Protocol:

Peer Delivery of HIV Self-Screening to Support Linkage to HIV Prevention in Rural KwaZulu-Natal, South Africa: A Cluster Randomized Control Trial (cRCT)

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29th of September 2018 – Version_6 which supersedes version dated 4th of September 2018 and Version 1 dated 11 May2018.

We can confirm that none of the investigators listed here have a conflict of interest

STUDY SUMMARY

Title: Peer delivery of HIV self-screening (HIV-SS) to support linkage to HIV prevention in rural KwaZulu-Natal (KZN), South Africa: a cluster randomized control trial (cRCT)

Study Hypothesis: HIV-SS will allow peer delivered or peer led networks to effectively and efficiently link older adolescent girls and young women into HIV prevention and care services.

Design: A cluster randomized control trial comparing two models of peer delivery of HIV-SS, through incentivized respondent driven peer networks and direct distribution by peer navigators compared to standard of care (referral to HIV testing, prevention and care services by peer navigators) in improving the uptake of HIV prevention and care amongst young women (18-24) living in the rural uMkhanyakude district of KwaZulu-Natal, South Africa.

Population: The study population will include 21 peer navigators working with over 2000 young people particularly young women aged 18-24 years. More than 2000 young people (males and females) will be reached during the trial in the 21 wards/iZigoldis representing the study arms.

Study Duration: 18 months from Institutional Review Board approval to data dissemination.

Objectives:

1. To increase the knowledge of HIV status among young women aged 18-24 years old and their male partners through distribution of HIV-SS through incentivized peer networks or direct distribution by peer navigators compared to peer navigators referring into HIV testing services.
2. To determine an increase in the rate of linkage among young women aged 18-24 to HIV prevention and treatment services facilitated by distribution of HIV-SS through incentivized peer networks or direct distribution by peer navigators compared to peer navigators referring into services.
3. To conduct a process evaluation of the acceptability, feasibility, and reach (out of school, recently migrant and living in remote areas) in linking 18-24-year-old women to HIV prevention and treatment services of HIV-SS distribution through incentivized peer networks, or direct distribution by peer navigators or peer navigators referring into services.
4. To measure the cost per 18-24-year-old linked to prevention and care through peer-led incentivized HIV-SS delivery system or direct distribution of HIV-SS by peer navigators, compared to peer navigator referring into services.

Primary Outcomes:

The difference between the rate of linkage within three months of 18-24 years old women to HIV confirmatory testing and pre-exposure prophylaxis (PrEP) eligibility screening if HIV-negative and antiretroviral treatment (ART) starting if HIV-positive. It will be between the two peer-delivery approaches to HIV-SS distribution (incentivized HIV-SS delivery through peer network and direct distribution of HIV-SS by peer navigators) compared to standard of care (peer navigator referral to HIV testing, treatment and prevention services). Rate is defined as the number of linkages per month of peer navigator outreach activity.

Secondary Outcomes:

1. The number of linkages per 100 clinic referral slips distributed per arm;
2. The change in proportion of all residents (men and women) aged 18-24 years who are aware of HIV-SS and who have used HIV-SS over time using the existing surveillance and routinely collected data (PIPSA BE290/16 and DREAMS BFC339/16).
3. Comparison of the difference per study area in the proportion of 18-24 year olds who report knowledge of HIV status and uptake of ART, PrEP and voluntary medical male circumcision (VMMC) in the surveillance area (PIPSA BE290/16 and DREAMS BFC339/16).
4. Comparison of the pattern of recruitment per arm of study: the proportion of hard to reach adolescent girls and young women (aged 18-24 years) - defined as out of school, recently migrated and those who live in remote areas - linked to care in the three arms of study.
5. Comparison of costs in intervention and control arms. Cost per case linked to PrEP eligibility assessment (HIV-) and cost per case started on ART (HIV+). To establish costs, we will use both a bottom-up ingredient-based costing approach and a top-down costing approach using the study budgets and expenditure reports.

Study Locations/Sites: 21 wards/iZigoldis in uMkhanyakude district, KZN.

Study oversight: STAR has formed a Technical Advisory Group (TAG) to monitor and supervise progress of data collection, provide independent review of data collected during all cluster-randomized trials conducted under the STAR project, and assist investigators in disseminating results.

Abbreviations and Acronyms

ART	Antiretroviral Treatment
ARV	Antiretroviral
DREAMS	*D*etermined, *R*esilient, *E*mpowered, *A*IDS-free, *M*entored and *S*afe
HIV-SS	HIV Self-Screening
KZN	KwaZulu-Natal
DoH	National Department of Health
PIPSA	Population Intervention Platform Surveillance Area
IDI	In-Depth Interview
PrEP	Pre-exposure Prophylaxis
VMMC	Voluntary Medical Male Circumcision
ARHI	Africa Health Research Institute
WHO	World Health Organization
RDS	Respondent-Driven Sampling

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1 Background/Rationale

Globally, most people living with HIV do not know their serostatus (1) and only one third of the world young people know their HIV status (2). Evidence from our settings and other countries in sub-Saharan shows that most young people living with HIV are undiagnosed and thus not linked to care (3, 4). Research has shown that HIV testing in healthcare facilities are hampered by lack of privacy, long waiting times, stigma and discrimination associated with HIV diagnosis (5-8). South Africa is one of the countries that suffers the burden of HIV (an estimated 7 million people living with HIV) (9) and KwaZulu-Natal (KZN) is the most affected province by the epidemic with an estimated 27.9% in 2012 (10). Despite the huge investments in HIV prevention in South Africa, the HIV incidence continue to rise particularly in KZN with an estimated of 3.2 million young people between the ages 10 and 24 years (9).

There are increasing range of effective HIV prevention and treatment services available for both adolescent girls and young men and women, including antiretroviral (ART) based prevention e.g. Pre-exposure Prophylaxis (PrEP) and Universal Test and Treat (UTT) (11, 12) and Voluntary Medical Male Circumcision (VMMC) in uMkhanyakude district, yet, there is high HIV incidence rate in adolescent girls and young women (AGYW) with an estimated 5% per annum in aged 15-19 years and 8% per annum in aged 20-24 years respectively (13). Our recent TasP trial failed to show an impact on incidence in part due to the challenge of testing and linking young people and men. Patient level fears (stigma, labelling and discrimination) and facility level barriers (distance and waiting times) continue to be barriers to young people not seeking testing and services in health facilities (14-16). There is an urgent need to increase the proportion who know their status and support linkage to care and preventions – including ART based care and prevention and VMMC. Therefore, access to confidential HIV testing is essential to reduce the HIV incidence and improve access to treatment and support for people living with HIV (PLHIV) in our settings.

To increase global testing rates and early access to treatment, HIV self-screening (HIV-SS) – which refers to a simple saliva self-test similar to a pregnancy test- has been identified as a potential method given its privacy and convenience (17-19). Different studies and systematic reviews have shown high acceptability and uptake of HIV-SS particularly amongst first time testers (18-21). Fifty percent (50%) of newly seropositive were detected through HIV-SS in Malawi (19). Another study from Malawi shows high uptake of HIV-SS and linkage to care particularly amongst young people (22). Similarly, HIV-SS accuracy was high in a study, but its performance relies on the education of the person conducting the test (19, 21). Research has shown that rapid oral fluid testing was generally preferred to blood-based testing (23-25). It should be noted that highly accurate HIV-SS kit (OraQuick) product is currently available in South Africa, has been endorsed by the National Department of Health (NDoH) and is being widely distributed

and evaluated by Wits Reproductive Health and HIV Institute (Wits RHI) in Inner City of Johannesburg. The OraQuick® Inhome HIV test (OraSure Technologies, Inc.) has a sensitivity of 92% and a specificity of 99.9% and was recently approved by the U.S. Food and Drug Administration for over-the-counter sale (18).

Despite widespread awareness of the acceptability of HIV-SS and its positive role in supporting HIV testing in those hitherto untested such as men and young women, there is limited evidence of the use of HIV-SS to improve linkage to prevention. Effectiveness of biomedical innovations such as PrEP will depend on uptake (26-28). As described above, there are challenges to HIV testing that can be overcome by HIV-SS, however, those challenges also create significant barriers to linking and keeping young men and non-pregnant women in the cascade of HIV care and prevention. The key findings from systematic reviews looking at different aspects of the HIV treatment cascade of uptake, retention and adherence are: 1) A range of community-based delivery models, which have included adherence clubs, community health workers delivering decentralized care, improves both ART uptake and sustained retention in low and middle-income settings. Common features are task shifting to lay caregivers who often provide other health-related support(29-31); 2) Peer interventions have been effective in an array of interventions (32, 33). Suggesting models of community-based peer-support may improve the effectiveness of HIV-SS to link young people to HIV care and prevention.

