ANTIRETROVIRALS FOR HIV PREVENTION AND TREATMENT AMONG ZIMBABWEAN SEX WORKERS

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TRIAL SUMMARY

PURPOSE:
Our research seeks to simultaneously enhance HIV treatment and prevention among sex workers (SW) attending mobile clinics in Zimbabwe by enhancing the existing targeted sex work services to increase the uptake and frequency of HIV testing, demonstrate acceptability and feasibility of delivering pre-exposure prophylaxis (PrEP) to HIV-negative SW, maximize retention in care of HIV-infected women currently ineligible for anti-retroviral therapy (ART), promote timely initiation of ART for those eligible, and maximize adherence to both ART and PrEP and retention on ART, thereby establishing a positive foundation for future engagement with medical services and reducing HIV transmission through transactional sex.

SPECIFIC AIMS:
Aim 1: To implement and document the key components of a novel intervention combining community mobilisation activities with the targeted provision of antiretroviral drugs for SW attending mobile clinics in Zimbabwe, to improve uptake of HIV testing and subsequent engagement in prevention and care across the continuum, to promote PrEP and timely ART initiation, and maximize adherence to these drugs.

Aim 2: To estimate the effect of this novel intervention on the proportion of sex workers who are infectious with HIV (viral load >1000 copies/ml) and on key indicators of SW engagement with HIV prevention and care, using a cluster-randomized trial design.

Aim 3: To ascertain the uptake of offer of PrEP, the pattern and duration of use, and the adherence to PrEP in a SW population.

Aim 4: To estimate the potential impact of this novel SW intervention on HIV transmission in Zimbabwe through use of an adapted dynamic stochastic simulation model.

Aim 5: To estimate the cost and cost-effectiveness of this novel SW intervention in Zimbabwe through a within model cost-effectiveness analysis

TRIAL DESIGN:
Using a matched pair cluster-randomized trial design, research activities will be conducted among SW working in seven enhanced intervention communities and seven matched comparison (usual care) communities where the Sisters With a Voice Programme is being delivered. One cluster in each pair will be randomly allocated to receive the enhanced intervention. SW in each trial community will be surveyed at baseline and after 24 months using respondent driven sampling in order to assess 'population level' effects of the programme.
USUAL CARE: As per WHO guidelines for targeted SW services, the Sisters With a Voice programme provides free condoms and contraception, HIV testing and counselling, syndromic management of sexually transmitted infections, and legal advice supported by a network of peer educators. The programme is currently expanding to additionally provide long-acting reversible contraception, cervical cancer screening, community mobilisation, and real-time electronic data collection. The programme is run by programme staff through dedicated drop-in centres based at primary care clinics along each highway in Zimbabwe, available once every two weeks. Women who require HIV care/ART initiation are referred to government services. This set of standard services will be provided in the comparison communities.

ENHANCED INTERVENTION: The enhanced intervention communities will receive these usual care services plus i) intensified community mobilisation of SWs to further improve social cohesion and support for HIV testing, retention in care, treatment, and adherence; ii) a repeat HIV testing program for women who test HIV negative or initially decline testing; iii) on-site availability of PrEP for HIV negative SWs, supported, where requested by the woman, by SW care supporters and text messaging; iv) on-site provision of CD4 count testing, provisions of ART for eligible HIV positive SWs based on international guidelines for ART initiation, viral load monitoring for those on ART, through the program clinics and supported by SW care supporters and text messaging; and v) tuberculosis screening for those with symptoms suggestive of infection.

The enhanced intervention services will be implemented for the duration of the funding cycle for the SW programme (until November 2015). We will recruit all comers to the programme over this period, and encourage women to adhere to their visit schedule as appropriate to their place on the care continuum. Routine programme data collected at both intervention and control sites will be supplemented by more intensive clinical/biologic data collection for women attending the enhanced intervention programme, again depending on their identified care needs.

PRIMARY OUTCOME: Our primary outcome is the proportion of all SW who are infectious (viral load >1000 copies/ml).

SECONDARY OUTCOMES WILL INCLUDE: i) the proportion of all HIV-infected women who are infectious; ii) the costs of our enhanced and usual care intervention packages; iii) using both quantitative and qualitative methods combined with programmatic indicators we will document: uptake and acceptability of ART provided through the SW clinics; adherence to ART (measured by self-report, pharmacy refill data, virological response to treatment at 48 weeks); uptake of repeat testing programme; uptake and acceptability of PrEP offered to HIV-negative SW; adherence to PrEP as measured by tenofovir level testing on dried blood spot (DBS) samples; patterns of PrEP use; incident HIV infection; proportion of those taking ART or PrEP with drug resistance, proportion keeping all clinical appointments on time (i.e. engaged in prevention/care) appropriate to their individual place on the care continuum; and proportion lost to follow up.
PROCESS EVALUATION OUTCOMES will include: i) assessment of whether activities were conducted as scheduled; ii) identification of any delays or gaps; iii) indicators of “sex worker friendliness” of clinics; and iv) SW participation in the intervention sites.

COST EFFECTIVENESS ANALYSIS: We will determine the cost–effectiveness of the enhanced intervention taking into account the potential reduction in transmissions via transactional sex, due to the reduction in the proportion of sex workers who are infectious. For this we will use an existing individual-based dynamic stochastic model to predict the potential impact of this intervention on HIV incidence in the population of Zimbabwe.
LIST OF ACRONYMS

ACTG – AIDS Clinical Trials Group
AIDS – Acquired immune deficiency syndrome
ART – Antiretroviral therapy
CAB – Community advisory board
CAPI – Computer administered personal interview
CDC – Centers for Disease Control and Prevention
CESHHR – Center for Sexual Health and HIV/AIDS Research
CrCl - Creatinine clearance
DBS - Dried blood spot sample
DSMB - Data and Safety Monitoring Board
EDTA - Ethylenediaminetetraacetic acid
FTC/TDF - tenofovir disoproxil fumarate and emtricitabine
GCP – Good clinical practices
HIV – Human immunodeficiency virus
ICER – Incremental cost effectiveness ratio
LSHTM – London School of Hygiene and Tropical Medicine
MCAZ - Medicines Control Authority of Zimbabwe
MOHCW – Ministry of Health and Child Welfare
MRCZ – Medical Research Council of Zimbabwe
NCCLS - National Committee for Clinical Laboratory Standards
PE – Process evaluation
PrEP – Pre-exposure prophylaxis

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PSI – Population Services International
PTID – Participant identification number
QALYs - Quality adjusted life years
RDS – Respondent driven sampling
SW – Sex workers
TDR – Transmitted drug resistance
UCL – University College London
UNFPA – United Nations Population Fund
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TRIAL PURPOSE AND BACKGROUND

Since the emergence of HIV as a serious public health threat in sub-Saharan Africa, the particular vulnerability of sex workers has been extensively documented. HIV prevalence rates as high as 60-90% were reported for sex workers in Kenya,2 Central and East Africa,3 and Rwanda.4 Current data suggest that sex workers in Africa typically have HIV prevalence 10-20 times higher than the general population5 as well as high prevalence of other sexually transmitted infections (STIs) that further increase risk of contracting and transmitting HIV.6 In Zimbabwe, current estimates for HIV prevalence among sex workers range between 40-70%.7,8

Despite long-standing acknowledgement of their enhanced risk, sex workers continue to be largely neglected by HIV programmes in Africa.5 Delivering services is complicated by the fact that sex work is illegal in countries throughout the region.9,10 Stigma, marginalization, and abuse of human rights have been highlighted as key determinants of reduced access to health care among sex workers in southern Africa.11 Sex work remains criminalized in Zimbabwe, with reports of police extortion, confiscation of condoms, and sexual assault.12

Historically data on sex worker rates of HIV testing are scant, although sub-optimal when reported, e.g. 4% of sex workers surveyed in Somalia in 2008 had ever tested,13 and 38% in the Democratic Republic of Congo in 2005/6.14 Barriers to testing among sex workers include those faced by others in developing country settings, including lack of awareness of services, distance to facilities, transportation costs, opportunity costs, time constraints, and fear of a positive result.15-17 Barriers unique to sex work include anxiety about contact with authorities and concern about confidentiality, particularly that other sex workers or potential clients may learn their status.18

Learning one’s HIV status is a prerequisite for entry into HIV care, and there is evidence that people modify their behaviour to engage in less high risk behaviour after receiving a positive HIV result.19-25 There have been successful interventions to increase HIV counselling and testing among sex workers.26 Furthermore, strengthened peer support and a more cohesive social environment are associated with sex workers’ willingness to engage in care (testing, treatment initiation and adherence) thus providing empirical rationale for the research described here.27,28 In the US, CDC recommends that people who exchange sex for drugs or money test annually.29 WHO in their most recent guidance for HIV prevention and care in sex workers30, refer to their guidance on retesting in adults which states that individuals at high risk of infection should ‘test at least annually’31. There is little evidence on sex workers’ uptake of and retention in HIV treatment programmes in Africa; little is known about their progression through the “care cascade” compared to HIV positive clients in the general population.

Even when sex workers have access to health facilities, the atmosphere and perceived quality of care are crucial determinants of sex workers’ willingness to attend. There is a rich literature around the importance of “sex worker friendly” clinics and their ability to attract and retain sex workers.32-35 Experience with our Sisters With a Voice programme, and formative research conducted among our
clients, confirm that sex workers in Zimbabwe confront judgmental and discriminatory health workers, contributing to their reluctance to use available services.

While offering “friendly” clinics (with well-trained, non-judgmental staff, an appropriate location, hospitable environment, and commitment to privacy and confidentiality) is likely to improve health-seeking behaviour, additional support will be required to address the full spectrum of social and structural barriers to sex workers’ uptake of services. Experience from prevention interventions demonstrates benefits of including empowering components, particularly those that strengthen community support structures, facilitate sex workers’ identification of shared priorities, and provide opportunities for collective action. These interventions result in better sexual health outcomes such as increased condom use with clients and reductions in STI. Based on peer-driven and participatory activities, community mobilisation approaches actively involve sex workers in project planning and implementation, and seek to address some of the underlying causes of sex workers’ vulnerability including those that undermine their engagement with care.

Despite its widespread acceptance, community mobilisation is often poorly defined, conflated with similar social constructs, and refers to numerous different activities. We adopt the definition from Evans 2010:

\[\text{Community mobilisation efforts... seek to construct a collective entity out of a group of individuals... to empower sex workers through the development of group solidarity that enables workers to collectively enforce safer sex norms among their clients (rather than acting as rivals in a demand-led market), and to pursue collective action to improve their lives.}\]

Strategies for catalysing collective identity combine activities that strengthen interpersonal cognitive skills (self-defence; condom negotiation) with participatory activities to build cohesive networks (peer led initiatives; regular meetings). Efforts to create a wider enabling environment can also be included (liaison with police; outreach to male clients and partners). Evaluations of community mobilisation for sex workers suggest that they are most successful when they encourage a sense of shared identity and camaraderie, and address concerns beyond HIV and sexual health, such as violence, stigma and discrimination; this evidence underpins the community mobilisation portion of our intervention design.

