkins School Bloomberg School of Public Health Institutional Review Board. They will explain the study in detail, outlining the purpose, sequence of events, rights, potential risks and benefits to participants. This information, along with local study phone number that can be called with questions or concerns, will be available on a paper version of the approved version of the information sheet. Moreover, clients will be reminded that their participation will not affect their ability to access health services from TB HIV Care in the future. The information sheet and consent or assent form will be given to the participant (woman or girl) for review and will be read-aloud by the researcher, who will provide an opportunity for the potential participant to ask questions and seek clarification. The consent and assent forms and information sheet will be made available in English, Zulu, siSwati, and Setswana. Participants will be asked to sign the consent or assent form (as applicable) indicating their agreement to participate. If a participant is illiterate and cannot sign their name, they will be able to provide consent indicated with an 'X' on the consent form along with an additional researcher or programme team member's signature as witness. Participants will be provided with an opportunity to take a paper consent or assent form and information sheet with them, though this will not be required. Note we are requesting permission to waive parental consent for the cross-sectional surveys with the additional witness signature of another research or programme member. The justification for this waiver request is that we are conducting a marketing/attitudes survey around individual and community (including parental) perceptions of PrEP and will not be conducting any physical or psychological assessments with the adolescents but rather gathering opinions. Not only do these activities hold minimal risk, parental engagement is not typically viable given that children are frequently not comfortable

talking to their parents about PrEP which is precisely what we are trying to measure (communication around PrEP).

Social media metrics: We request a waiver of informed consent. We are not collecting identifiable individual-level data about social media usage or personal information, and all individuals will have agreed to the terms and conditions of the given social media platform which allows for sharing of aggregate data and publicly posted comments/posts.

In the cases of the social influence campaign which utilizes PrEP programme data, and in the use of social media metrics, we are requesting waivers of informed consent for these individuals for the following reasons:

1. We believe the research poses minimal risk to individuals;
2. The waiver will not adversely affect the rights and welfare of the subjects;
3. The research activites described could not be feasibly carried out without the waiver;
4. Whenever appropriate, we will ensure that the subjects are provided with additional pertinent information after participation and/or passive use of their data

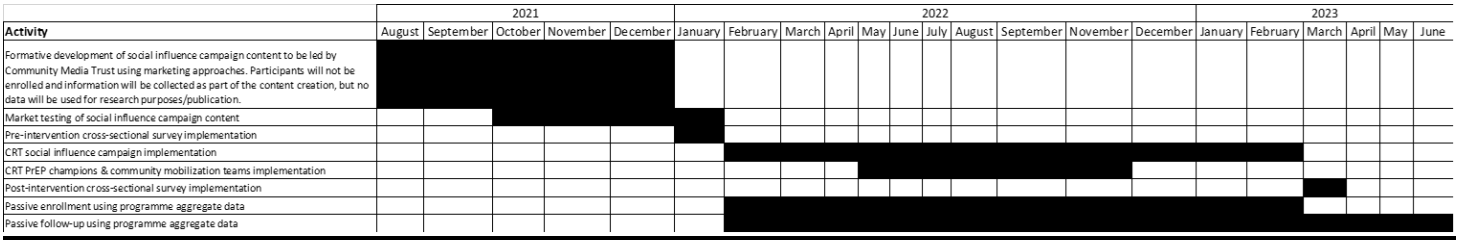
To summarize, the below table outlines the consent documents and the languages they will be translated into. Languages were selected based on the dominant languages in the 6 sites selected for implementation of the cross-sectional survey.

Table 5. Consent documents required and languages for translation

Country	Consent Document(s) (Adult Consent, Parental Permission, Youth Assent, etc.)	Languages
South Africa	1. Written adult consent (Cross-sectional survey) 2. Adolescent assent (Cross-sectional survey)	English, Zulu, siSwati, Setswana

11. TIMELINE:

Anticipated timeline of study implementation:



12. DISSEMINATION:

Aggregate study findings will be shared with all members of the study team, but no identifiable data will be shared. Data will be presented to TB HIV Care programme team leads as well to be used as an indicator for ways that programme performance can be improved, however information about

individual service users will not be shared. Results will also be shared with the community advisory boards and input sought on the findings. Finally, dissemination of implementation outcomes and PrEP uptake and retention measures will be shared outside of the programme through publications, through the social media website created for the study, the CDC (programme funder), NIH (grant funder) and the Provincial Departments of Health as well and will be utilized to inform modeling strategies.

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