To achieve the proposed objectives in this study, respondent driven sampling will be used. Respondent-driven sampling (RDS) method is based on an incentive system (34, 35). It is a dyadic incentivized (monetary or non-monetary incentive) recruitment method that is best used to reach a hard-to-reach or hidden population. In RDS sampling, behavioural compliance can be driven by individual-sanction-based control or group-mediated social control. It could be individually motivated in a situation where for example a peer navigator targets a potential interviewee by promising a reward while respondents in a group driven situation may be rewarded for their participation as well as participation they invoke from a peer (34, 35). In this case to use the HIV self-screen to know their status and then be motivated to link to care that will keep them healthy (negative if still negative or treatment if already positive).

Like other chain-referral methods, an important assumption in RDS is that peers within the same population group are best in accessing and motivating a hard to reach population within the group (35). Given the importance of this trial, we hope that the rewards offered will foster a robust recruitment in which a few initial subjects (peer navigators) each will produce chain-referral systems that will yield a large number of motivated recruits (seeds) over the course of successive waves. Therefore, peer navigators will recruit initial seeds that will recruit subsequent seeds until the target communities are saturated or when a minimum time (6 months) has been reached.

Given the high HIV incidence rate and low uptake of HIV testing, care and prevention services amongst young people in our settings, this cluster randomized control trial (cRCT) seeks to assess the effectiveness and efficiency of two different models of community-based delivery of HIV-SS with standard of care (health care delivered point of care HIV testing) on linkage to HIV prevention and care amongst older adolescent girls and young women (AGYW).

Study Setting:

The proposed research will build on one of the largest population-based HIV incidence cohorts in the world and the longstanding research infrastructure - in the Africa Health Research Institute (AHRI) based in uMkhanyakude district, KZN (see figure 1): The study area is mostly rural, and poor compared with other parts of South Africa, with high levels of unemployment. The demographic surveillance area provides 16 years of household history, and over a million person-years of follow-up through annual individual-level surveys, which capture sexual behaviour and partnerships, reproductive histories and contraception use, access to HIV testing and care, access to HIV prevention services (including VMMC), as well as socio-demographic information. The data are linked to the annual HIV sero-surveillance and HIV viral load testing using dried blood spots in all consenting individuals aged over 15. AHRI has a memorandum of understanding with the national Department of Health that enables linkage of the population surveillance data at individual level to the HIV care and treatment programme electronic patient records management system (TIER.Net), using the South African Identity number. This allows the measurement of linkage to HIV care and use of contraceptive services. As part of the new Wellcome Trust award, since 2017 data collection teams are embedded in all of the primary health care clinics in the surveillance area. They capture data on all attendees and their reason for attendance; these data are linked back to the surveillance data and routine data from the Department of Health (PIPSA BE290/16) (36).

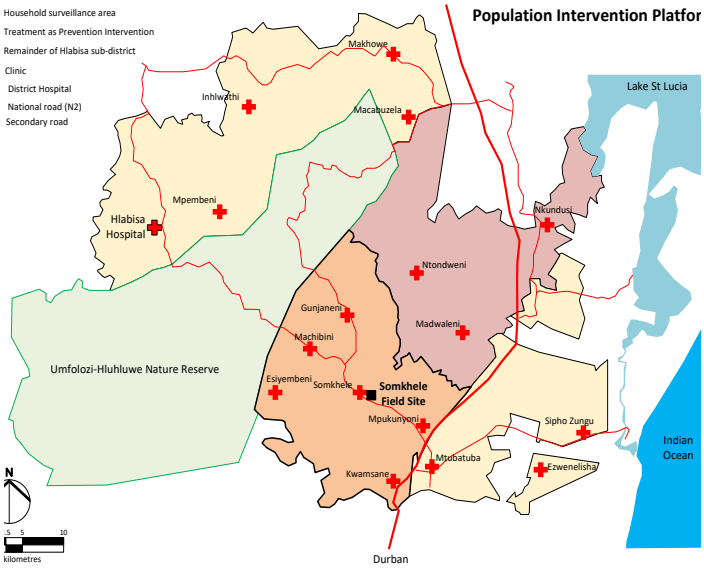


Figure 1. Map showing the location of AHRI's population-based HIV surveillance (N= 114,000 are as well as the location of the primary health care clinics (red crosses) dispensing ART. From 2017 HIV surveillance expanded to cover the TasP trial area.

Through separate EPSRC (Engineering and Physical Science Research Council) funding a digital application (EPIC HIV) to support testing and linkage to care is being developed which has informed this

study delivery model (mAfrica BE435/17). Since September 2017, a US National Institute of Health (NIH) R01 will support a peer led outreach team of navigators to support uptake and retention of adolescents and young adults in existing HIV prevention (Shahmanesh PI - DREAMS BFC339/16). This trial will be delivered by the peer navigators who support uptake and retention in HIV for adolescents and young adults in rural KwaZulu-Natal, including referral to mobile and fixed clinic delivery of HIV confirmatory testing, ART treatment and PrEP to young adults.

2 STUDY GOALS AND OBJECTIVES

This study seeks to identify the most efficient and effective way to use peer-led HIV testing, including HIV-SS to link older adolescent girls and young women into HIV prevention and care services.

Specifically, this study seeks to test the hypothesis that HIV-SS either delivered by peer navigators or through peer networks will be more effective and efficient than peer outreach work alone in linking older adolescent girls and young women and their male partners into HIV prevention and care services.

Objectives:

1. To increase the knowledge of HIV status among young women aged 18-24 years old and their male partners through distribution of HIV-SS through incentivized peer networks or direct distribution by peer navigators compared to peer navigators referring into HIV testing services.
2. To determine an increase in the rate of linkage among young women aged 18-24 to HIV prevention and treatment services facilitated by distribution of HIV-SS through incentivized peer networks or direct distribution by peer navigators compared to peer navigators referring into services.
3. To conduct a process evaluation of the acceptability, feasibility, and reach (out of school, recently migrant and living in remote areas) in linking 18-24-year-old women to HIV prevention and treatment services of HIV-SS distribution through incentivized peer networks, or direct distribution by peer navigators or peer navigators referring into services.
4. To measure the cost per 18-24-year-old linked to prevention and care through peer-led incentivized HIV-SS delivery system or direct distribution of HIV-SS by peer navigators, compared to peer navigator referring into services.

Primary Outcomes:

The difference between the rate of linkage within three months of 18-24 years old women to HIV confirmatory testing and pre-exposure prophylaxis (PrEP) eligibility screening if HIV-negative and antiretroviral treatment (ART) starting if HIV-positive. It will be between the two peer-delivery approaches to HIV-SS distribution (incentivized HIV-SS delivery through peer network and direct distribution of HIV-SS by peer navigators) compared to standard of care (peer navigator referral to HIV testing, treatment and prevention services). Rate is defined as the number of linkages per month of peer navigator outreach activity.

Secondary Outcomes:

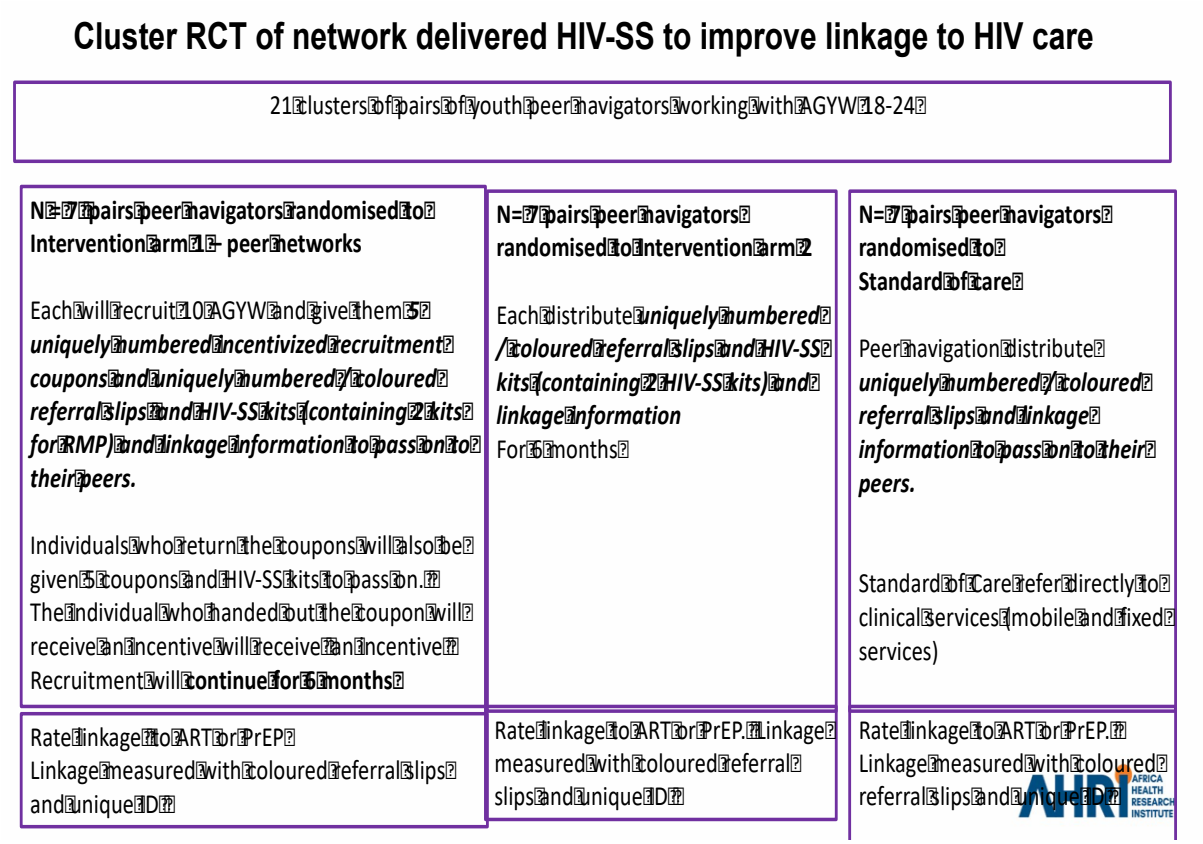
1. The number of linkages per 100 clinic referral slips distributed per arm;
2. The change in proportion of all residents (men and women) aged 18-24 years who are aware of HIV-SS and who have used HIV-SS over time using the existing surveillance and routinely collected data (PIPSA BE290/16 and DREAMS BFC339/16).
3. Comparison of the difference per study area in the proportion of 18-24 year olds who report knowledge of HIV status and uptake of ART, PrEP and voluntary medical male circumcision (VMMC) in the surveillance area (PIPSA BE290/16 and DREAMS BFC339/16).

4. Comparison of the pattern of recruitment per arm of study: the proportion of hard to reach adolescent girls and young women (aged 18-24 years) - defined as out of school, recently migrated and those who live in remote areas - linked to care in the three arms of study.
5. Comparison of costs in intervention and control arms. Cost per case linked to PrEP eligibility assessment (HIV-) and cost per case started on ART (HIV+). To establish costs, we will use both a bottom-up ingredient-based costing approach and a top-down costing approach using the study budgets and expenditure reports.

3 Method

3.1 Study Design

This is a two-phase cluster randomized control trial (cRCT) with 3 arms (2 intervention and 1 control arms). Through the cRCT, we will test whether two peer-delivery approaches to HIV-SS distribution (incentivized HIV-SS delivery through peer network or direct distribution of HIV-SS by peer navigators) will improve the uptake of HIV prevention (including Pre Exposure Prophylaxis if HIV negative and eligible) or HIV confirmatory test and antiretroviral start if HIV positive, in 18-24 years old females compared to standard of care (peer navigator referral to existing HIV testing, treatment and prevention services) in rural KwaZulu-Natal, South Africa.



3.2 Population and Sampling Strategy

3.2.1 Study population

The study population will include 21 pairs of area (Ward/iZigodi) based peer navigators working with over 2000 young people particularly young women aged 18-24 years. More than 2000 young people (males and females) will be reached during the trial in the 21 wards representing the study area.

3.2.2 Study Inclusion and Exclusion Criteria

Table 1: Inclusion and exclusion criteria for receiving the intervention, i.e. the recruitment by Peer Navigators and/or Seeds to receive HIV-SS or clinical referral vouchers

Inclusion Criteria	Exclusion Criteria
Participant must not be older than 24 years and younger than 18 years	Participants under 18 years or older than 24 years
Participant must agree to participate	Participant unwilling to participate
Both males and females can be included	None
Must not be known to be on ART – based on self-report	If on ART

Table 2: Inclusion and exclusion criteria for ascertaining the outcome i.e. inclusion in the research

Inclusion Criteria	Exclusion Criteria
Participant must not be older than 24 years and younger than 18 years	Participants under 18 years or older than 24 years
Provide written informed consent	Participants not willing to consent or unable to provide informed consent
Females	Males
Must not be known to be currently on ART	Currently on ART

3.2.3 Randomization

The unit of randomisation will be pairs of peer navigators: 21 pairs of peer navigators will be randomised to 3 arms: two intervention arms, and standard of care (7 pairs per arm). Pairs of peer navigators will cover geographic areas that are purposively selected from the demographic surveillance area to reflect a range both rural and peri-urban and urban settings and will be located a sufficient distance (based on the cost and ease of transportation) apart to minimise the risk of contamination/spill-over between the clusters. This is a demographic surveillance site, with tri-annual household surveys and so we have detailed understanding of the sociodemographic composition of the areas, as well as the size and density of the young adult population. We will use restricted randomisation to ensure that the arms are

reasonably balanced with respect to key characteristics (e.g. adolescent and young adult population size and density, % of population living <5km from clinic, and the sociodemographic characteristics of the area)

3.2.4 Sample size calculations

Based on 2017 data, we estimate ~500 age eligible 18-24 years olds will be enrolled per peer navigator team catchment area, of whom we anticipate at least 200, 18-24-year-old females will be handed a coupon (so cluster size at least 200). We estimate this based on 2 peer navigators working approximately 1000 hours over the study period per cluster. We estimate that they will reach 2 young adults per each 4 hour of work and at least one will accept a coupon. We calculated the sample size calculation using the primary outcome, the rate of linkage after 3 months among women ages 18-24 years. Using our existing data on uptake of HIV testing in the DREAMS interventions as well as our data on uptake of testing and linkage to HIV care in the demographic surveillance rounds of, we estimate that 1 woman will link per 7 months of peer educators outreach work time in the standard of care. With 7 peer educator pairs (or clusters) per arm and a cluster coefficient of variation (k) of 0.25, we have 80% power to detect a 100% increase in rate from 1 woman to 2 women per 7 months of follow-up, and 90% power to detect a 150% increase from 1 woman to 2.5 women per 7 months of follow-up. We have chosen policy and clinically relevant increases in linkage to care.

Assuming additional clustering of the outcome within peer educators and increasing the coefficient of variation (k) to 0.35, we have 80% power to detect a 150% increase in rate from 1 woman to 2.5 women per 7 months of follow-up.

All sample size calculations assume two-tailed statistical tests with alpha=0.05.

3.3 Study Phases and Processes

Standard of care:

All three arms will receive the standard of care. Peer navigator pairs in all arms are from the community and recruited from recently matriculated students and university graduates, looking for a first job (unemployment levels in both these groups is extremely high). The peer navigators in all three arms of this study are supported through an exiting US National Institute of Health (NIH) R01 grant to improve uptake and retention of adolescents and young adults in existing HIV prevention (Shahmanesh PI - DREAMS BFC339/16). The Peer navigator intervention has been developed in close collaboration with the DoH and mirrors the South African cadre of community caregivers. We therefore anticipate that any effective intervention can be easily adapted to the current SA plans to deliver care in the

community through community care givers.

Peer navigators are a cadre of recently matriculated youth aged 18-30 who have been recruited in collaboration with local communities (traditional leaders and municipal authorities). We identified over 100 men and women aged 18-30 who underwent 8 weeks of training in HIV, sexual and reproductive health, HIV counselling and testing, HIV self-testing, youth development, research methods, confidentiality, good clinical practice, and child protection. During the training they have multiple assessments to identify a smaller group of ~50 that were recruited to the cadre of peer navigators. The cadre of peer navigators are area based, work in male- female pairs, work part-time and receive enumeration in keeping with SA guidelines for enumerating community care givers. The areas are based on sub-wards that have ~ 500 older adolescents and young adults within walking or affordable transportation reach. The peer navigators have been introduced to and work closely with the primary health care workers and community caregivers, school health team, department of social welfare community social worker, and local champions and leaders. Following the formal training the peer navigators are provided on-going training and supervision from a team of professional nurses and counsellors, through bi weekly debriefing meetings and weekly field visits. They support the following activities in the geographical area that they cover:

- Support the uptake of multi-level HIV prevention interventions being provided through the department of health, social welfare and basic education as well as She Conquers and the PEPFAR funded DREAMS programme: Parenting support, gender-based violence interventions, safe spaces, mentoring, life-skills, and support around knowing and getting social entitlements and financial literacy.
- Support and encourage uptake of HIV testing through Primary Health Clinics and community-based organization providing HIV testing through DREAMS; condom promotions and linkage and retention in HIV treatment and contraception.