Establishing community level prevention and care for sex workers is central to achieving universal access and redressing prior neglect and essential from a public health perspective if incidence is to be sustainably reduced for future generations. Currently, rates of sex worker enrolment in HIV treatment and retention in care do not reflect their heightened levels of risk. This is not only an issue of health equity, it also of great public health importance. Sex workers with untreated HIV risk onward transmission to their clients and regular partners, with whom condom use is rarely consistent. In a recent national survey around 15% of 18-49 year old Zimbabwean men reported ever having had transactional sex and around one in ten reported at least one transactional partner in the previous 6
months. In 2001, we estimated that xx-yy% of all HIV infections among men in rural Zimbabwe were potentially attributable to transactional sex. Also of importance, is that poor retention and adherence to ART will greatly increase the risk of drug resistant virus.

There is a growing body of evidence supporting the use of ART as both a tool for treatment and for prevention of sexual transmission of HIV. Most compelling are the recent results of HPTN 052, a multinational trial to evaluate whether immediate versus delayed ART decreases sexual transmission of HIV in serodiscordant couples. HPTN 052 found ART reduced risk of transmission to partners by 96%. Antiretrovirals have also been shown to reduce risk of acquiring HIV in uninfected people. Results from trials of daily oral combination tenofovir disoproxil fumarate and emtricitabine (FTC/TDF) pre-exposure prophylaxis (PrEP) have been promising. Although, two studies, one among young women at risk of HIV in South Africa, Kenya and Tanzania and one among sexually active women in South Africa, Zimbabwe and Uganda did not show any efficacy, demonstrated to be due to poor adherence, most studies have demonstrated efficacy with reductions in HIV acquisition ranging from 42%-75% among a variety of populations including men who have sex with men and transgenders, heterosexual men and women, and HIV serodiscordant couples. In July 2012 the US Food and Drug Administration (FDA) approved the use of Truvada (FTC/TDF) as PrEP, based on the safety and efficacy results of two large randomized placebo-controlled trials. The first was the iPrEx trial, among 2,499 men or transgender women having sex with men. Efficacy in this trial was 42%. The second was the Partners PrEP study, among 4,758 heterosexual serodiscordant couples, where they found a 75% reduction in HIV transmission. The efficacy of FTC/TDF PrEP was strongly correlated with levels of adherence to daily dosing. Data on the acceptability, uptake and adherence to PrEP among SW are limited and WHO has recently released guidance on protocol development for PrEP.

Promoting the engagement of SW in HIV prevention and care, using ART-based strategies to decrease acquisition among negatives, increase timely initiation of ART among positives, and to improve drug adherence and retention in care is likely to reduce sexual transmission of HIV in SW, their partners and their clients. In sub Saharan Africa 10-33% of new infections have been attributed to sex work. Observational studies and mathematical models support the use of targeted HIV prevention for most-at-risk populations, as this is likely to be sustainable and cost effective. The rationale for prioritizing sex workers for interventions that optimize engagement in HIV prevention and care is compelling for its own sake and for wider public health gain.

In 2009, as part of Zimbabwe’s National Behaviour Change Programme, we established a demonstration SW programme called Sisters With a Voice (Director Dr F Cowan), which was then rolled out nationally to three cities and thirteen highways across Zimbabwe. From September 2012 to November 2015 this programme is expanding to 36 sites including six fixed sites. The programme has seen over 11,000 women since 2009. HIV prevalence among SW is high. Among the 2,812 women tested so far, prevalence is 61%. However, many are reluctant to test, with only 70% having ever tested for HIV. Qualitative data suggest that women have difficulty accessing HIV care in the public sector because they
face stigma and discrimination at clinics. Among the women who are HIV positive only 35% report taking antiretroviral therapy (ART). Anecdotally, retention in care is poor.

**Overview of Trial Design:**
Using a matched pair cluster-randomized trial design, our research seeks to implement an enhanced intervention which will simultaneously increase uptake of HIV treatment and prevention among SWs attending mobile clinics as compared to the existing targeted services, thereby establishing a positive foundation for future engagement with medical services. Our research activities will be conducted among SW working in seven enhanced intervention communities and seven matched comparison (usual care) communities where the *Sisters With a Voice* Programme is being delivered. One cluster in each pair will be randomly allocated to receive the enhanced intervention. SW in each trial community will be surveyed at baseline and after 24 months using respondent driven sampling (RDS) in order to assess 'population level' effects of the programme (Fig 1).

**Usual Care:** As per WHO guidelines for targeted SW services, the *Sisters With a Voice* program provides free condoms and contraception, HIV testing and counselling, syndromic management of sexually transmitted infections, and legal advice supported by a network of peer educators. The program is currently expanding to additionally provide long-acting reversible contraception, cervical cancer screening, community mobilisation, and real-time electronic data collection. The program is run by programme staff through dedicated drop-in centres based at primary care clinics along each highway in Zimbabwe. Women who require HIV care/ART initiation are referred to government services. This set of standard services will form the comparison communities.

**Enhanced Intervention:** The enhanced intervention communities will receive these usual care services plus i) intensified community mobilisation of SWs to further improve social cohesion and support for HIV testing, retention in care, treatment, and adherence; ii) a repeat HIV testing program for women who test HIV negative or initially decline testing; iii) on-site availability of PrEP for HIV negative SWs,
supported, where requested by the woman, by SW care supporters and text messaging; iv) on-site provision of CD4 count testing, provisions of ART for eligible HIV positive SWs based on international guidelines for ART initiation, viral load monitoring for those on ART, through the program clinics and supported by SW care supporters and text messaging; and v) tuberculosis screening for those with symptoms suggestive of infection. While the offer of PrEP will be included as part of the intervention, the trial is not designed to assess PrEP efficacy, but to explore how/if PrEP is used by SW if made available to them.

We will utilize mixed methods research to determine the individual, programmatic and population effects of our intervention on SW engagement in HIV prevention and care across the continuum. The results of this research will inform SW treatment and care services programming across southern Africa. If successful the research would likely lead to more wide-spread implementation of this approach, with predicted reductions in HIV incidence. In addition the results will be directly applicable to the debate around the feasibility of implementing ‘test and treat’ approaches in the region more broadly.

The trial will be run through the Centre for Sexual Health and HIV Research, Zimbabwe, in collaboration with UNFPA, PSI Zimbabwe, the Zimbabwe Ministry of Health and Child Welfare, University College London, the London School of Hygiene and Tropical Medicine, Health Economics and Policy Research Initiative (HEPRI) and RTI International.

GOAL AND OBJECTIVES

THE OVERALL GOALS OF THE TRIAL ARE:

i. To determine whether it is possible to reduce the proportion of sex workers with a viral load >1000 copies/ml by an enhanced HIV prevention and care intervention

ii. To determine the likely effect of this enhanced intervention on the general population epidemic

THE SPECIFIC OBJECTIVES ARE:

i. To implement and document the key components of a novel intervention combining community mobilisation activities with the targeted provision of antiretroviral drugs for SW attending mobile clinics in Zimbabwe, to improve uptake of HIV testing and subsequent engagement in prevention and care across the continuum, to promote PrEP and timely ART initiation, and maximize adherence to these drugs.

ii. To estimate the effect of this novel intervention on the proportion of sex workers who are infectious with HIV (viral load >1000 copies/ml) and on key indicators of SW engagement with HIV prevention and care, using a cluster-randomized trial design.

iii. To ascertain the uptake of offer of PrEP, the pattern and duration of use, and the adherence to PrEP in a SW population.
iv. To estimate the potential impact of this novel SW intervention on HIV transmission in Zimbabwe through use of an adapted dynamic stochastic simulation model.

v. To estimate the cost and cost-effectiveness of this novel SW intervention in Zimbabwe through a within model cost-effectiveness analysis

**HYPOTHESES**

We hypothesize that the targeted and dedicated delivery and support of our enhanced intervention will reduce HIV viral load among SW when compared with the current WHO-guideline usual care offered to SW. This effect will come about through an approach that decreases incident HIV infection, decreases the time before HIV-infected SWs are diagnosed, decreases the time to initiation of ART, and improves adherence and retention in care. We will determine this through a cluster-randomised trial.

We also hypothesize that this impact on viral load among the SW community will decrease the rate of transmission of HIV between SWs and their clients and ultimately have an impact on the general population. We will study this question through mathematical modelling linked to the trial.

We hypothesize that this enhanced, targeted approach for SW will be highly cost-effective by improving the health of SW and averting new HIV transmissions. We will collect cost data and integrate this with effectiveness data generated by the trial.

**THEORY OF CHANGE**

*Figure 2: Theory of change diagram*
We will enhance existing services for sex workers with targeted community mobilisation activities to actively engage women in prevention and treatment by (1) raising awareness of the benefits and availability of ART and PrEP; (2) strengthening networks of support to encourage health-promoting behaviour; and (3) building leadership skills among sex workers to increase coverage and sustainability. For women who access services and test HIV-negative we will also implement a programme of activities designed to increase repeat HIV testing, including with the use of SMS messaging reminders. These demand creation components should provide an enabling environment leading to uptake of HIV testing, prevention and treatment services.

On the supply side we will enhance clinical services to make ARV for treatment and prevention more readily available to SW. These services will meet the needs of SW with high quality, accessibility and acceptability. We will include an offer of PrEP for HIV-negative SW, on-site initiation of ART in line internationally accepted guidelines for those who have tested HIV-positive, and clinical and social support services delivered by clinical staff within this package.

These combined and mutually re-enforcing supply and demand-side efforts will increase the effective access by SW of ART for both treatment and prevention of HIV infection, as well as fostering greater behavioural efforts to stay HIV-negative. ART adherence will be supported and thus maintained at appropriately high levels. Over time these actions will reduce the proportion of SWs with transmissible levels of the HIV virus, thereby reducing the number of new infections in the general population. This effect will be accompanied by clinical benefits to SW while preventing significant increases in drug resistance.

STUDY ENDPOINTS

PRIMARY ENDPOINT

Primary endpoint data will be collected through respondent driven sampling surveys. These will be conducted using the same methodology, described in detail below, at baseline and after 24 months.

i) Proportion of all SW who are infectious (viral load >1000 copies/ml).

