PROTOCOL

CAPRISA 097

A prospective cohort study assessing implant site healing, implant acceptability and PrEP user preferences post removal of the tenofovir alafenamide sub-dermal implant in CAPRISA 018 study participants

Study Design and Conduct by:
Centre for the AIDS Programme of Research in South Africa (CAPRISA) Durban, South Africa

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ABBREVIATIONS AND ACRONYMS

AGYW	Adolescent girls and young women
ART	Antiretroviral therapy
ARV	Antiretroviral
BCEPS	Biometric Co-enrolment Prevention System
BREC	Biomedical Research Ethics Committee
CAB	Community Advisory Board
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CRS	Clinical research site
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
EDCTP	European and Developing Countries Clinical Trials Partnership
ECRS	eThekwini Clinical Research Site
FGD	Focus Group Discussion
FTC/F	Emtricitabine
GCP	Good clinical practice
GFR	Glomerular filtration rate
HIV	Human Immunodeficiency Virus
ICH	International Council on Harmonization
IDI	In-depth interview
IQR	Interquartile range
IRB	Institutional Review Board
IVR	Intravaginal ring
MSM	men who have sex with men
NRTI	Nucleotide reverse transcriptase inhibitor
PEP	Post exposure prophylaxis
PID	Participant identification
PK	Pharmacokinetics
PrEP	Pre-exposure prophylaxis
QA	Quality assurance
QC	Quality control
SAHPRA	South African Healthcare Products Regulatory Authority
SA MRC	South African Medical Research Council
SAR	Serious Adverse Reaction
STI	Sexually transmitted infection
TAF	Tenofovir alafenamide
TasP	Treatment as Prevention
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
UKZN	University of KwaZulu-Natal

CAPRISA 097 STUDY SCHEMA

Purpose:	To assess post removal implant insertion site healing, implant acceptability and pre-exposure prophylaxis (PrEP) product user preferences in previous CAPRISA 018 trial participants.
Design:	Prospective cohort study
Study Population:	Women previously enrolled in the CAPRISA 018 trial
Target Sample Size:	N= 36 (maximum sample size)
Study Duration:	Approximately 12 months
Primary Objective:	• To evaluate the severity, duration and resolution of any ongoing implant insertion site reactions including post implant removal local reactions.
Secondary Objectives:	• To assess the acceptability of the implant as an HIV prevention option post implant removal. • To assess implant product attribute preferences. • To assess HIV PrEP user/method preferences. • To assess the tenofovir alafenamide (TAF) implant use experience amongst participants and clinical research staff. • *To assess changes in the genital microbiome post implant removal • *To assess for the presence of TAF resistance mutations amongst HIV positive participants, after implant removal *(*if clinically appropriate and participant is not co-enrolled in an investigational drug trial)*
Study site:	CAPRISA eThekwini Clinical Research Site (ECRS), Durban, South Africa

1 INTRODUCTION

1.1 Background and study rationale

Despite the global decline in HIV infections by 23% since 2010, the number of people who acquire HIV each year remains unacceptably high (1). Adolescent girls and young women (AGYW) in sub-Saharan Africa account for approximately 25% of all new HIV infections globally (1). Young women in this region are particularly vulnerable and acquire HIV infection 3 to 5 years earlier than their male peers (2, 3). Despite their greater vulnerability, young women have limited access to non-user-dependent prevention options to reduce their risk for HIV acquisition.

Since antiretrovirals (ARVs) were first shown by the CAPRISA 004 trial (4) in 2010 to prevent sexual transmission of HIV, the HIV prevention landscape has been transformed, principally through oral tenofovir (TFV)-containing pre-exposure prophylaxis (PrEP) (5-10) or through early antiretroviral therapy (ART) initiation in HIV-positive individuals (Treatment as Prevention [TasP]) (11). Although daily oral PrEP has been shown to be consistently effective in men who have sex with men (MSM) and transgender women globally (5, 6), results have been inconsistent in African women, due to varying adherence (7-10) and biological factors (12, 13). More recently, newer classes of long-acting ARV) drugs including intravaginal rings (IVRs) and injectables have been evaluated (8). Lenacapavir, is being studied as an injectable agent in the Gilead PURPOSE set of trials (14). The dapivirine-containing vaginal ring has been approved for HIV prevention by the South African Health Products Regulatory Authority (SAHPRA) (15), and the long-acting injectable integrase inhibitor cabotegravir is under review at SAHPRA, however these two products are currently not available in South Africa and concerns about cost and accessibility remain (16).