We anticipate the recruitment of young women will take place in the community settings, near schools, where young women gather and from their homes.

PrEP clinics: confirmatory HIV testing, and linkage to PrEP and ART for AGYW aged 18-24 years will be provided through mobile clinics that will be attending areas accessible to the 21 peer navigator catchment areas once a week as well as a fixed clinic in the urban area Mtubatuba. All adolescent girls and boys and young men and women aged less than 30 will be eligible to receive the full array of clinical services provided in these three PrEP clinics. They will also be able to attend any of the 11 Primary Health Care Clinic in the study area where, as standard of care agreed with the DoH, they will be screened by an AHRI clinical research assistant and referred to an AHRI nurse for HIV POCT. The AHRI nurse will start ART if they test positive or refer them for PrEP counselling to the PrEP service if negative.

HIV incidence in women aged 18-24 in this setting is above 5% per annum and so many sexually active

young women are eligible for PrEP. In the PrEP clinics consenting individuals who test HIV-negative will undergo eligibility screening by the professional nurses for PrEP and other HIV prevention interventions. If eligible they will receive counseling around the benefits of PrEP and information about the study. If they agree they will undergo clinical **screening** for PrEP. Screening includes Point of Care (POC) tests for creatinine to assess renal function and Hepatitis B, with vaccination offered to those who are negative, and sexual behavior questionnaire to assess eligibility. **Enrollment**: HIV-negative persons who meet the eligibility criteria and agree to start PrEP will be offered PrEP as per South African guidelines. HIV-positive individuals will be offered and started on ART as per DoH guidelines.

In order to ensure that there is clear differentiation between the intervention teams and the research teams: 1. The intervention teams will be managed separately from the research teams. The intervention team will be managed by a senior professional nurse who will manage a team of ~50 area based peer navigators, and a team of three professional nurses and a pharmacist that will manage the PrEP clinics. She/he in conjunction with the AHRI clinical department, will be responsible for regular meetings, onging supervision, oversight of clinical processs and good clinical practice. 2. The intervention will be embedded within the wider health and social welfare system and the nurse co-ordinator will co-ordinate reporting to the DoH and liaise with the wider AHRI clinical department. 3. The intervention team will wear clothing that will differentiate them from the research staff. 4. All participant information will clarify that receciving the HIV self-screen, ART or PrEP are NOT contigent on consenting to the research. Similarly withdrawing from the research will not effect access to the HIV self-screening or PrEP.

Phase 1 (September– December 2018): To pilot the use of social networks of adolescents and young adults to deliver HIV self-test. It involves the following:

- Train n=42 peer navigators to deliver/promote HIV-SS to individuals (male and female) aged 18-24 years that they are reaching through the area-based peer outreach activities described above.
- Adapt the manuals and material provided with OraQuick to support network delivery of HIV-SS in this rural setting.
- Develop materials to support linkage to PrEP and ART
- Pilot the study tools, SOPs and CRFs
    - Topic guides for in-depth interviews (IDIs) and key informant interviews (KII)
    - eligibility screening and baseline questionnaire for each arm (date of recruitment and id of peer navigator who recruited them, a unique identifier generated, name, age, ID (DSID or SA national number), telephone or WhatsApp contact, network size, barcode of kit provided for themselves and the kits provided for network).
    - Referral slip – color coordinated by arm with Hotline Freephone number, mobile clinic and fixed clinic details – bypass queues
    - Questions for referral clinic to establish linkage by arm: referral slip, color of referral slip, HIV self-screen or not, how received HIV self-screen, ID number, name, DOB. These will be added to all clinic-link software in the DSS.

- Pilot and test understandability and usability of the material to support individuals (male and female) aged 18-24 years to receive HIV-SS and PrEP information from a peer with cognitive testing (n=10).
- Pilot the study tools with cognitive testing (n=10)
- Pilot the process of distributing Respondent Driven Sampling vouchers through social networks with n=10 pilot seeds following one round of distribution. During each dummy we will measure the number of peers that the seeds recruit, we will iron out any practical issues with the materials and we will conduct interviews with seeds and their recruits to identify facilitators, barriers and practical challenges to 1) seeds accepting the RDS vouchers and OraQuick; 2) Distributing OraQuick and the information; 3) support needed to use the test; 4) support needed to link to UTT and PrEP; 4) further distribution along the networks 5) means of returning the incentives.

Phase 2 (January 2019 – October 2019): To conduct a cluster randomized control trial of the impact of HIV-SS distributed through a network of peers, on linkage to ART based HIV care and prevention services among adolescents and young adults aged 18-24 years. We will conduct an interim analysis at the end of April 2019.

Intervention arm 1 – Incentivised network delivery of HIV-SS: n=7 pairs of peer navigators will use a respondent-driven sampling (RDS) approach to distribute HIV-ST kits and coupons. Each pair of peer navigators will recruit n=10, 18-24 years old female seeds. Each seed will fill a brief *service recipient questionnaire* – self-filled on a tablet. Following which they will receive a session from the peer-navigator on the HIV prevention services available, the importance of sexual health, the benefits of HIV testing PrEP and ART, and a demonstration of HIV self-screening. Seeds will be asked to recruit AGYW aged 18-24 years preferentially but not exclusively and to avoid distribution of HIV-SS to those under the age of 18. All participants will be asked to complete a brief check of their understanding of the information provided to them, particularly the unreliability of HIV-SS on ART, the window period, the recommended support to those under 18 using HIV-SS, and the need for confirmatory testing.

They will be then given up to 5 uniquely numbered incentivized recruitment coupons with five HIV-Self screen (HIV-SS) kits(packs) to pass on to their peers. Their own pack will contain:

- A participant information sheet, descrbing their arm of the study and the process of recruitment to the study, which is separate to linkage to care when they attend the clinic.
- Color coordinated by arm HIV SS kit
- Two HIV-SS tests with barcode and a unique identifier (for themselves and a sex partner) with information on how to use it and a free hotline for support
- Referral slip with barcode and the same unique identifier – color coordinated by arm with Hotline freephone number, mobile clinic and fixed clinic details – bypass queues
- Written Information on HIV self-screening and PrEP and importance of linkage

The five packs will each contain:

- Color coordinated by arm HIV-SS kit
- 5 uniquely numbered incentivized recruitment coupons with barcoded unique identifier
- Two HIV-SS tests with barcode the same unique identifier (for themselves and a sex partner) with information on how to use it and a free hotline for support

- Referral slip with barcode and the same unique identifier – color coordinated by arm with Hotline Freephone number, mobile clinic and fixed clinic details – bypass queues
- Written Information on HIV self-screening and PrEP and importance of linkage

Individual who return the coupons will undergo the same procedure as the seeds above. They will also be given up to 5 uniquely numbered incentivized recruitment coupons and HIV-SS kits to pass on. When coupons are returned, the original individual who handed out the coupon will receive a sum of 20 rand ($1.5) in airtime per friend or peer who returns the coupon. This sum is as a reimbursement for the time that they have spent in explaining and demonstrating the use of an HIV-SS and is not seen to be an undue incentive to coerce members of their social network to participate. The process will continue for six months. We will not restrict the gender of those recruited through the networks, however the primary outcome will be measured in the AGYW (aged 18-24) only.

Intervention Arm 2: Peer Navigator distributed HIV-SS: n=7 pairs of peer navigators will directly distribute HIV-SS kits to females aged 18-24 years over a period of six months. Each person recruited will fill a brief *service recipient questionnaire* – self-filled on a tablet. Following which they will receive a session from the peer-navigator on the HIV prevention services available, the importance of sexual health, the benefits of HIV testing PrEP and ART, and a demonstration of HIV self-screening. All participants will be asked to complete a brief check of their understanding of the information provided to them, particularly the unreliability of HIV-SS on ART, the window period, the recommended support to those under 18 using HIV-SS, and the need for confirmatory testing.

They will be then given up a HIV-SS to use. Each pack will contain

- A participant information sheet, descrbing their arm of the study and the process of recruitment to the study as separate from linkage to care when they attend the clinic.
- Color coordinated by arm HIV-SS kit
- Two HIV-SS tests with barcode and the same unique identifier (for themselves and a sex partner) with information on how to use it and a free hotline for support
- Referral slip with barcode and the same unique identifier– color coordinated by arm with Hotline Freephone number, mobile clinic and fixed clinic details – bypass queues
- Written Information on HIV self-screening and PrEP and importance of linkage

The process will continue for six months.