SECONDARY ENDPOINTS

i) Proportion of HIV-infected women who are infectious
ii) Proportion of those taking ART who have viral load >1000 who have drug resistance
iii) Self-reported quality of life, psychological health and functioning
iv) Incidence of HIV infection in the 6 month period before the RDS survey
v) Proportion adherent to ART for treatment, as assessed by:
   a. pharmacy refill data
   b. virological response to treatment at 48 weeks
vi) Proportion of SWs always using condoms with clients in last month
vii) Proportion of SWs reporting condom-less sex with clients in last month

viii) Proportion of sex workers offered, initiating and, where appropriate, adhering to/participating in:
   a. Community mobilisation activities
   b. HIV testing, including repeat testing programmes for HIV-negatives
   c. ARV for treatment of HIV infection
   d. Pre-exposure prophylaxis for HIV-negatives
   e. Support for HIV prevention and treatment

ix) Proportion of SWs who know HIV status (i.e. are diagnosed HIV positive or were tested HIV negative in last 6 months)

x) Perceived levels of peer support

xi) Acceptability and perceived quality of services

xii) Proportion keeping all clinical appointments on time (i.e. engaged in prevention/care) appropriate to their individual place on the care continuum

xiii) Proportion lost to follow up

COST EFFECTIVENESS ENDPOINT

The cost-effectiveness of our intervention package will be evaluated, taking into account the potential reduction in transmissions via transactional sex due to the reduction in the proportion of sex workers who are infectious.

i) Resource use (number of clinic visits, CD4 counts, viral loads, hospitalisations, adherence counsellor time, HIV tests done, etc)

ii) Unit costs of those resources

PROCESS EVALUATION ENDPOINTS

Process evaluation activities will be linked to a monitoring and process evaluation framework designed to capture inputs, activities, outputs and their relationship with outcomes and impacts. These will be monitored through a variety of data collection approaches including programme checklists, staff and training records, programme records, qualitative research methods and a programme diary to record key environmental/contextual factors. This will include data collection activities in both enhanced intervention and standard care comparison sites as appropriate.

i) Inputs
   a. Assessment of start-up activities, e.g. staff appointed and trained; activities designed; preparatory meetings held.

ii) Activities
a. Assessment of whether activities were conducted as planned/scheduled, e.g. new clinic sites opened; opening times; waiting times; sites offering intervention components.
b. Assessment of whether activities were conducted as planned/scheduled, e.g. new clinic sites opened; opening times; waiting times; sites offering intervention components.

iii) Outputs

a. Knowledge and awareness of services; indicators of “sex worker friendliness” of clinics.
b. Frequency of stock-outs.
c. Uptake of repeat testing program in intervention sites.
d. Uptake of CD4 count testing.
e. Uptake and acceptability of ART.
f. Proportion of those taking ART with drug resistance.
g. Uptake and acceptability of PrEP offered to HIV-negative SW in intervention sites.
h. Adherence to PrEP among women who say they are taking it, as measured by tenofovir drug levels on dried blood spots.
i. Patterns of PrEP use.
j. Proportion of those taking PrEP with HIV (and drug resistant HIV).
k. Evidence of pill sharing.

iv) Environment, context

STUDY LOCATION

This study will run through the Centre for Sexual Health and HIV Research (CeSHHAR), Zimbabwe. CeSHHAR is a not for profit Trust founded in 2012 with a portfolio of research studies from various funders. Dr Cowan is the founder of CeSHHAR. The study will be conducted in partnership with UNFPA, PSI/Z and MOHCW. The Sisters With a Voice programme will have a total of ~30 mobile drop-in centres across Zimbabwe. The enhanced intervention and standard care comparison clinics will be at 14 mobile sites across seven provinces around the country (see Figure 3).

Figure 3: Trial sites within ‘Sisters With a Voice’ Programme
SEX WORKER PROGRAMME: USUAL CARE AND ENHANCE INTERVENTION

USUAL CARE

The existing Sisters with a Voice programme provides free condoms and contraception, provider initiated HIV testing and counselling, syndromic management of sexually transmitted infections, health education and legal advice. With the expanded program currently being implemented, clinics are additionally providing long-acting reversible contraception (intrauterine device and implant) and cervical cancer screening. There will be accompanying community mobilisation, and data on the programme will be collected electronically in real-time. The programme is supported by peer educators and is run by programme staff through dedicated drop-in centres based at primary care clinics along each highway in Zimbabwe, where approximately 85-300 SW are seen at each clinic annually. Women who test positive for HIV are referred to government services for HIV care/ART initiation. This set of WHO-guided standard services will form the comparison communities in this trial.

ENHANCED INTERVENTION

The enhanced intervention communities will receive the usual care services described above plus i) intensified community mobilisation of SWs to improve social cohesion and support for HIV testing, PrEP use, retention in care, treatment, and adherence; ii) a repeat HIV testing program for women who test HIV negative or initially decline testing; iii) on-site availability of FTC/TDF PrEP for HIV negative SWs,
supported, if consented to, by SW care supporters and telephone and text messaging; iv) point of care CD4 testing for HIV positive women, on-site provision of ART for those eligible based on international guidelines for ART initiation, and viral load monitoring for those on ART through the programme clinics and supported by SW care supporters and telephone and text messaging; and v) tuberculosis screening for those with symptoms suggestive of infection.

I) INTENSIFIED COMMUNITY MOBILISATION

Participatory Planning Sessions: Sex workers at all Sisters sites are invited to attend regular (monthly) participatory discussions. A CeSHHAR outreach worker will act as facilitator. She will explain the objectives of the programme, encourage sex workers to raise issues of interest, and lead interactive activities to engage groups in shared problem solving. Topics will include: i) the context of sex work and its risk environment; ii) the current barriers and facilitators to HIV testing, care-seeking and adherence; iii) determinants of vulnerability; iv) existing peer support; and v) SW suggestions for skills and resources. Social events will be held, and support given to SW-led initiatives as they emerge; by definition, participatory sessions need to remain responsive to participants’ needs, and will evolve during the programme.

Community Mobilisation Agents: The current Sisters program has trained up to five peer educators in each site, who are paid a small monthly stipend to provide information on HIV transmission, distribute condoms, and inform other sex workers about available services. In the enhanced intervention we will build on this model by extending their role from ‘peer educator’ to one of ‘community mobilisation agent’. Their expanded role will include organizing activities, recruiting peers into the health and social program, and maintaining contact with registered clients through mobile phone technology to ensure that clinic appointments are kept. All community mobilisation agents will receive additional training and will be supported and mentored by programme staff. They will link social and clinical components of the intervention by convening meetings, inviting sex workers to participatory sessions, helping to select topics and learning to lead interactive discussions. Community mobilisation agents will publicize the advantages of testing, treatment, prevention (including PrEP) and care, to extend interest in the project beyond women already enrolled.

SW Care Supporters: Among sex workers eligible for ART, peer adherence counsellors, known as SW Care Supporters (four at each site), will be recruited to provide community-based support for timely initiation of ART, support for the use of PrEP, adherence particularly in the period after initiation of ART or PrEP, and sustained retention in prevention/care. HIV positive SW who volunteer for this role will complete a formal training programme for lay counsellors. SW who are initiated on ART or PrEP will be referred, with their consent, to a SW Care supporter. With their SW care supporter and ART nurse counsellor they will be encouraged to draw up a personal adherence plan. The SW care supporter will arrange to meet them individually in the community and, when possible, in small support groups for ART adherence, to discuss barriers experienced as they progress through the treatment cascade. Support groups will work together to put in place measures to overcome these, such as reminding each other, providing practical assistance, and mutual psychosocial support. SW care supporters will themselves be
supported and supervised by intervention staff, and given skills training as required. Peer-driven adherence interventions have been trialled successfully among sex workers in urban, industrialised settings,\textsuperscript{28} and mobile-phones used to maintain contact with clients in sub Saharan African contexts.\textsuperscript{67,68} These interventions will be adapted in consultation with our participants.

**Supporting engagement with prevention and care activities as part of the Sisters programme:** The Sisters programme will establish an electronic register to log attendance at Sisters and PSI/Z services, generate reminders of scheduled visits, and to alert programme staff to defaulters. All women (HIV positive and negative) who have consented to do so will be contacted by text-message reminders prior to appointments. Defaulters, who will include HIV negative women who fail to attend their 6 month repeat test visit; HIV negative women on PrEP who fail to attend their monthly visit for HIV testing, drug refill and counselling; HIV positive women ineligible for ART who default from their 3 or 6 monthly CD4 testing; and HIV positive women eligible for ART who default from their recommended clinical care, will be followed up in person by a SW care supporter or by phone or text messaging.

**II) Repeat HIV testing programme**

Clinical services will be provided by the Sisters program through clinics held for one day every second week. At each enhanced intervention site women who are HIV negative or of unknown HIV status will be asked to enrol in a programme whereby they return to the clinic every 6 months for repeat testing and counselling. All women will be asked to consent to receive appointment reminders by clinic staff in person, by phone, or by text message. Those who default on their appointment will be followed up in a similar manner, up to three times per missed visit. Women will also be encouraged to attend the clinic if they have other reproductive tract symptoms or concerns, and to attend Sisters events.

**III) On-site availability of FTC/TDF PrEP**

PrEP will be delivered in line with WHO recommendations for PrEP demonstration projects.\textsuperscript{59} Those women of known HIV negative status will be offered FTC/TDF PrEP for the prevention of HIV acquisition at each enhanced intervention site. Known negative status is defined as receiving a negative HIV result at a Sisters clinic immediately prior to PrEP prescription, and monthly thereafter. All women will be required to provide written consent. FTC/TDF PrEP (i.e. Truvada) will be administered according to manufacturer instructions of one tablet taken once daily orally (see Appendix C for full manufacturer prescribing information). It will be explained to women that FTC/TDF PrEP is approved for use in the United States but has not yet been approved for general use in Zimbabwe, and that while studies with good adherence have shown that PrEP can reduce HIV acquisition by 42%-75%, other studies with less good adherence have not shown any protective effect. Women will be told that intermittent dosing is not protective. Those opting to initiate FTC/TDF PrEP will have creatinine clearance (CrCl) assessed, assessment of the presence of clinical symptoms consistent with acute viral infection, liver function tests and hepatitis B testing before initiating treatment. They will receive comprehensive counselling and management to reduce the risk of acquiring HIV-1, and to reduce the risk of acquiring drug resistance, as per manufacturer indications. In addition they will counselled against sharing drug with friends/partners. They will be given a one month supply of Truvada and asked to return after each
month in which they have used PrEP for repeat HIV testing, further counselling on safe sex and PrEP use, assessment of drug adherence and side effects, and for drug refill should they wish to continue. Those opting to continue with PrEP longer term creatinine clearance and liver function tests will be assessed, 6 monthly. At all stages, it will be emphasised that the initial or continued use of PrEP is entirely voluntary and there is no commitment to continued use.

At months 3 and 12 after starting PrEP, women who report on-going PrEP use will be asked to provide a dried blood spot (DBS) sample which will be stored for future testing for tenofovir drug levels and, if the woman is subsequently identified as HIV-infected, for HIV viral load and drug resistance testing. Data on self-reported adherence (any missed pills in last 7 days) and a pharmacy refill data will be collected at each visit and will be used to inform adherence counselling but it is recognised that such a measure is likely to substantially over-estimate adherence. The primary measure of adherence will be levels of tenofovir in DBS measured at 3 and 12 months on PrEP. As part of the process of consent to take PrEP, all women will be asked to consent to receive appointment reminders in person, by phone or by text message, and to provide the DBS samples after 3 and 12 months, if still on PrEP at those time points. Measurement of drug levels on DBS will be done in a batch at the end of the trial. Results will not be fed back in real time to staff. This sub-study of PrEP uptake differs fundamentally from PrEP efficacy studies in that it seeks to determine real-world uptake, adherence and patterns of use.

iv) On-site provision of ART
A team from PSI/Z will accompany the Sisters programme to provide HIV care to positive SW at each enhanced intervention site. Clients will be asked for consent to receive appointment reminders in person, by phone or by text message from programme staff. Women who test HIV positive will be referred to the PSI/Z treatment services for clinical staging, point of care CD4 testing, and ART initiation for women eligible according to international guidelines (currently CD4 count <350 cells/ml (but likely to rise to 500 cells/ml) or WHO stage 3 or 4). Those ineligible for ART will be asked to attend for repeat point of care CD4 count testing according to National Guidelines (every 3 months if CD4 count is between 350-500 cells/ml and 6 monthly if >500 cells/ml). Women initiated on ART will attend the service 2 and 4 weeks post initiation then monthly for 6 months to get ART prescription refills. After 6 months if stable on treatment prescription refills will be reduced to 2-3 monthly. In line with National guidelines, data on reported adherence (any missed pills in last 7 days) and a pharmacy refill count will be collected at each visit. For HIV-infected women who have initiated ART, viral load monitoring will be conducted at ART initiation, at 3, 6 and 12 months post ART initiation then 6 monthly. In addition, positive women with low CD4 count will receive prophylactic cotrimoxazole. Data will be collected at each clinic visit for all positive women on WHO stage, CD4 count (6 monthly), ART status, and if on ART, adherence (as outlined above).

v) Tuberculosis screening
For women presenting with symptoms of infection, tuberculosis screening will be performed, and treatment provided as necessary according to national guidelines. These activities will be conducted by the PSI/Z outreach team.
PROGRAMME RECRUITMENT AND FOLLOW UP

All clinics in the usual care comparison arm of the Sisters programme will continue to operate as usual throughout the trial period. Any client engaged in commercial sex who presents at a clinic will be seen, with no further eligibility criteria, and may take advantage of any or all of the services offered. Women may be seen at the clinic as frequently as they choose, but are not scheduled to return for regular visits. Follow up visits are only scheduled for contraception refills, or cervical cancer treatment, as necessary.