Pharmacological models suggest that while men only need 2-3 doses per week of oral tenofovir diphosphate/emtricitabine (TDF/FTC) to successfully prevent HIV infection via receptive anal intercourse, 6-7 doses per week are needed to successfully prevent HIV infection via receptive vaginal intercourse, because drug concentrations in the lower female genital tract after oral administration are 10 times lower than those found in the colorectal mucosa (17). An effective, low-cost, method of HIV prevention that overcomes adherence challenges is needed. Furthermore, products that have fewer renal and bone mineral density side effects are also desirable given that TDF/FTC oral PrEP has been shown to decrease creatinine clearance and lower bone density (18-21).

Sustained-release ARV formulations can potentially reduce the dosing frequency and inherently increase the effectiveness of HIV PrEP. ARV containing IVRs and long-acting injectable ARVs have specific advantages over daily oral PrEP, however their disadvantages present challenges that sub-dermal implants have the potential to overcome. Previously, sub-dermal implant technology to formulate a sustained-release approach for ARV delivery was not possible due to the impractical amounts of drug required. For example, the 300mg/200mg of TDF/FTC required for PrEP for just one day cannot fit into a 4cm standard sub-dermal implant. Currently, the lead antiretrovirals formulated as implants in the long-acting PrEP field are tenofovir alafenamide (TAF) (22) and Islatravir (23). However, all clinical trials studying Islatravir have been placed on hold due to observations of decreases in total lymphocyte and CD4+ T-cell counts in some participants (24). TAF is therefore a particularly promising ARV for formulation as a sub-dermal implant, for the PrEP indication, due to its track record for improved systemic safety compared to TDF, high potency and prolonged intracellular activity (15, 18).

The high potency of TAF and the consequent small quantities of drug required for several months make an implant product providing 12 months of drug for PrEP feasible. However, concerns have emerged about topical reactions when inserted under the skin. *In vitro* and *in vivo* evaluation of a subcutaneous reservoir implant (polyurethane membrane) filled with tenofovir alafenamide hemifumarate capable of delivering drug over 90 days were conducted (25). The implants were

assessed for implantation site histopathology and pharmacokinetics in plasma and tissues for up to 12 weeks in New Zealand White rabbit and rhesus macaque models. A dose-ranging study in the rabbits demonstrated dose-dependent pharmacokinetics and local inflammation including tissue necrosis. In rhesus macaques, the histological inflammatory response to the implant at 4 and 12 weeks was graded as severe. This study utilised the acidic TAF salt (hemifumarate), with a poorly tolerated polyurethane extrusion and clamped sharp implant ends that possibly also contributed to the local reactions demonstrated (25).

The CAPRISA 018 Phase I/II trial (22) (BREC REF:107/18) was the first in human study designed to assess the safety, acceptability and pharmacokinetics of a novel sustained-release implant technology (OCIS-001) containing 110mg of micronized TAF free base microtablets loaded into a medical grade silicone extrusion. The study master protocol consisted of four potential groups to be enrolled in sequence. Participants, assessed to be at low risk for HIV infection, were exposed to 1 implant for 28 days in Group 1(n=6, open label) and exited 4 weeks after implant removal. Following DSMB review of the Group 1, 28-day safety data, Group 2 was approved for enrolment and 30 participants were randomised in Group 2 (double-blinded), to receive 1 or 2 implants in a 4: 1 active to placebo ratio and were followed up for a maximum of 48 weeks on product. The dose escalation component was assigned to Group 3 to assess safety and PK of the open label insertion of 3 or 4 implants. The safety and PK data produced from Phase I Groups1-3 would determine the optimal dose (number of implants) for the larger Phase II (n=490), extended safety part of the trial. The CAPRISA 018 Phase I trial screened 244 participants and enrolled a total of 36 participants, comprising Group 1 (n=6) and 2 (n=30) of the trial. Under DSMB oversight, Group 2, participants were followed through week 48 when the implant was scheduled to be removed with a study exit visit occurring four weeks later at week 52. Some Group 2 participants had implants removed early (n=11) and if this occurred prior to week 24 of follow up then they were followed up for a minimum of 24 weeks before study exit, otherwise participants with early removals were exited 4 weeks after implant removal.