Arm 3: Control: n=7 teams of peer navigators will conduct their usual mobilization activities (see standard of care activities above) and encourage females aged 18-24 years to test for HIV at clinics, and link to services/care. Each female aged 18-24 approached will fill a brief service *recipient questionnaire*

– self-filled on a tablet. Following which they will receive a session from the peer-navigator on the HIV prevention services available, the importance of sexual health, the benefits of HIV testing PrEP and ART, and a demonstration of HIV self-screening. They will then be given:

- A participant information sheet, descrbing their arm of the study and the process of recruitment to the study as separate from linkage to care when they attend the clinic.
- Referral slip with barcode and unique identifier– color coordinated by arm with Hotline Freephone number, mobile clinic and fixed clinic details – bypass queues
- Written Information on HIV self-screening and PrEP and importance of linkage

The process will continue for six months.

Enrolment and procedures for the participants in the clinics:

Intervention Recruitment: Peer navigators in all three arms will be delivering services to the young people as described above and encouraging linkage to care. Once they distribute the color coordinated coupons and information on linkage, the barcode with the unique identifier on the referral slip and HIV SS (they are the same) will be scanned in and participants will be provided with information about the study and fill a brief *service recipient questionnaire* to be completed within REDCAP on a tablet. This will include information relevant to service delivery only, the date of recruitment, and the id of peer navigator who recruited them their age and area of residence. Name, ID (DSID or SA national number), and telephone or WhatsApp contact are optional. Those who are recruited through RDS will also be asked to provide data on network size, barcode of the RDS coupons and the additional HIV-SS kits (they are the same) will be scanned in. We anticipate that peer navigators will be spending ~ 30 minutes with each willing participant to explain the benefits of linking to care. Those who will be explaining HIV-SS may need 15-20 minutes more time. However, some young people may need more time or more visits. This data will be captured in REDCap for the purpose of process evaluation and costing. This data will only be used in an aggregate way to understand the process and cost of ther service delivery. Individualise data from the questionaires will only be used in those participants that consent to their clinical data being linked and used for research purposes. If a participant withdraws their consent at any time their data will be deleted from the research data set.

Study enrolment: Peer navigators in all three arms will be encouraging attendance at the clinic for linkage to care participants. Participants will be offered study enrollment at the point that they enter any service for the purpose of confirmatory HIV test, and/or eligibility screening for PrEP or HIV treatment. This will be conducted by the trained study research assistants in mobile clinics and fixed clinic. All young women aged 18-24 coming to one of the the 11 primary health care clinics (PHC) in the surveillance sites, will be directed by the AHRI data collection clerks to the AHRI research nurses. In both setting the research assistants or the research nurses will explain the study, and will screen the young person for

eligibility using a brief eligibility screening questionnaire on REDCAP on a tablet. This will include questions to ascertain eligibility as well as arm of the study. If available, the barcode with the unique identifier on the referral slip or the participant's demographic data will be used using the ClinicLink system to identify potentially eligible attendees (women aged 18-24 who have been linked to clinic through the peer navigators). **Enrolment**: Eligible participants who agree will be directed to the study research assistant or nurse in a private room who will provide information about the study and go through the process of informed consent. Participants will provide written informed consent for enrollment into the study and specifically to use the information on their linkage to care as an outcome and to link their baseline questiona.

Irrespective of whether or not they consent to the study individuals who test HIV-negative will receive counseling around the benefits of PrEP and HIV-positive individuals will receive counselling around the benefits of immediate starting of ART. If they agree they will undergo clinical **screening** for PrEP and ART. Screening includes Point of Care (POC) tests for creatinine to assess renal function and Hepatitis B, with vaccination offered to those who are negative, and sexual behavior questionnaire to assess eligibility. ART can be started by the professional nurses in any of the clinics. Patients who are eligible for PrEP will be started in the three PrEP providing clinics (the mobile vans or the fixed urban adolescent and youth friendly clinic). Persons who are not eligible for the PrEP will receive counseling and, as indicated, a clinic referral with the screening results. A professional nurse will initiate PrEP or ART usually on the same day or within two weeks of the screening visit.

The professional nurse will provide PrEP counselling that includes (1) ***sexual health promotion,*** with an emphasis on tackling the multiple health-related behaviors that will affect fertility and sexual pleasure (STIs, mental health, alcohol, diet and exercise); (2**)** assessment of fertility desire and contraception counselling; (3) choice of contraception and condoms; (4) HIV negative men are also counselled around the benefits of voluntary medical male circumcision (VMMC) and referred accordingly.

The counsellors will provide counseling on adherence and develop an individualized adherence plan with the offer of face to face or virtual (WhatsApp/ text based) adherence support. If the participant agrees to immediate PrEP initiation, s/he will be issued with a month's supply of generic tenofovir disoproxil fumerate and emtricitabine (TDF/FTC). Baseline and follow-up bloods will be taken and processed as per national guidelines; The professional nurse will register the participant at the clinic (or update the record if the participant is already registered) so that the participant's records are available should the participant seek care there. Participants will receive a phone call seven days after initiating PrEP to complete a standard symptom screen for adverse effects and be referred to clinic for care if necessary. Participants will have a clinic appointment scheduled one month, after PrEP initiation, as per national guidelines; appointments for refills and monitoring will be three monthly thereafter through either the mobile clinic, or other community-based refill points. Neutral text message reminders will be provided for participants who have access to private messaging and phone calls. Participants will be able to reschedule their appointments by text message or WhatsApp. Contact information will be provided for

the clinic whom participants can contact at any time.

Referral to the clinic for symptoms and clinical events: Participants will be encouraged to visit the clinic for medical concerns outside of the study. During participant resupply and monitoring visits, they will complete a standardized symptom screening questionnaire for adverse effects of PrEP as per South African clinical guidelines. Further, all participants will receive regular creatinine tests to monitor their renal function. Participants who have severe (grade 3/4) adverse effects, according to the DAIDS guidelines (https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-%28daids%29-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2) and serious adverse effects, will be referred to the clinic for medical evaluation. All participants who experience adverse events will receive follow-up until the adverse event is resolved. The peer navigator STAR Clinical Monitor, based at AHRI, will review all severe (grade 3/4) and serious adverse events to ensure follow-up and reporting. This will include any adverse events recongnised through the community based process evaluation or the community engagement unit.

STAR has formed a Technical Advisory Group (TAG) to monitor and supervise progress of data collection, provide independent review of data collected during all cluster-randomized trials conducted under the STAR project, and assist investigators in disseminating results.

Informed consent for participation in the study will be collected at any point that data will be used for research purposes. For example. at the point that they link to HIV confirmatory testing, treatment and prevention services and thus provide data for the primary outcome. Peer navigators in all arms will be delivering a service (HIV-SS in arms 1 and 2 and referral to services in arms 3) and therefore will be providing information about the service and the study but will not be collecting informed consent for the purpose of receiving the services.

3.4 Process Evaluation

We will conduct process evaluation to assess the acceptability and feasibility of HIV self-screening, and whether it did or did not facilitate linkage to care. We will also explore potential unintended consequences and ethical issues that arise during peer referral and HIV-SS and ascertain what works for whom and when to be able to modify the intervention to improve equitable reach and coverage. We will explore the reach of network recruitment compared to peer outreach work, in terms of reaching more vulnerable groups (out of school, recently migrated, and those who live more remotely). Our process evaluation will include a mixed method evaluation to investigate implementation, mechanisms of impact and contextual factors, informed by the medical research council (MRC UK) guide and wider implementation science literature with a focus on fidelity, reach and acceptability.

Fidelity - Understanding what is implemented and how this is achieved is integral to explaining how an intervention works. We will use the methods listed below to capture what is delivered in practice in order

to avoid dismissal of sound intervention theories due to a failure to implement them effectively.

Reach and acceptability - Reach is the extent to which the target audience come into contact with the intervention. The process evaluation will include quantitative assessment of reach, in terms of the proportions of the target population who are made aware of the intervention and who actually have contact with it from our population surveillance data as well as the differences in the patterns of uptake per arms with a focus on the hard to reach groups (out of school, recently migrated and living in remote areas).

Acceptability refers to how intervention participants, providers or other stakeholders received or engaged with the intervention. Acceptability, however, is a dynamic characteristic and will be continually assessed, both through the surveys of participants and the sub-set of in-depth qualitative interviews with participants and providers.