The enhanced intervention services will be implemented through November 2015 (the duration of the funding cycle for the SW programme). All comers to each of the trial sites will be seen over this period, with no further inclusion/exclusion criteria other than being engaged in commercial sex work. In the intervention arm women will be able to ‘drop-in’ for any services as happens in the usual care arm but will also be scheduled for follow up visits and encouraged to adhere to their visit schedule as appropriate to their place on the care continuum. Visit schedules according to prevention and care needs are described above, and are summarised in Table 1 below:
### Table 1: Enhanced intervention arm visit schedule by individual place on the HIV care continuum

<table>
<thead>
<tr>
<th>Care continuum status</th>
<th>Visit schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown HIV status</td>
<td>Every 6 months</td>
<td>Return to the clinic every seven months for the offer of an HIV test, safe sex counselling, and any other services as appropriate.</td>
</tr>
<tr>
<td>HIV-negative, accept PrEP</td>
<td>Every 1 month</td>
<td>Return to the clinic each month for HIV testing, assessment of the presence of clinical symptoms consistent with acute viral infection, collection of adherence data and sexual behaviour/condom use data, evaluation of side effects, drug provision, and safe sex and adherence counselling and any other services as appropriate.</td>
</tr>
<tr>
<td>HIV-negative, decline PrEP</td>
<td>Every 6 months</td>
<td>Return to the clinic every six months for an HIV test, safe sex counselling, re-offer of PrEP, and any other services as appropriate.</td>
</tr>
<tr>
<td>HIV-positive, ART ineligible</td>
<td>Every 6 months</td>
<td>Return to the clinic for point of care CD4+ count testing every 3–6 months depending on CD4 count and any other services as appropriate.</td>
</tr>
<tr>
<td>HIV-positive, on ART</td>
<td>Regularly scheduled visits as per government guidelines</td>
<td>Upon initiation of ART women will be scheduled to return to the clinic at 2 and 4 weeks, after which they will be scheduled monthly for 6 months, there after 2 monthly for some or all of the following services, as necessary: point of care CD4+ testing, viral load monitoring and evaluation of side effects, collection of adherence data, drug provision, and safe sex and adherence counselling and any other services as appropriate.</td>
</tr>
</tbody>
</table>

### TRIAL DESIGN

The trial will be a matched cluster randomised controlled trial.

### SITE SELECTION

From the 36 SW clinic sites located across Zimbabwe in which dedicated SW HIV services are either already or are to be made newly available from early 2013, we selected 14 in 7 matched-pairs in which to conduct the trial (Figure 3). These 14 trial “clusters” were purposively selected to be reflective of a range of settings, of adequate size to ensure participation of between 85–300 new SW annually, and to maintain adequate levels of geographic spacing to ensure that the risk of contamination/spill over of intervention effect between study clusters through SW mobility and migration would be minimised.

### CLUSTER DEFINITION

A cluster was defined as the SW ‘catchment’ population around a government health clinic where dedicated SW services are being delivered.

### MATCHING

Matching was based on the following criteria:

i. Setting/context (e.g. town, growth point, colliery/army base);

ii. Whether the site is new or has been providing dedicated SW services since 2009/10.
iii. Whether there was limited mobility between sites (determined by distance between sites and mobility data collected at existing programme sites)

The underlying HIV prevalence in the general population is fairly similar across Zimbabwe so we did not specifically match on this criterion.69

The following paired sites were selected for inclusion:

Ngundu - Juru
Bindura - Kariba
Magunje - Hwange
Chivhu - Marondera
Gwanda - Chinhoyi
Zvishavande – Kadoma
Chipinge - Gutu

RANDOMISATION

One cluster in each pair will be allocated to the enhanced intervention through an automated procedure with a 50% chance of allocation to either arm. We will use restricted randomisation to maximise the chance of balance between arms. The procedure will be undertaken in a public randomisation ceremony involving key stakeholders from Zimbabwe including Ministry of Health, Community Advisory Board (CAB) members, and representatives of SW communities.

MEASUREMENT OF PRIMARY AND SECONDARY ENDPOINTS

Endpoint data will be collected from the following sources. The methods of data collection are described below the tables.

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of all SW who are infectious (viral load &gt;1000 copies/ml).</td>
<td>Respondent driven sampling survey (RDS)</td>
</tr>
</tbody>
</table>
### Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Data Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td>Proportion of HIV-infected women who are infectious</td>
<td>RDS</td>
</tr>
<tr>
<td>ii.</td>
<td>Proportion of those taking ART who have viral load &gt;1000 who have drug resistance</td>
<td>RDS</td>
</tr>
<tr>
<td>iii.</td>
<td>Self-reported quality of life, psychological health and functioning</td>
<td>RDS</td>
</tr>
<tr>
<td>iv.</td>
<td>Incidence of HIV infection in the 6 month period before the RDS survey</td>
<td>RDS</td>
</tr>
<tr>
<td>v.</td>
<td>Proportion adherent to ART for treatment, as assessed by:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. pharmacy refill data</td>
<td>Pharmacy records</td>
</tr>
<tr>
<td></td>
<td>b. virological response to treatment at 48 weeks</td>
<td>Programme data</td>
</tr>
<tr>
<td>vi.</td>
<td>SWs who have had condomless sex with clients in last month</td>
<td>RDS, Programme data</td>
</tr>
<tr>
<td>vii.</td>
<td>For each sex worker enrolled in RDS survey and or the programme, the number of clients and non-commercial partners with whom they had condomless sex in past month.</td>
<td>RDS, Programme data</td>
</tr>
<tr>
<td>viii.</td>
<td>Proportion of sex workers offered, initiating and, where appropriate, adhering to/participating in:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Community mobilisation activities</td>
<td>RDS, Programme data</td>
</tr>
<tr>
<td></td>
<td>b. HIV testing, including repeat testing programmes for HIV-negatives</td>
<td>RDS, Programme data</td>
</tr>
<tr>
<td></td>
<td>c. ARV for treatment of HIV infection</td>
<td>RDS, Programme data</td>
</tr>
<tr>
<td></td>
<td>d. Pre-exposure prophylaxis for HIV-negatives</td>
<td>RDS, Programme data</td>
</tr>
<tr>
<td></td>
<td>e. Support for HIV prevention and treatment</td>
<td>RDS, Programme data</td>
</tr>
<tr>
<td>ix.</td>
<td>Proportion of SWs who know HIV status (ie are diagnosed HIV positive or were tested HIV negative in last 6 months)</td>
<td>RDS</td>
</tr>
</tbody>
</table>
x.  | Perceived levels of peer support                                              | RDS                                    |
xii. | Acceptability and perceived quality of services                              | RDS                                    |
xiii. | Proportion keeping all clinical appointments on time (i.e. engaged in prevention/care) appropriate to their individual place on the care continuum | Programme data                        |

### Cost Effectiveness Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td>Resource use (number of clinic visits, CD4 counts, viral loads, hospitalisations, adherence counsellor time, HIV tests done, etc)</td>
<td>Programme data</td>
</tr>
</tbody>
</table>

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**PROCESS EVALUATION ENDPOINTS**

<table>
<thead>
<tr>
<th>i. Inputs</th>
<th>Data Source(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Assessment of start-up activities, e.g. staff appointed and trained; activities designed; preparatory meetings held.</td>
<td>Checklists</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ii. Activities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Assessment of whether activities were conducted as planned/scheduled, e.g. new clinic sites opened; opening times; waiting times; sites offering intervention components.</td>
<td>Log books, Staff and training records</td>
</tr>
<tr>
<td>b. Adherence supporters recruited, trained, retained; adherence activities conducted as planned/scheduled; community mobilisation activities conducted regularly.</td>
<td>Community mobilisation data; SW care support data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>iii. Outputs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Knowledge and awareness of services; indicators of “sex worker friendliness” of clinics;</td>
<td>RDS</td>
</tr>
<tr>
<td>b. Frequency of stock-outs;</td>
<td>Clinic Programme Data</td>
</tr>
<tr>
<td>c. Uptake of repeat testing program in intervention sites;</td>
<td>Clinic Programme Data</td>
</tr>
<tr>
<td>d. Uptake of CD4 count testing;</td>
<td>Clinic Programme Data</td>
</tr>
<tr>
<td>e. Uptake and acceptability of ART;</td>
<td>Clinic Programme Data</td>
</tr>
<tr>
<td>f. Proportion of those taking ART with drug resistance;</td>
<td>RDS</td>
</tr>
<tr>
<td>g. Uptake and acceptability of PrEP offered to HIV-negative SW in intervention sites;</td>
<td>Clinic Programme Data</td>
</tr>
<tr>
<td>h. Adherence to PrEP among women who say they are taking it, as measured by tenofovir drug levels on dried blood spots</td>
<td>Clinic Programme Data, RDS</td>
</tr>
<tr>
<td>i. Patterns of PrEP use;</td>
<td>Clinic Programme Data</td>
</tr>
<tr>
<td>j. Proportion of those taking PrEP with HIV (and drug resistant HIV).</td>
<td>RDS</td>
</tr>
<tr>
<td>k. Evidence of pill sharing.</td>
<td>RDS</td>
</tr>
</tbody>
</table>

| iv. Environment / context | Programme Diary |

**RESPONDENT Driven Sampling Data**

Respondent Driven Sampling (RDS) is an adaptation of chain referral sampling, where initial “seeds” are selected to represent a range of characteristics (e.g. diversity in age, location, type of sex work). After
completing the questionnaire, each seed starts a recruitment “chain” by recruiting a specified number of peers into the survey. Each subsequent respondent is further provided with coupons to give to several peers to refer them into the study; participants receive financial compensation for completing the survey themselves as well as for each of their recruits who participates.