We will collect routine programme data, n=20 peer navigator field notes and data on awareness and uptake of HIV-SS and HIV prevention interventions in 18-24-year olds participating in the annual demographic surveillance. Peer navigators will be trained to keep very brief notes of their daily activities such as challenges experienced while distributing the HIV-SS kit. This will be used to support the peer navigators in reflecting on their work during bi weekly debriefing sessions and ongoing training and supervision. We have extensive experience of using this technique in our participatory ethnographic research and we will ensure that the peer navigators are trained in how to keep notes and to ensure that personal and identifying information, including the use of dates, identifiable meeting areas or memorable anecdotes, are not included. All data including diary entries will be entered into password secure tablets and as soon as there is connectivity off the tablet and onto a secure server. These field observations will be analysed alongside the other qualitative data to understand the process of the intervention.

We will conduct IDIs with n=20 peer navigators, clinic nurses (6) and 18-24-year-old women living in the community (n=10 per intervention arm) to understand perceptions and experiences of the different peer delivery methods for HIV-SS, including rationales for accepting or refusing the offer of HIV-SS and linkage to care and prevention, and the acceptability and feasibility of peer delivery of HIV-SS, and any unintended consequences. The community participants will be purposively young women aged 18-24, living in any of the areas involved in the study. Similar to other community studies that we have conducted in the area, social science research assistants will approach women both in community and in clinical settings, they will explain the study and if the person accepts will go through the process of informed consent. The sample will be purposive to reflect the different arms of the study, different ages, and rural, semi-urban and urban settings.

Informed consent will also be collected for all participants that provide data for the process evaluation. Interviews will be based on a topic guide and it is estimated that they will take up to an hour. They will be recorded and transcribed verbatim, with the permission of participants. A thematic analysis of all interview data will be conducted using framework approach.

3.5 Cost-Effectiveness Evaluation

We will measure the costs in both interventions and control arm, to compare the two arms in their cost-effectiveness in achieving endpoints, i.e., cost per case linked to PrEP (HIV-) and cost per case linked to ART (HIV+). To establish costs, we will use both a bottom-up ingredient-based costing approach and a top-down costing approach using the study budgets and expenditure reports.

3.6 Data Collection Methods

This study employs the following data collection methods:

(1) Participant Survey and Clinic Linkage

A short survey (described above under enrolment and procedures) will be administered to consenting young women participating in the study. The questionnaire will be used to collect data on participant's demographic info and voucher identification. The data will be captured on REDCAP on a tablet. The survey will take approximately 5 minutes to complete and will be administered in both English and isiZulu.

The primary outcome of linkage will be measured through identifying the consenting eligible young women who link to care through the 11 primary health care clinics and the mobile clinics. The ClinLink software which is used in all the clinics in the demographic survey area and has been effective to data in linking individuals in the surveillance area when they attend clinic. We will use an algorithm to identify which arm the individual came from, including the bar code on the coupon they bring, the colour of the coupon or HIV-SS pack, their area of residence, and the identity of the peer-navigator that recruited them.

(2) Programmatic Data

In addition to the questionnaire, we will collect the programme data records from the peer navigators daily reporting of their outreach activities. This includes the number of AGYW they have counselled and the numbers they have referred to services and the brief service recipient data they have collected on those who have received referral coupons or HIV-SS. We will use the programme data in an aggregate way (disaggregated only by gender) to understand the reach and coverage of the programme and compare that with those who link to care.

We will also use data on changes in self-reported HIV-SS and linkage services collected through the AHRI population intervention surveillance platform and nested cohorts of adolescent girls and young women in 2018 and 2019 (BFC339/16 and BE290/16).

(3) Participant in-depth interviews (IDI)

IDIs will be conducted peer navigators (n=20), AHRI nurses (n=6) stationed in clinics in the participating communities and a purposive sample of young women aged 18-24 in participating communities and clinics (n= 10 per arm)
The interviews will be conducted by ARHI trained fieldworkers including a senior social scientist in English and isiZulu and will take approximately 60 minutes in length depending on the participant's responses, and this will enable the researchers to understand, contextualize and explore some of the issues around the trial. The small number of IDI participants in qualitative study is allowed since deeper meanings of concepts and thematic areas are explored. To limit disturbances and ensure privacy, the IDI will be conducted in a private space suitable for the participant, and audio recorded with interviewees' consents. Prior to the interview, participants will be encouraged to use pseudo names instead of their real names to ensure anonymity.

4 Data Collection Plan

4.1 Data Collection Team

This study will be managed by the project research team at ARHI. Depending on need, the data collection team will consist of some ARHI trained social science research assistants and the Senior Social Scientist. Data collectors will be selected based on their experience with both quantitative and qualitative data methods.

4.2 Data Collection Training Requirements

The data collectors will undergo a 2-day training which will include the following content:

1. ***Protocol training***: this entails the study objectives, the administration of the short survey and IDI guide as well as participant confidentiality and voluntary participation.

2. ***Redcap training:*** This will cover familiarization with survey questions and how it can be captured successfully on Redcap. This will also involve data quality, fidelity and analysis exercise.

3. ***IDI Data Collection refresher training:*** this covers IDI guide content, including training on probing and interview techniques in order to collect quality data. The IDI guide will be available in English and isiZulu, and the training of interviewers will entail a question-by-question discussion exercise as well as relevant terminologies to be used. This process will be led by the Senior Social Scientist.

4.3 Approvals

Institutional Ethical Review Board

Ethical approval will be sort from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC), World Health Organization (WHO) and London School of Hygiene and Tropical Medicine (LSHTM).

See section 6 for Ethics and Informed consent

5 Data Management

5.1 Electronic Capture of Data and Storage of Electronic Data

Data collectors will administer the short survey using tablets thereby ensuring capturing of real time anonymized data. The questionnaire will be loaded onto REDCap and will be accessed for data collection as an application on the tablet. The data management system for these will be based on REDCap (research electronic data capture) developed at Vanderbilt University. The REDCap database resides within a single MySQL database server within a secure server cluster at the Africa Centre. Laboratory data collected for the trial will be output electronically directly from the analyzer and imported into the database. Data extractions will be converted to Stata for analysis. Data can be extracted in a variety of formats for analysis. Qualitative data will be stored in the form of Word files or in Excel both of which can be uploaded into Nvivo qualitative data management and analysis programme; the use of MS Word will ensure that data can in future be shared for use in different analysis programmes. These files will be kept on a secure access-controlled folder on a file server at AHRI.

5.2 Hardcopy Data and Storage

All study-specific data will be stored on a server at AHRI, access to which is strictly controlled. Users are given individually-tailored access only. AHRI has a comprehensive set of SOPs covering the use, validation and security of their computer systems. To avoid loss of data during power fluctuations, servers are installed with stable UPS batteries, with a standby generator in case of power cuts. The server is backed up daily with twice weekly off-site backups. While the study is in progress, study-related forms will be maintained in locked cabinets; access to these cabinets is limited, at study conclusion these documents will be digitized, and the original paper documents destroyed. Digitized document images are indexed and stored indefinitely on the central server. Identifying information will be held by the field team and not kept with the questionnaires. Study-specific electronic laboratory results will be transferred directly from the LIMS. These data will be stored on the AHRI server after transfer. Qualitative data will be managed, stored and archived in consultation with the data manager

5.3 Audio Data and Storage

The IDI will be tape recorded after prior consent has been obtained from the participant. The audio files will be stored on password protected ARHI PCs and only authorized personnel will have access to them. It is important to mention that audio files will be used for the purpose of this study only. Once the audio files have been transcribed and translated and quality controlled they will be destroyed.

5.4 Data for sharing

Anonymized quantitative data-sets collected in the study will be suitable for sharing. Sharing qualitative transcripts is more challenging. However, we are committed to open access data and so we have developed systems described below to support researchers that may want to use the qualitative data to answer research questions.

Discovery by potential users of the research data: The results of the study will be published in a peer-reviewed journal. Potential users of the research data will be able to contact the investigators for further information. Furthermore, in accordance with the AHRI Data Sharing Policy, the data will be registered with the AHRI Data Repository. Details of the project and data collected will be available through a URI that will be cited in published papers.

Governance of access: The data custodian has the administrative control over granting access to the data to researchers. Anonymized electronic quantitative datasets will be archived and made available to interested external researchers under a data-sharing agreement, after a period of use by the study team. Interested researchers will be required to submit a proposal to use any data for independent analyses. Applicants will be asked to state their analysis objectives, demonstrate they have the capacity to conduct the intended investigations, and to show they understand the local study context to be able to interpret the results appropriately. Qualitative data is more challenging to anonymize. Investigators who are interested in using existing data to answer research questions will be asked to submit letters of intent, with an AHRI named Faculty member as a collaborator. If approved the study would have to undergo relevant IRB and ethical review processes. If analysis is to be undertaken, qualitative data will be stripped of any information that can identify participant before sharing. All data sharing, even those without identifiers, will be through a secure and password-controlled data sharing site, with access strictly limited to transcripts that are relevant to the analysis planned. Requests for data sharing are reviewed by the data custodian and a Data Sharing committee at AHRI. All AHRI staff are bound by the AHRI Data Access Policy, which prohibits any sharing of data with third parties, unless a formal Data Use Agreement has been signed with the third party. For all analyses, AHRI researchers sign a specific Data Use Agreement that defines the analyses to be undertaken.