RDS has been shown to reduce sampling bias and to improve representativeness of “hard-to-reach” populations by limiting the number of referrals any one respondent can have (thus creating “deep” rather than “wide” sample networks), and through the use of specific statistical techniques that weight the recruitment patterns in a way to balance out inconsistent recruitment.

Sex workers in each trial community will be surveyed at baseline and after 24 months using RDS in order to assess ‘population level’ effects of the program. Surveys will aim to include 200 women per cluster in each of the 14 clusters.

**INCLUSION AND EXCLUSION CRITERIA FOR SURVEY**

Seeds will be selected for each RDS site after formative research is conducted there. The formative research phase consists of 2–3 days of geographic and social mapping of sex work in each location, and will assist in understanding the local context adequately to identify specific criteria for seeds and how many should be selected. Formative research includes informal discussions with trained peer educators, healthcare staff, and community informants.

Inclusion criteria will be as follows:

- Age 18 or older
- Currently working as a sex worker (has exchanged sex for money in the past 30 days)
- Living or working in the study site (for at least 6 month)

Exclusion criteria include:

- Under 18
- Already participated in the current round of survey
- Visiting the study site temporarily (for less than 6 month)
- Not currently working as a sex worker (verification questions will be used to prevent fraudulent participation, such as about how sex work is organised in the area and the cost of different sex acts)

Eligibility will be determined by research staff on arrival to the RDS survey site. Research staff will check that each recruit reporting for enrolment has a valid referral coupon from a previous survey participant (except for seeds), meets the eligibility criteria and can answer the verification questions, understands the purposes of the study and can provide informed consent. Research staff will review the consent form with the participant. If the participant acknowledges full understanding of her participation in the
survey, she will be enrolled. The RDS survey instrument itself further contains questions that will check eligibility (such as current age and whether or not she has sold sex in the previous 30 days).

**SURVEY DESIGN, METHODS, AND PROCEDURES**

**INTERVIEW SITES:** One location for interviewing will be established in each study site, and selected for its accessibility to local sex workers, relative discreetness, and availability of enough space to arrange a waiting room (for screening and payments for recruiters) as well as a private room for behavioural interviews and blood sample collection. Formative research will assist in determining suitable location in each of the study sites.

**RECRUITMENT:** Between 6 and 10 seeds will be selected to reflect salient SW socio-demographic characteristics, as identified through mapping during the formative research phase. Usually, it is recommended to select 6-8 seeds, although more seeds will lead to faster attainment of sample size. Seeds are likely to be selected by peer educators, outreach workers, in consultation with local NGO, and through approaching women in any locations identified during the mapping exercise where peer educators currently do not have contact. Seeds will then be provided with two numbered coupons to recruit the first wave of peer participants.

**MULTIPlicity:** Duplication of respondents is a concern in any survey, but may be more likely in our RDS survey if (a) sex workers do not understand the process of peer recruitment, and refer the same peers more than once or refer reciprocally or (b) sex workers attempt to return using the same coupon in order to redeem the compensation payment more than once. Efforts to avoid duplicate participation will be made. First, coupons will be collected by survey staff when brought in by recruits; similarly, the portion of the coupon retained by the recruiter will be collected by staff when secondary compensation is made. Furthermore, ID cards will be requested on enrolment into the survey. Although no identifying information will be recorded, a study “code” will be compiled made up of the respondent’s initials and birthday and recorded for cross-checking against new study recruits.

**INCENTIVES:** Participants (including seeds) will receive compensation of US$5 for completing the interview (primary incentive) and further compensation of US$2 (secondary incentive) for each of their peers whom they recruit and who complete the survey (so up to a total of US$9 per participant). Recruiters will receive their secondary incentives as long as her recruit presents a coupon, fulfils the eligibility criteria, and enrols in the survey. The amount of compensation was set within the requirements of the MRCZ, and are designed to be high enough to compensate for potential loss of 1 client during study participation, but not so high as to encourage significant fraudulent enrolment.

**TOOLS:** The RDS survey will consist of two components, a behavioural questionnaire and a biological sample for anonymous HIV testing, along with a blood draw for viral load testing (for those testing positive, and among a sub-sample of those testing negative to explore pill sharing). All participants will be asked to complete a behavioural questionnaire that will be administered by survey staff using computer assisted personal interviewing (CAPI). The questionnaire will collect basic socio-demographic
information (age, marital status, education, etc.), economic characteristics, sexual behaviour, alcohol use, psychological health, physical health, past history of sexually transmitted infections, sexual and social networks, social capital, utilisation of services including HIV testing, ART, PMTCT and family planning. The questionnaire will be developed in English and then translated into local languages (Shona and Ndebele). The questionnaire will also include specific RDS network questions to allow for RDS analysis of recruitment chains. The questionnaire will be labelled with a unique Participant ID number (PTID) and linked to the biological specimen through a CAPI log. The CAPI log will link an individual’s PTID with their biological specimen labels which will use a unique non-human readable bar code.

LABORATORY METHODS

At each RDS survey, participants will have finger prick blood sample taken for rapid HIV testing using Rapid Immunoassay Determine HIV 1/2. The rapid test will be labeled with the unique study identifier and will be conducted anonymously at the survey site by an appropriately qualified nurse counselor. In addition, a dried blood spot (DBS) sample will be collected from the same finger prick according to standards set by the United States National Committee for Clinical Laboratory Standards (NCCLS) published in “Blood Collection on Filter Paper for Neonatal Screening Programs” (LA4-A; 1997). The DBS samples will be air dried onto filter paper and stored at room temperature until they are transported to the Flowcytometry laboratory in Harare. A random 2% of DBS samples will be tested for HIV antibody and the results will be compared with rapid test results. Testing for viral load will be carried out on all samples which are HIV antibody positive (as well as a sub-set of those HIV antibody negative) using the NucliSENS EasyQ HIV-1 assay (BioMe´rieux, Inc., Madrid, Spain)70-72. After testing, these dried blood specimens will continue to be stored at -80°C to allow the possibility for additional testing.

All HIV negative women who opt to take PrEP will be asked to provide a DBS specimen at 3 and 12 months post PrEP initiation. The procedures for collecting DBS described above will be used. DBS samples will be stored at -80°C before being shipped to University of Colorado Denver for tenofovir level testing.

VALIDATION OF DBS FOR VIRAL LOAD ASSAY: It is logistically much simpler and cheaper to collect DBS samples for viral load estimation than DBS. Previous studies suggest that DBS samples provide a valid estimate of viral load but that DBS is likely to result in slightly lower values than plasma. In order to determine the sample to be collected to determine trial outcomes, we propose to conduct a small comparative sub-study of viral load estimation using two sample types (DBS and cell free plasma). For this sub-study, in addition to providing a DBS sample, a convenience sample of 500 participants will be asked to provide 7ml blood collected into EDTA tube (resulting in an estimated 250 samples collected from HIV positive participants). The EDTA samples will be taken to the Flowcytometry laboratory where the plasma will be separated and aliquotted as outlined by the ACTG Laboratory Technologist Committee and stored at -80°C until batch testing at baseline survey completion. Again all those HIV antibody positive on DBS will be tested for viral load using cell free plasma using the NucliSENS EasyQ HIV-1 assay (BioMe´rieux, Inc., Madrid, Spain)in addition to viral load using the DBS sample as described above. We
will compare the results of HIV RNA using the two specimens and if necessary will amend the protocol to include collection of an EDTA sample for the endline respondent driven sampling survey.

**PROGRAMME RECORDS**

Programme data will be collected at both intervention and usual care comparison site clinics. These data include clinician completed form to collect basic socio-demographic information (age, marital status, education, etc.), physical health, past history of sexually transmitted infections, utilisation of services including HIV testing, ART, PMTCT and family planning and details of current clinical issues, any diagnostic tests undertaken, diagnoses made and or treatments prescribed. Responses will be compiled directly into an electronic patient record by nurse counsellors.

HIV testing will be offered. A pelvic exam will be performed for women reporting symptoms of STIs and syndromic management for STIs will be administered as necessary, according to Zimbabwe MoHCW guidelines. Each of these steps will be documented within the programme records. At the intervention sites routinely collected data will be supplemented by more intensive clinical/biologic data collection pertaining to the enhanced services, again depending on women’s identified care needs.

Routine programme data will be collected and regularly compiled to record uptake and use of services. Each clinic will keep:

- A calendar of days it was open
- Numbers of SW attending for different services (proportion repeat clients; proportion clients who return for scheduled appointments, site visited),
- Proportion of clinical clients initiating treatment or PrEP;
- Number and proportion of SW testing for HIV (first time and repeat)

**INTERVENTION MONITORING AND PROCESS EVALUATION FRAMEWORK**

The Intervention Monitoring and Process Evaluation (PE) framework accompanies the project Theory of Change and provides a structure for data collection to capture progress along the hypothesised pathway from provision of the intervention activities to their intended outcomes. While the overall trial will answer the primary research question, “can an enhanced package of community mobilisation and clinical service activities increase sex workers’ engagement in care to reduce community-level viral load?”, the process evaluation will provide some understanding of why and how the intervention was able to lead to improved retention at all stages along the HIV care continuum (or suggest reasons for lack of any observed change).
The PE framework depicted below provides a structure for measuring progress. This figure (4) can be related to the Theory of Change diagram developed for the enhanced SW programme, with separate steps at input, process and output levels for the “demand creation” and “strengthening supply” components, but both of these are designed to lead to the same behavioural outcomes (in terms of increased service use and appropriate health behaviours) and impact (biological & clinical results).

Figure 4. Process evaluation framework

The framework captures our theory of change hypothesis in detail. We hypothesise that:

- If there are adequate project inputs (financial and human resources, partnerships and collaboration, established procedures and protocols, effective trainings),
- these will ensure a smooth process of implementation,
- producing well-functioning outputs (efficient and high quality clinic services, motivated and skilled staff, sex workers’ participation in community mobilisation, and uptake of HIV testing, PrEP and ART).
- Subsequently, if the intervention outputs have good coverage, are feasible to deliver, and considered acceptable to sex workers,
- they will contribute to outcomes necessary for achieving the intervention’s ultimate goals or impact including sustained behaviour change (uptake of and adherence to PrEP, adherence to ART, condom use) and a broadly supportive environment (sex worker empowerment).

The intervention impacts will be assessed through the trial, and the primary and secondary outcomes are thus not included in the monitoring and process evaluation framework, which documents only the lower stages of the pathway. Although data collected through the framework cannot prove causal relationships between stages, they can build up a more comprehensive picture of what “actually happened” during implementation and how this may have affected observed outcomes. The research questions for each level of the framework are as follows:

(1) Inputs:  
How many resources were required to deliver the intervention?  
Were these adequate given the activities implemented?  
Were resources well managed and appropriately allocated?
(2) Process: Did activities occur according to the intervention design?
Were these all intervention components delivered?
How did timing of implementation compare to plans?

(3) Outputs: What was the coverage of each intervention activity?
Was implementation of the activities feasible (from the perspective of programme) and acceptable (from the perspective of SW)?
At what intensity was the intervention delivered (frequency of contact, number of different activities, length of events)?
What were the levels of quality achieved (assessed by external criteria according to standards set by the intervention, as well as from the perspectives of SW)?