The study team's exclusive use of the data: The study team will have exclusive use of the data for 2 years after the study and/or once the primary analysis of the study has been published, whichever comes first. Data may be made available sooner at the discretion of the investigators, where this does not conflict with the publication plans for the study. After the period of exclusive use, data will be made available to potential new users on request.

Restrictions or delays to sharing, with planned actions to limit such restrictions: Data sharing will follow the procedures outlined above. All data available for sharing will be anonymized. Consent forms will include a statement to inform study participants that their data may be shared with other users for secondary analyses, with the goal of advancing knowledge

Regulation of responsibilities of users: Users will be asked to abide by the AHRI Data Access and Sharing Policy.

6 Data Analysis

6.1 Participant Survey/Programmatic Record

The data from the client survey captured on REDCap dashboard will be exported into STATA, cleaned and analyzed. Descriptive analysis will be performed. Identified variables captured via programmatic monitoring tool will also be exported from the PIPSA platform and analyzed using STATA to compare data and linkage to care.

We will use standard methods for the analysis of cluster randomized trials with small numbers of clusters (CITE Hayes and Moulton), and reporting will confirm to CONSORT guidance for cluster randomized trials (CITE Consort). Cluster-level summary rates will be calculated and used to estimate the unadjusted rate ratio. T-tests will be used to test the difference between the SOC and each adjustment arm.

Rate ratios adjusting for substantial imbalances in population across arms will also be calculated using a two-stage process. Substantial differences will be identified by comparing frequencies or means of variables known to be associated with the primary outcome. These will be assessed by investigators without the use of statistical tests. A detailed statistical analysis plan will be completed prior to the end of data collection.

6.2 In-depth Interview

Data from the IDIs will be analyzed using NVIVO software. The software will be used for categorization and coding of identified themes from the interview transcripts. Identified themes (including participants' quotes) and interview transcripts will be reviewed and compared by the research team for inconsistencies and adequate representation of participants' comments. Emerging themes that address the key focus of the study will be examined and analyzed following an interpretivist approach (37).

7 Study Team

This study will be conducted and managed by the following research team:

Research Team Members

Dr Maryam Shahmanesh	Principal Investigator	Africa Health Research Institute
Prof Janet Seeley	Co-Investigator	Africa Health Research Institute
Prof Kathy Baisley	Co-Investigator	Africa Health Research Institute
Prof Deenan Pillay	Co-Investigator	Africa Health Research Institute
Dr Olivier Koole	Co-Investigator	Africa Health Research Institute
Dr Oluwafemi Adeagbo	Senior Social Scientist	Africa Health Research Institute
Mrs Carina Herbst	Study Coordinator	Africa Health Research Institute

Study progress and updates will be shared on a regular basis with consortium partners and relevant stakeholders.

8 Ethical Considerations

Reiterated, all staff (including peer navigators) will be provided with training on research ethics such as confidentiality, voluntary participation and good clinical practices. We will ensure anonymity and confidentiality at all levels of the research process, and none of our reports, presentations or articles will contain study participants identifying information. Pseudo names will be used when reporting the data particularly qualitative data. Each participant will be assigned a unique non-identifying participant identification number. Prior to their involvement in the study, participants will be provided with adequate information about the study and they will be allowed to ask questions for clarifications. Voluntary informed consent will be ensured once participants have the full understanding of the study procedures and a copy of the signed consent form will be given to them. Also, participants will be informed about the importance of the confirmatory diagnostic testing. The study will conform to the ethical guidelines and standards of ARHI, UKZN, LSHTM and WHO.

CONFIDENTIALITY

All staff (including peer navigators) will be provided with training on research ethics such as confidentiality, voluntary participation and good clinical practices. Each participant will be assigned a unique identifier to be recorded on all questionnaires and samples. Study-specific data will be captured electronically using tablets. Study participants will not have their names used during any stage of data collection except in consent forms, which will be electronic and kept securely in password controlled, encrypted and secure data havens. The data management system for these will be based on REDCap (research electronic data capture) developed at Vanderbilt University. The REDCap database resides within a single MySQL database server within a secure server cluster at the Africa Centre. Laboratory data collected for the trial will be output electronically directly from the analyzer and imported into the database. Data extractions will be converted to Stata for analysis. Data for individuals surveyed in health facilities are similarly captured on REDCap using tablets and stored. Data can be extracted in a variety of formats for analysis. Qualitative data will be stored in the form of Word files or in Excel both of which can be uploaded into Nvivo qualitative data management and analysis programme; the use of MS Word will ensure that data can in future be shared for use in different analysis programmes. These files will be kept on a secure access-controlled folder on a file server at AHRI. All data will be anonymized at the time of transcription with names of respondents replaced by a unique anonymized participant identifier. Any names of other persons mentioned during interviews/discussions will be recorded in the text with a single initial. Names of areas will be replaced with the general location (district or ward). We will ensure confidentiality at all levels of the research process, and none of our reports, presentations or articles will contain study participants identifying information. Pseudo names will be used when reporting the data particularly qualitative data.

INFORMED CONSENT

Prior to their involvement in the study, participants will be provided with adequate information about the study and they will be allowed to ask questions for clarifications. Voluntary informed consent will be ensured once participants have the full understanding of the study procedures and a copy of the signed consent form will be given to them. Also, participants will be informed about the importance of the confirmatory diagnostic testing. The study will conform to the ethical guidelines and standards of ARHI, UKZN, LSHTM and WHO.

Informed consent for participation in the study will be collected at the point that data will be used for research purposes, i.e. at the point that they link to HIV treatment and prevention services and thus provide data for the primary outcome. Informed consent will also be collected for all participants that provide data for the process evaluation (key informant semi-structured interviews with peer navigators, nurses and community members) and/or through our routine surveillance. Peer navigators in all arms will be delivering a service (HIV-SS in arms 1 and 2 and referral to services in arms 3) and therefore will be providing information about the service and the study but will not be collecting informed consent for receipt of services.

If written consent is required, the investigator will first provide the potential participant with an explanation of the study as well as an information sheet with study details. The investigator will also explain that any individual-level data collected by the study may be shared publicly but will not contain the name of the individual. The investigator will answer any questions raised by the individual and allow them sufficient time to come to a decision. Participants will then be required to give consent. In cases where participants are illiterate, they will be asked to give verbal consent plus a thumb print certified by a witness.

Respect for Autonomy: potential participants have the right to make an informed decision whether or not to participate in this study. Voluntary participation will be ensured, and we will provide participants with the required information such as detailed information sheet and informed consent document prior to commencing any research activity. The research assistants will be available to assist with reading and understanding the informed consent if needed. At this point the individual can decide whether or not to participate in the study. If they decide to participate in the study, participants and research assistants must sign and date the informed consent form, as written proof. The information sheet and informed consent will be provided to individuals in English and isiZulu and they will not be disadvantaged in any form if they do not want to participate in the study.

Justice: it will be stated clearly to participants that their refusal to participate in the study will not affect them or any other health related services they are currently accessing.

We are requesting waiver of informed consent for the individuals accepting HIV self-testing (HIV-SS) kits for the following reasons:

- Peer navigators in all arms will be delivering a service (HIV-SS in arms 1 and 2 and referral to services in arms 3) and therefore will be providing information about the service and the study but not collecting study related data
- HIV-SS is now recommended as best practice by WHO, and the OraQuick HIV Self-Test has been evaluated and approved by WHO Prequalification and being distributed widely in other areas of South Africa
- Community-based HIV testing are established practices in South Africa.
- The trial aims to assess a pragmatic, unrestricted intervention, with potential integration and scale-up by MoH. The intervention is also a community-led process, with any request for formal consent by definition affecting the scope of the intervention.
- Peer-navigators along with intervention materials, will aim to adhere to international best practice for HTS, stressing that HIV testing is a voluntary process.
- The study team will continue to closely monitor any social harms or breach of voluntariness

COMPENSATION

In the network distribution arm seeds will be asked to recruit AGYW aged 18-24 years preferentially but not exclusively and to avoid distribution of HIV-SS to those under the age of 18. They will be then given up to 5 uniquely numbered incentivized recruitment coupons with five HIV-Self screen (HIV-SS) kits to pass on to their peers. Individual who return the coupons will undergo the same procedure as the seeds above. They will also be given up to 5 uniquely numbered incentivized recruitment coupons and HIV-SS kits to pass on. When coupons are returned, the original individual who handed out the coupon to the peer or friend who returned it, will receive a sum of 20 rand ($1.5) in airtime. This sum is as a reimbursement for the time that they have spent in explaining and demonstrating the use of an HIV-SS and is not seen to be an undue incentive to coerce members of their social network to participate. The process will continue for six months. We will not restrict the gender of those recruited through the networks, however the primary outcome will be measured in the AGYW (aged 18-24) only. Participants of semi-structured interviews will receive refreshments and be reimbursed for any travel costs.