(4) Outcomes: Have programmatic messages been adopted?
Are behaviours that are known determinants of expected impacts being taken up?
Is there evidence of changing environmental factors?
### Figure 5. Monitoring and Evaluation Framework

<table>
<thead>
<tr>
<th>Implementation of Intervention</th>
<th>Coverage &amp; Intensity</th>
<th>Behaviour Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inputs/ Preparation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Partnership with relevant partner agencies established (UNFPA, MoH, PSI, Gilead)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• New staff recruited, trained and deployed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clinic sites upgraded for enhanced intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Referral mechanisms put into place</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Community mobilisation activity protocols and tools introduced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Outreach activities to inform &amp; recruit sex workers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Checklist of planned activities, with dates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Staff records: % of staff hired in 2013 still in place each year;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Trainings # conducted and % staff attending</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Programme records: # community mobilisation activity protocols and tools designed; # sensitisation meetings to inform SW</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activities</th>
<th>Programme Delivery</th>
<th>Quality of Activities</th>
<th>Acceptability of Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEMAND CREATION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Enhanced Community Mobilisation</td>
<td>Number of community mobilisation meetings held</td>
<td>Frequency of attendance by SW</td>
<td>Staff Perceptions</td>
</tr>
<tr>
<td>• Promotion of Repeat HIV Testing</td>
<td>Numbers of automated and individualised SMS messages sent</td>
<td>SW contact with SW care supportees</td>
<td>Positive &amp; negative experiences</td>
</tr>
<tr>
<td>STRENGTHENING SUPPLY</td>
<td>Numbers of SW attending meetings</td>
<td>Drugs &amp; info available w/out stock out</td>
<td>Programme strengths &amp; weaknesses</td>
</tr>
<tr>
<td>• On-site delivery of ARV at international guidelines</td>
<td>Numbers of SW trained in peer/adherence support &amp; leadership</td>
<td>Knowledge &amp; awareness of testing, PrEP &amp; ART increased</td>
<td>SW Perceptions</td>
</tr>
<tr>
<td>• Offer of PrEP</td>
<td></td>
<td></td>
<td>Positive &amp; negative experiences</td>
</tr>
<tr>
<td>• Enhanced support for treatment &amp; PrEP</td>
<td></td>
<td></td>
<td>Likes &amp; dislikes in content &amp; delivery</td>
</tr>
</tbody>
</table>

#### Tools

- Programme records: # and % clinics offering ARV & PrEP; frequency of clinic openings; average waiting time from eligibility to treatment initiation
- SW adherence support worker records: # identified and trained; % retention over time
- RDS surveys: knowledge & awareness; % SW covered by activities; frequency
- Programme records: analysis of clinic records, stock-outs, % participating
- SW adherence support worker records: Provided contact w/ peers
- Semi-structured interviews with CeSHARR staff 3 times over project.
- In-depth interviews with SW 3 times over project at intervention sites.
- Interviews w/ other stakeholders i.e. referral organisations & PSI staff at end of intervention

### Diminishing control

Project Diary to record external events affecting implementation

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**ARV for HIV prevention and treatment among SW study protocol_v0.75**

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MONITORING AND PROCESS EVALUATION DATA COLLECTION

CHECKLISTS
A retrospective record should be maintained of if/when planned activities (as per protocol) were implemented.

STAFF AND TRAINING RECORDS
Routine programme documentation on start-up activities of the project, including the number of staff hired and deployed, and how many attended all relevant trainings. These will be reviewed annually and at the end of the project if staff retention/performance considered to be an issue affecting the delivery of intervention components.

SEX WORKER ADHERENCE SUPPORT RECORDS
SW trained as peer educators or SW care supports will be given forms on which to record all contact with peers, through one-to-one outreach or organised activities. Similarly, staff facilitating community mobilisation meetings will fill out similar forms to capture the following:

1. Location, duration & topics covered at each organised meeting/event
2. Number of SW present at meeting
3. Number of SW contacted per week (by means of contact e.g. in person, phone call, text message)
4. Number of referrals made, and to where
5. Number of referrals/appointments accompanied by SW workers or facilitator

In addition, an open-ended section will record:

- What is going well?
- What is going less well?
- What should be changed?
- Main issues raised by SW during meetings/events/one-to-one contacts, including challenges related to services and ART/PrEP

RDS SURVEYS
In addition to being the method for assessment of the primary outcome and some secondary outcomes (methods described in detail above), the RDS survey questionnaire will cover some process endpoints. These will include: sexual behaviour, condom use, current use of sexual health services, PMTCT and obstetric history, contraception use, experiences of violence, alcohol use, and levels of social support, networking and community identity among sex workers.

QUALITATIVE DATA
Semi-structured interviews with staff at intervention clinics (including any staff who have left the programme) will be conducted to elicit perceptions of the feasibility and acceptability of the intervention and their own levels of satisfaction and perspectives on its quality. Specific issues will be probed, such as ease of delivering the enhanced package, particularly challenges faced in increasing community mobilisation efforts, promoting repeat testing, timely uptake of treatment, and introduction of PrEP.
In-depth interviews with SW will be conducted at three intervals across the project (baseline, mid-implementation, end) in both enhanced intervention and comparison sites. SWs will be purposively selected for specific attributes such as high or low levels of engagement in activities (in intervention areas), experience as peer educators or SW care supporters, users and non-users of clinical services for SW, those eligible and ineligible for treatment, and different ages and types of sex work. Interviews will explore perceptions of community cohesion and social support among SW, perceptions of clinical and other available services, and positive and negative experiences of the intervention (or reasons for choosing to participate or not) in intervention sites.

Semi-structured interviews with key stakeholders, including CeSHHAR management and staff, and representatives of other partner organisations such as MoHCW, UNFPA, PSI and services to which referrals were made.

**PROJECT DIARY**

A calendar or diary will be kept by a member of the CeSHHAR research team to record any events (particularly external) that may affect ability of the intervention to be delivered as planned. Elections, police crackdowns, local festivities, other health promotion campaigns should all be noted, with a description of their activities and effect. Internal events that have bearing on implementation (such as increased funding, or break-down of a project vehicle) will also be noted to help contextualise other information collected.

**DATA REPORTING REQUIREMENTS**

For questionnaire data collected during routine programme activities, incident signs/symptoms/diagnoses/lab data will not be reported to regulatory authorities.

Reporting requirements to regulatory authorities will be limited to the research portion of the project only, i.e. the RDS survey and administration of PrEP. The following reporting requirements will be used:

Was there any untoward event potentially related to procedures specific to the enhanced intervention?

- Related to the enhanced community mobilisation, such as loss of confidentiality
- Related to the use of PrEP
- Related to follow up procedures
- Related to adherence procedures

General signs/symptoms/diagnoses that are definitely not related to the RDS survey procedures will be recorded in source documents, but will not be reported to MRCZ and other regulatory authorities, regardless of grade.

**SAE REPORTING**

The Standard Level of SAE reporting (see Division of Acquired Immunodeficiency Syndrome [DAIDS] Manual for Reporting of Adverse Events to DAIDS, dated June 1, 2010) will be used, for reporting the following to the study leadership, MRCZ, MoHCW and other relevant authorities within two (2) working days of becoming aware of the event:

- All deaths
• All disabilities/incapacities
• All hospitalizations that are “suspected adverse drug [procedure] reactions” (cannot rule out relationship to enhanced intervention procedures)
• All other Grade 4 events that are “suspected adverse drug [procedure] reactions” (cannot rule out relationship to enhanced intervention procedure)

DATA MANAGEMENT

CeSHHAR Zimbabwe will be the data coordinating centre. This unit is headed by an experienced data manager. Data will be cleaned, entered, analysed and safely stored here.

Data management and security standards will be equivalent for routine programme data and data collection in RDS surveys, though there will be significant differences in the way data are collected. For RDS, data will be collected using CAPI with assistance by a trained interviewer. Data validity checks will be built into the CAPI platform. In the field, data will be backed up daily onto a memory stick and/or into “cloud storage”. Laptop computers on which any data may be stored will be kept in locked storage at all times. Field teams will return to Harare at the end of each week to download data into a password protected database accessible only to the project data manager and named study personnel, on a central computer. This will be backed up daily. For programme data, one hard-copy file linking participants’ names with ID numbers, signed consent forms (for research participants only, i.e. RDS survey participants), and contact/locator information will be maintained by the Project Coordinator and stored in a secure locked cabinet separate from participant data. Other hard-copy data will be stored separately in participant files and locked in a file cabinet located in a secure room accessible only to key study personnel. Participants will be asked to provide written informed consent for participation (see Appendix B).

SAMPLE SIZE CONSIDERATIONS

We will enrol 14 clusters in 7-matched pairs and, in both baseline and final RDS surveys, will recruit 200 SW at each site of whom 50% are expected to be HIV positive at baseline. As shown in Figure 6, this sample size will give >80% power to detect a plausible effect size of our intervention on our primary outcome measure (assuming between-cluster coefficient of variation is 0.187 or below), i.e. the proportion of SWs participating in the final RDS survey (conducted after 24 months of intervention implementation) with confirmed HIV infection and a detectable viral load (>1000 copies/ml).

We used the approach of Hayes and Bennett to determine sample size. First, we estimated that in the comparison arm (Arm A, WHO-guideline standard care SW outreach) 41% of SW will have a detectable viral load, actively replicating, at 24 months. The breakdown of the assumed effect of the intervention on HIV prevalence, the proportion of HIV infected women who are diagnosed, the proportion of diagnosed women who are on ART, and the proportion of women on ART with actively replicating virus is shown in Table 2. We hypothesize that with realistic estimates of the size of the potential effect of our intervention on improving knowledge of HIV status among HIV-infected SW, decreasing time to treatment initiation and improving adherence, in the enhanced intervention arm (Arm B) 28% of SW should be expected to have detectable viral load at the time of the final RDS survey. Table 2 shows these estimations alongside more ‘optimistic’ and ‘pessimistic’ scenarios.
Taking these estimates forward, Figure 6 shows the number of matched paired clusters and the number of SW per cluster required to detect a reduction of 0.13 in the proportion of SW with a detectable viral load (from 0.41 to 0.28), with 80% power and a level of significance of 5% for different values of the between-cluster coefficient of variation in the primary outcome measure (\( k_m \)). We assumed this reduction would be achieved through four mechanisms. First, by reducing HIV prevalence by 2%, due to the reduction in incidence achieved by introducing PrEP and to the potential reduction in the number of unprotected sex acts in women who receive HIV testing and counselling and due to community mobilisation resulting in higher levels of condom use. Second, by increasing the proportion of HIV-infected women who have been diagnosed up to 80%, obtained by asking women to test every 6 months, sending out appointment reminders, and following them up if they do not attend the clinic to be tested for HIV. Third, by increasing the proportion of women diagnosed with HIV who are on ART, by providing POC CD4 count testing and offering them the opportunity to initiate ART on-site rather than by referring them, and by using as criterion to initiate people on ART the CD4 threshold indicated in international guidelines (likely to be modified up to CD4<500 cells/mm³). In a cohort of sero-converters in high-income countries, it has been estimated that on average at 1 year of infection 48% will have a CD4<500 and 26% a CD4 <350 cells/mm³, therefore if the eligibility criteria are going to be modified from CD4<350 to CD4<500 cells/mm³, this will substantially increase the proportion of people who are eligible for treatment. Finally, we will decrease the proportion of women on ART who are not virally suppressed from 33% to 20%. It has been shown that it is possible to achieve a low level of virological failure, close to those assumed. A systematic review of studies in sub-saharan Africa estimated that 78% (in on-treatment analysis) of patients were virological suppressed after 6 months of antiretroviral therapy, 76% after 12 months, and 67% after 24 months, and in a study in Zimbabwe these estimated were 85% and 74% at 6 and 12 months since ART initiation, respectively. With our enhanced adherence support we think it is achievable to reduce the proportion on ART with a detectable viral load above 1000 copies/ml to 20%.

In Figure 6, It can be seen that as \( k_m \) increases the number of clusters required to achieve 80% power for a given cluster size increases. It can also be seen that at all values of \( k_m \) it is relatively inefficient to increase the within-cluster size above about 150 SWs as the lines flatten out beyond this point. However, our prior experience and initial estimates of the size of the SW population accessing services in each site suggest it will be feasible, and in some cases necessary because of lower than expected HIV prevalence, to recruit at least 100 HIV-positive SWs and thus to recruit up to 200 SWs total in each site. We do not think that it will be feasible to recruit more than seven matched pairs of clusters across Zimbabwe without significant risk of contamination of the effect of the intervention because of clusters being relatively accessible to each other. In Figure 7 we show the association between the power of the study and the between-cluster coefficient of variation for the primary outcome (\( k_m \)) in a study of seven matched-pair clusters with 200 SW (100 HIV-positive SW) in each cluster for three different scenarios: “realistic” the one that is considered achievable once the intervention is implemented, “optimistic” (21% of SW not virally suppressed by the end of the study) and “pessimistic” (35% not virally suppressed). The figure shows that if we achieve “optimistic” improvements in the different aspects of our intervention, the study will have >80% power even in situations where matching is poor and there is significant inter-cluster variability in viral load among HIV-infected SWs (i.e. \( k_m \) is moderately high, between 0.2 and 0.3). If more “realistic” success is achieved, the study will have >80% power if kms0.187. If the effect of the intervention is only in line with our pessimistic estimates we will not have >80% statistical power to detect a relatively small effect.
Figure 6. Number of matched pairs of SW clinics (clusters) and number of women per clinic required to detect a reduction in proportion of women not virally suppressed (not on ART or virologically failing) from 41% to 28% (80% power, 5% level of significance) for various values of the between-cluster coefficient of variation (km) in the proportion not virally suppressed within matched pairs.
Figure 7. Power and between-cluster coefficient of variation (km) in the proportion not virally suppressed within matched pairs for different scenarios for different level of reduction in proportion of women not virally suppressed (not on ART or virologically failing) with 7 pairs of matched pairs and 200 women per cluster (5% level of significance)

![Graph showing power and between-cluster coefficient of variation](image)

Table 2. Specifications of the primary outcome in the control arm and for three hypothetical scenarios in the intervention arm

<table>
<thead>
<tr>
<th></th>
<th>Control arm (A)</th>
<th>Intervention arm (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Realistic</td>
<td>Optimistic</td>
</tr>
<tr>
<td>HIV Prevalence among SW</td>
<td>0.50</td>
<td>0.48</td>
</tr>
<tr>
<td>Proportion of SW diagnosed with HIV</td>
<td>0.66</td>
<td>0.8</td>
</tr>
<tr>
<td>Proportion of SW diagnosed with HIV on ART</td>
<td>0.40</td>
<td>0.65</td>
</tr>
<tr>
<td>Proportion of SW on ART not virally suppressed (&gt;1000 copies/ml)</td>
<td>0.33</td>
<td>0.2</td>
</tr>
<tr>
<td>Primary outcome: Proportion of SW not virally suppressed</td>
<td>0.41</td>
<td>0.28</td>
</tr>
</tbody>
</table>

While we do not have prior data on our primary outcome of interest (detectable viral load among SW) we based our estimates on a number of data sources from our own work and that of others in Zimbabwe. Among SW in three locations in Zimbabwe (Victoria Falls, Hwange and Mutare) in 2011 HIV prevalence was estimated at 50% in Hwange and Mutare, and 70% in Victoria falls, with 60-70% of HIV-positive women reporting that they had been diagnosed with HIV. SW friendly HIV testing, STI syndromic management and other services had been available in these sites in a manner similar to that expected in our comparison arm (Arm A) clusters. Among women seen within the Sisters program, the proportion of those HIV-infected reporting that they were on ART was 40%. In a qualitative study among Sisters program SWs who Sisters referred for ART, 50% (56 out of 113) reported attending their referral to ART services, but only 18% (n=20) attended ART services more than once [S. Mtetwa, personal communication]. Among HIV positive adolescents attending public ART clinics in Harare, the
Statistical analyses will be conducted and reported in line with CONSORT guidelines for cluster randomised trials.

**Cluster summaries for unadjusted analysis**

We will first use unadjusted statistics to describe the population recruited. As recommended for RDS data, we will exclude the seeds from all of our analyses. While RDS seeds are not intended to be representative of the population of female sex workers in each site it will be hoped that over successive waves the population recruited will become more representative of this population. While it is not possible to empirically confirm this, it will be informative to explore whether the prevalence of the primary outcome measure “stabilises” over multiple waves of recruitment. We will therefore first explore whether the (unadjusted) prevalence stabilises over the waves of recruitment. We will also explore whether socio-demographic characteristics of recruiters are associated with these same characteristics and with the key outcome measures in their recruits. Social network theory suggests that there may be autocorrelation of this type since individuals are likely to be friends with (and thus recruit) individuals more like them than would be expected on average.

The first stage of the analyses will be to estimate the prevalence of the primary outcome in each cluster. We will adapted a method proposed by Szwarcwald and used by our group in recent work to estimate predicted prevalences of the primary outcome in the source population. We will use random effects logistic regression for this purpose. We will fit models including weighting for the inverse of participant degree (using the measure of network degree ‘how many of those sex workers whom you know personally would you consider recruiting into this study’?). We will also specify a random effect term for “seed” such that the variance of responses from individuals who were part of the same recruitment chain will be modelled to take some account of potential clustering.

**Unadjusted analysis**

The second stage of the analysis will be to compare the cluster primary endpoint prevalences in the two arms in an unadjusted analysis. These will be compared across treatment arms using a matched t-test. We will calculate the crude odds ratio in each matched pair since each pair provides an independent estimate of the odds ratio. If \( p_{ij} \) is the observed odds of the primary endpoint in the \( j \)th matched pair \( (j=1,\ldots,c) \) and intervention arm \( i \) where \( i \) is 1 for the treatment arm and 0 for the controls, then we can calculate the pair-specific odds ratios as:

\[
\text{Estimated odds ratio from the } j \text{th matched pair } = \frac{p_{j1}}{p_{j0}}
\]

The odds is likely to be skewed, so to account for this the log of the odds will be more appropriate and we will work with the \( \log(\text{odds}) = \log(p_{ij}) = l_i \). To estimate the overall log odds ratio we will take the un-weighted mean of the pair-specific log odds ratios by dividing the sum of the log odds ratios by the total number of pairs \( c \):

\[
\log(\text{odds}) = \frac{\sum_j l_i}{c}
\]
The overall odds ratio, $\hat{\theta}$, will be calculated by taking the anti-logarithm of $l_1 - l_0$.

If $h_j = l_{1j} - l_{0j} = \log(\hat{\theta}_j)$, i.e. the observed log odds ratio for the $j$th matched pair, then we can test the null hypothesis that the true odds ratio is 1 by performing the following paired $t$-test:

$$t_m = \frac{\bar{h}}{\sqrt{s_m^2/c}}$$

Where $\bar{h}$ is the mean ratio across the pairs and $s_m^2$ is the empirical variance of the pair specific ratios from the mean given by:

$$s_m^2 = \frac{1}{c-1} \sum_j (h_j - \bar{h})^2$$

The computed value of $t_m$ will be referred to tables of the $t$ distribution with $v=(c-1)$ degrees of freedom. The 95% confidence interval for the odds ratio $\hat{\theta}$ will be calculated using:

$$\exp\left(\bar{h} \pm t_{v,0.025} \times \frac{s_m}{\sqrt{c}}\right)$$

**Assessment of balance and response rates between arms and adjustment for imbalances**

We will use descriptive statistics to assess whether there was balance across the two arms in key socio-demographic and potentially confounding variables at both baseline and final RDS surveys. Results will inform those variables to be adjusted for in the adjusted analysis, with particular attention paid to variable that are known a priori to be associated with the endpoints of interest. We will also explore and report response rates across the arms.

We will perform adjusted analysis for the effect of the intervention on the endpoints of interest and thereby account for the potential confounding effects of imbalanced variables. The statistical model will include suspected covariates while accounting for the sampling method. We will conduct pre-specified sub-group analyses, using statistical tests for heterogeneity, by looking at the effect of the intervention in the following sub-groups:

- Age
- Clinic location type
- Established vs new study sites
- Educational attainment
- HIV status
- Harassment and experience of violence
MODELLING ANALYSIS

On completion of the study, an individual-based stochastic computer simulation model will be used to explore the potential impact on HIV incidence (and incidence of HIV with transmitted drug resistance [TDR]) of this enhanced intervention among sex workers nationally, assuming the same efficacy as observed in the enhanced intervention arm of the trial.

The model we will use is an adaptation of an individual-based dynamic stochastic model, previously published\(^1\) calibrated to describe the HIV epidemic among heterosexuals in Zimbabwe. It has been used to predict the effects on transmission of drug resistant HIV-1 and other outcomes of delays in introducing viral load monitoring to determine switches from first- to second-line regimens in resource-limited settings,\(^2\) and contributed to joint modelling analyses on the impact of changing ART eligibility criteria, ART monitoring strategies and resistance due to PrEP. The model includes a high level of detail. Considering transmission, it separately takes into account, the number of short-term condom-less sex partners (occasional partners or clients) for each 3 month period and whether individuals have condom-less sex with long-term partners in each 3 month period. The impact on HIV incidence of this expanded intervention will depend on the extent to which the program is able to increase levels of HIV diagnosis, retain both HIV-positive and HIV-negative SW in care, promote PrEP, a potential reduction in unprotected sex following diagnosis and/or counselling, and to initiate ART in a timely way and suppress viral load by maintaining high levels of adherence.

We also model the processes of diagnosis, attendance for care, loss to care, adherence to ART and viral load, resistance and CD4 count changes both on ART and after stopping ART. This means the model is well suited to evaluate the impact of retention at the various stages on morbidity and mortality in infected individuals as well as on incidence of new infections, including with drug resistant virus.

COST EFFECTIVENESS ANALYSIS

Cost effectiveness analysis will be based on the modelling analysis and will also draw on the costing data (which will include costing of all aspects of HIV prevention and care in Zimbabwe, as well as specific costing of the SW programme and the enhanced intervention). This will be set against a background of current levels of HIV testing, diagnosis, ART use and virologic success in Zimbabwe. We will compare the Quality Adjusted Life Years (QALYs) and costs (both discounted) over a 30 year time horizon between the two scenarios of (i) sex worker programme as in the standard care sites and (ii) sex worker programme as in our intervention sites. This will allow us to calculate the incremental cost effectiveness ratio (ICER), from a health systems perspective.