HIV SELF-SCREENING PROCEDURES

Peer-navigators and respondent driven peer networks will be urged to observe international best practices for HTS, including voluntariness, adherence to the national age of consent for testing, provision

of pre-test information and information on follow-on services, and confidentiality. Peer navigators will be trained on provision of pre-test information, including how to perform the self-test, interpret results, and link to the mobile clinical services and/or the most convenient health facility offering HIV testing services, antiretroviral therapy, PrEP or circumcision services.

The HIV-SS packs distributed will contain

- A participant information sheet, descrbing their arm of the study and the process of recruitment to the study, which is separate to linkage to care when they attend the clinic.
- Two HIV-SS tests with barcode the same unique identifier (for themselves and a sex partner) with information on how to use it and a free hotline for support
- Referral slip with barcode and the same unique identifier – color coordinated by arm with Hotline Freephone number, mobile clinic and fixed clinic details to support bypassing clinic queues
- Information on linkage

All participants will be asked to complete a brief check of their understanding of the information provided to them, particularly the unreliability of HIV-SS on ART, the window period, the recommended support to those under 18 using HIV-SS, and the need for confirmatory testing.

ADVERSE EVENT REPORTING AND MANAGEMENT

HIV testing, including HIV-SS, is well established and known to have a high level of safety. However, harmful reactions can occur. Adverse events (AE) related to HIV-SS include all undesirable experiences that result directly from use of the HIV-SS kit itself or as a reaction from others due to the presence of the kit, use of the kit or results produced from the kit. AEs can be from one person to another, or a person to themselves, and can occur before, during or after self-testing.

AEs and Serious Adverse Events (SAE) will be captured through the process evaluation, community engagement units and community advisory boards, the hotline, as well as the peer navigators and clinic staff and logged using our incident reporting form for up to up to 12 months after the start of the intervention. Reported AEs and SAEs will be monitored, categorized based on an established grading system, and followed-up accordingly by AHRI.

The Standard Level of Serious Adverse Event will be used for reporting the following to study leadership within two 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 study procedures).
- All other Grade 4 events that are “suspected adverse drug [procedure] reactions” (cannot rule out relationship to study procedures).

SAEs will be logged, with the Principal Investigator evaluating the SAE for seriousness and likely relationship to the intervention. Related SAEs will be reported to UKZN Ethics Review Boards. All SAEs will also be reported though six-month progress reports to Technical Advisory Group members and local and international collaborators. Annual reports with full listings of SAEs will also be submitted to Ethics Review Boards.

9 RISK AND BENEFITS

There are no significant risks for potential participants in this study. The following risks are discussed with mitigation plans:

Biological risks: The gums need to be swabbed with a small plastic flat pad. The plastic paddle is made of a soft plastic with smooth edges, if use correctly, it will be painless. Pictures on how to use the swabs are provided in isiZulu in the accompanying pamphlet and where possible, the peer educator will give a demonstration with a similar HIV-SS to show the correct use.

Psychological risks: There are potential risks to becoming aware of one's HIV status. People who learn that they are HIV-infected may suffer from mental stress and depression as a result. They may also be stigmatized by their family and community and may, despite legal protection, be discriminated against. In order to minimize the risk of mental stress and stigma, HIV SS will be provided to individuals only within the context of voluntary testing. The peer navigators will be trained in counselling and confidentiality and will reiterate that when handing out test kits through the network. A hotline linked to a couple of stand-by AHRI nurses will be created and other referral information will be provided with each kit. To discourage the handing of the HIV SS to underage participants, no incentive will be given to a participant who gave a coupon and HIV-SS to anyone under the age of 18. Information on referral channels for under 18's, will be provided and peer navigators will be trained to deal with that.

Social Risks: Our field staffs have been trained in sensitive data collection and confidentiality. To minimize risks of psychological and physical harm, all staff are completing additional training on working with young people at risk of HIV and child protection procedures. Additionally, all health care workers employed by the study, including the peer navigators and all facilities receiving referrals of study participants for treatment will receive cultural and clinical competence training by trained AHRI team members, to address stigma reduction and specific health needs for adolescent girls and boys. This training for healthcare workers and facilities has been previously conducted multiple times across Africa by our group.

Data collection in public places is conducted through general, non-personal conversations and discussions about general community issues (not only related to HIV and sexual health) and any interviews that may be of a more sensitive nature will be conducted in a private and secure. In all communications with participants outside of the interviews, surveys, or other study activities, the investigators will not mention HIV. During phone calls and through text messages, the staff will only speak to the participant and will not leave a voice message or a message with another person. If necessary, the staff will simply call back another time. When the study is mentioned over the phone or text messages sent as part of the case management program, direct references to HIV will not be included. Phone numbers utilized to send SMS support messages will be recorded but will be kept in the link-log as well

and any messages sent to study participants will not disclose anything about the participant should someone else be using his/her phone.

The potential unethical use of HIV-SS kits due to coercion/undue influence. The social impact of HIV-SS reported so far include empowerment, ownership, choice of testing, reduction in access barriers, increase in acceptability and time efficiencies associated with HIVSS. Although HIV-SS may overcome some barriers to HIV testing, various stakeholders have expressed concerns that HIV self-testing may lead to unintended harm, including psychological and social harms such coercive testing. There is a dearth of evidence of actual occurrence of social harms associated with HIV-SS. We will monitor this closely in our study and the process evaluation and will discontinue the study if evidence for harm emerges.

We will build on our close relationship with the community and our community advisory board as well as the youth advisory board to ensure that our study design, all the study tools, and the ways in which we approach, and recruit are appropriate and acceptable.

If any study participants express the need for emotional support during or after the survey, interview, they will be referred to trained AHRI psychologist and/or counselors.

Study participants can leave the study at any time and continue to receive are through the PHC. We have a close relationship with the MoU and will ensure that systems are in place for transition in and out of the study.

Legal risks: We have extensive experience of undertaking research in the research area including HIV testing and linkage to care and we have very rigorous system to ensure confidentiality. All data will have unique numerical identifier and no personal identifying data or information. Any items with personal identifying features such as consent forms will be kept separate from the research data as described under data management.

Financial risks: no financial risk for participants

Having mentioned the above risks, the study's is very important and timely given that HIV incidence rate is high in our environs. We are hoping that many young people will test given the confidentiality of HIV-SS kit and link to care. The benefits of this study outweigh its risks.

Child protection issues: For the purposes of this grant we will not be recruiting anyone under the age of 18. The field workers and research team will be trained in issues related to child protection and clear standard operating procedures will be developed to guide the research teams as to what they should do if any issues of concern are raised. This will include appropriate referral pathways within the AHRI to

social workers, psychologist and trained counselors, and in liaison with the Department of Social Welfare or the Department of Health clinics. Research teams will undergo regular debriefing with the project management team and child protection issues will be discussed and overseen by the clinical governance team and a dedicated child protection lead at AHRI.

10 Dissemination and Use of Study Findings

The results of the proposed study will be disseminated through traditional academic channels (journal publications) as well as on different information dissemination platforms such as conferences, workshops and symposia. Particularly, the findings of this study will be documented in form of success stories, reports as well as articles in accredited peer reviewed journals. This will also be presented at both national and international platforms.

The following steps will be undertaken to ensure the dissemination of the findings of the study:

- The study report will be shared with stakeholders from NDoH, ARHI, community advisory boards (CABS) and other partners.
- Presentation of findings in local and international conferences/symposia/seminars and through academic and non-academic articles.

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11 Timeline

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
	July 2017	Oct 2017	Jan 2018	Apr 2018	July 2018	Oct 2018	Jan 2019	Apr 2019	July 2019	Oct 2019
Contracts Staff and Ethics			Submit ethics UKZN (May) LSHTM (May) WHO (May)							
Pilot RDS and tools					Using mAfrica Ethics					
RCT										
Outcome ascertain										
Analysis										
Disseminate										

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13 Appendices

- Interview Topic Guides
- Survey/Participant Demographic Form
- Information Sheet and Consent forms