In general, costing is an exercise conducted to estimate the opportunity cost of resources put to use for various reasons. The objective is to assess how much of a particular resource input is required to achieve a stated intervention. Costing exercises have two elements: measurement of the quantities of resource use (\(q\)) and the assignment of unit costs or charges (\(p\)). There are various approaches used to estimate the unit input cost in HIV services and these depend on the precision of the costing exercise required. Two general approaches are used to estimating the unit costs of any given services; top-down and bottom-up or ingredients approach to costing. The top down approach divides expenditure for a defined period by the number of services given for that time period. A much more accurate approach is the ingredients based
method which identifies the inputs to a service of interest, say treatment, quantifies the inputs and values them prior summing these costs to give a total unit cost for that service.

Several costing studies have been conducted to estimate unit costs of specific interventions, we will use secondary literature to standardize unit costs of interventions e.g. cost per CD4 done. However this will, in certain instances, be supplemented by the ingredients costing approach to estimating unit costs. Resource use data will be collected routinely during the trial.

**DATA REQUIREMENTS**

Resource Use data

A societal perspective will be assumed in the base case so that health sector costs and costs falling on the facilities providing ART, on the health system, and also on private households (both directly and through reduced productivity) will be incorporated into the economic model. This will help in assessing issues around access to services. A sensitivity analysis will be undertaken to determine the impact of adopting narrower perspectives on incremental cost-effectiveness. Resource use data which will be routinely collected during clinic days include the use of all services within arms and such medications, laboratory and other diagnostic tests & clinic visits. The costs of the alternative strategies will be determined by combining resource use with unit cost data.

**HEALTH OUTCOMES AND QUALITY OF LIFE**

Health outcome data, on mortality and CD4 status, collected in the clinic programme will be used in the Stochastic model. Quality of life data in the form suitable for calculating QALYs (utilities) will be collected alongside the trial data at baseline and final RDS surveys. We will adopt the EQ-5D tool to estimate the quality of life SW. The tool has been translated and used before in Zimbabwe.83

**TIMELINE**

<table>
<thead>
<tr>
<th>Communities</th>
<th>2011</th>
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<td>Q3</td>
<td>Q4</td>
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<tr>
<td>Modelling/Cost effectiveness</td>
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**ETHICAL CONSIDERATIONS**

This protocol will be subject to review and approval by institutional review boards at all participating institutions, including those in Zimbabwe (the Medical Research Council of Zimbabwe), University College London, London School of Hygiene and Tropical Medicine and RTI International. This will include, according to each IRB’s requirements, approval prior to the initiation of research, on-going adverse event monitoring,
periodic review, and final study reporting. We will seek approval from the Medicines Control Authority of Zimbabwe (MCAZ) for the use of Truvada as PrEP. The protocol will also be approved by the Ministry of Health and Child Welfare and the City Health and the National AIDS Council who work in partnership with Sisters program to implement this study.

**PARTICIPANT INFORMED CONSENT AND REMUNERATION**

Informed consent, for survey participation and for those who elect to use PrEP, will be carried out in the same manner as described above. Participants will be provided with information about the research and study procedures by a trained interviewer, and will have the opportunity to ask questions as part of the informed consent process.

Women who participate in the RDS surveys will be recruited through RDS survey techniques, which include recruiting 6 initial seeds at each site in both the intervention and control communities. Participants will receive financial compensation of $5 for completing the survey themselves as well as $2 for each of their recruits who participates. SW, health care workers and other stakeholders who are interviewed as part of process evaluation will also be recompensed with the standard $5.

**CONFIDENTIALITY**

The research team will ensure that all research data collected are numbered with a unique ID and not named. A link log which links the unique ID to name will be kept by the project coordinator in Harare in a locked and secure place, separate from the questionnaire/interview data. Names, addresses and other identifying information will be required at the clinic sites for follow up purposes, and will be kept separately from questionnaire and laboratory data. Only the site coordinator, data manager and principal investigator will have access to this information. Laboratory and questionnaire data will be linked using an individual's unique study ID number.

All study staff will undergo GCP and ethics training. All people working with CeSHHAR Zimbabwe sign a confidentiality agreement; they have very strict confidentiality procedures in place.

**DATA AND SAFETY MONITORING BOARD**

A Data and Safety Monitoring Board (DSMB) will be established and will meet at the outset of the trial in person, and then semi-annually by telephone. The DSMB will approve the overall protocol, assessments, and consent forms. The DSMB will receive all reports of adverse events, as will the IRBs overseeing this study. Meetings of the DSMB can be scheduled, as needed, to discuss and resolve AE issues. The DSMB will review semi-annually all accrued data to assess that study objectives are being met, and to ensure that benefit exceeds harm.

**COMMUNITY ADVISORY BOARD**

The trial will establish a community advisory board (CAB) comprising one SW and one community stakeholder from each of the trial communities. The mandate of the SW Community Advisory Board is to strongly link the trial steering committee and investigators to the SW community, ensure transparent and full communication between trial and the community it serves, and to ensure that the trial research findings
have a maximum impact on the communities from which the information is drawn. The CAB functions in an advisory capacity to the trial steering committee, which will be endeavor to respond appropriately to the issues raised. The CAB will assist trial staff in developing culturally and linguistically appropriate materials for study participants such as study specific fact sheets and informed consent forms.

STUDY MODIFICATION AND DISCONTINUATION

The study may be modified or discontinued at any time by the IRBs as part of their duties to ensure that research participants are protected.

PROTOCOL DEVIATIONS AND EXCEPTIONS

The investigator should not implement any deviation from, or changes of, the protocol without prior review and documented approval from the Ethical Committee of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects. The investigator should document and explain any deviation from the approved protocol and to file waivers received from the MRCZ, if applicable.

ORGANIZATION

PRINCIPAL INVESTIGATOR

Dr Frances Cowan, MBBS, MRCP, MSc, MD, FRCPE, FRCP; Reader, CeSHHAR Zimbabwe and University College London;

CO-INVESTIGATORS

Dr Andrew Phillips, PhD; Professor, University College London;

Dr James Hargreaves, MSc, DPhil; Senior Lecturer, London School of Hygiene & Tropical Medicine;

Ms Joanna Busza, MSc; Senior Lecturer, London School of Hygiene & Tropical Medicine;

Dr Sue Napierala Mavedzenge, MPH, DPhil; Research Epidemiologist, RTI International

Dr Karin Hatzold, MPH, MD; Deputy Director HIV &TB, Population Services International Global;

Dr Owen Mugurungi, MSc, MD; Director AIDS and TB, Ministry of Health and Child Welfare;

Mr Travor Mabugu, Pharm, Health Economics, MPS; Director Health Economics and Policy Research Initiative, Zimbabwe.

Professor Simbarashe Rusakaniko, Chair, Department of Community Medicine at University of Zimbabwe

STEERING COMMITTEE

The Sex Worker Program steering committee is vested with the primary responsibility for the ethical running of the study. It is responsible for assisting and guiding the research team. It also monitors the study
implementation. The steering committee will operate in an advisory capacity leaving the PI to implement the study procedures (See Appendix F).

**FUNDING ORGANIZATIONS**

United Kingdom Department for International Development (DfID)

UNFPA

PSI Zimbabwe
REFERENCES

8. Elmes J, Nhongo K, Hallett T, et al. Who are the women at risk of HIV infection in rural Zimbabwe and how many are there? Insights into their characteristics, locations and behaviours. 19th meeting of the International Society for Sexually Transmitted Disease Research (ISSTDR). Quebec City, Canada; July 11-July 13, 2011.


34. Parivartan P. Sex Work(er) Interventions in Developing Countries: An Annotated Bibliography, 2006.
46. Voeten HACM, Egesah OB, Varkevisser CM, Habbema JDF. Female sex workers and unsafe sex in urban and rural Nyanza, Kenya: regular partners may contribute more to HIV transmission than clients. Tropical Medicine & International Health 2007; 12(2): 174-82.
APPENDIX A – INVESTIGATOR AGREEMENT FOR PROTOCOL

I have read the foregoing protocol “Treatment for Prevention among Zimbabwean Sex Workers”, and agree to:

· Conduct the study as outlined herein;
· Maintain the confidentiality of all information received or developed in connection with this protocol and;
· Conduct this study in accordance with GCP Standards and any other applicable local / state laws and regulations;
· Comply with the signed investigators agreement.

__________________________________ ___________________________________
Investigator Signature Date

______________________________________________________________________
Investigator name in capital letters

______________________________________________________________________
Telephone number:

______________________________________________________________________
Fax number:

______________________________________________________________________
Email address:
Appendix B – Informed consent form
Appendix C – Truvada (FTC/TDF PrEP) prescribing information
Appendix D - Records handling and keeping

Source Documents

Source documents are the initial documents whereon subject data are recorded. This includes, but is not limited to, original subject files, hospital records, and original recordings/tracings from automated instruments, etc.

The MRCZ allows use of dedicated work sheets to serve as source documents to collect the available source data, on top of all other applicable source documents in the site. All information captured on the CRF should be accurately supported by the source documents unless specifically approved and documented by MRCZ. For example, each subject’s source documents should include (but not be limited to):

- Documenting the Informed consent process
- Subject full name and identification
- Date of each study required visit with a description of the visit and the results of each procedure that was performed
- A full and comprehensive anamnesis that will cover subject's medical history, current disease etc.
- All concomitant procedures and medications for the screening eligibility purposes and regular visits

Any additional information relevant to the study should be included in the subject’s source documents. In particular, any deviations from the study protocol or procedures should be recorded in the source documents, if noted. For example, if study required procedures or visits are not completed or are completed outside the time frame specified in the protocol, the reasons for the departure should be explained in the source documents, or mentioned whether it was waived by the MRCZ in advance. The investigator must maintain all study documentation at least 2 years after the last approval of marketing application and until there are no pending or contemplated marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational
product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the MRCZ. The MRCZ should inform the investigator in writing when the trial-related records are no longer needed.
Appendix E - Regulatory obligations

Investigator’s Obligations

Clinical research studies are subject to the regulations of the Regulatory Authority of the country. Upon signing the protocol, the PI agrees to assume the following responsibilities and to keep the required records for a period of three years following completion of the study and to file the required reports in a timely manner:

1. Conduct the investigation in compliance with the protocol. Changes to the protocol may only be made after approval by the DSMB and the Ethical Committee, or when necessary to protect the safety, rights or welfare of a subject.

2. Personally conduct or supervise the investigation.

3. Read and understand the information in the Protocol and Investigator Brochure.

4. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations.

5. Inform all subjects that the device is being used for investigational purposes and ensure that the requirements related to obtaining the informed consent are met.

Maintain the following records (for a period of three years following completion of the study):

1. Signed copy of the protocol.

2. Signed consent forms

3. All correspondence as relates to the clinical trial

4. Case Report Forms

File the following reports:

1. Severe unexpected adverse device related effects reports received by the MRCZ.

2. Regular Severe Adverse Event reports produced by the PI.

3. Deviations, which were made from the protocol for emergency use, must be reported to the MRCZ as soon as possible, but no later than five working days after its occurrence.