In Group 2, where there were high rates of implant insertion site reactions amongst active arm participants, where 100% had induration and above 90% had hyperpigmentation. Amongst Group 2 active arm participants with 2 implants inserted (n=12) there was waning implant acceptability from 100% at enrolment willing to recommend the intervention to others, down to 56% at study exit. All 30 participants, regardless of whether they were in the active or placebo arm, had 1 or more implant insertion site reactions that were ongoing at study exit and these include skin scarring, hyperpigmentation, hypopigmentation and induration. In addition, PK data indicated that the TAF implant drug release rates was not consistently at or above the estimated threshold for protection from HIV. Consequently, following the 5th DSMB meeting assessing safety in the CAPRISA 018 trial, while no systemic safety concerns were identified by the DSMB, the study investigators decided not to proceed with recruitment into Groups 3 and 4 and to end the study of the current candidate TAF implant.

Considering the local safety events, it is important to follow the previous CAPRISA 018 participants to monitor resolution or any long-term sequelae and/resolution of local side effects after implant removal. This proposed 12-month post-trial follow-up cohort study will enrol consenting participants who participated in the CAPRISA 018 trial, will monitor the implant insertion site healing and assess post removal implant acceptability. Also, if HIV infections occur in the follow-up period post-implant removal, there is an opportunity to assess HIV resistance mutations in previous active arm participants. Moreover, if the TAF implant, had any impact on the genital microbiome a minimally invasive assessment post implant removal will be useful to assess for vaginal dysbiosis.

In addition, the following laboratory investigations that are part of the secondary objectives of the CAPRISA 018 trial and are currently underway:

1. Residual drug analysis of the used implants will estimate the amount of drug that was released from the inserted implants up to the time of removal
2. Genital tract pharmacology studies in participants exposed to one or two implants to measure TFV and TFV-DP levels from genital tissue and genital fluid to determine what levels of drug reached the genital tract
3. Measurements of the genital tract and systemic cytokine and immunology profiles to determine any interactions between drug levels and vaginal health

The data generated from this proposed CAPRISA 097 study, and 1-3 above from CAPRISA 018 stored samples will be considered together with available safety and PK data to inform the go/no-go decision to proceed TAF implant research and development. If genital tract PK and residual drug are consistently within the target range and local reactions resolve well, then there is a good case, despite local reactions, to proceed further with product development. If any of these 3 requirements are not met, then there is no good reason to continue this product, and priority may be for a more appropriately designated next generation implant that is more inert and has optimised release characteristics.

At the conclusion of this study, the long-term post-implant removal healing data generated will supplement the data available from the CAPRISA 018 trial, additionally a more granular understanding of implant acceptability, ideal product attributes, PrEP choice preferences and in depth understanding of the implant user experiences during CAPRISA 018 will be gleaned to contribute to the HIV prevention space.

There remains a major need for slow release, long-acting HIV prevention technologies like annual implants, particularly for young women at high risk of acquiring HIV, who are rarely able to adhere to more frequent dosing regimens. It is therefore critically important to learn as much as possible from the CAPRISA 018 trial to inform the development of the next generation TAF implant; and to provide the HIV prevention field with critically needed information to advance long acting, slow-release product development and acceptability. The data generated in this study is key to informing next steps with for an ARV based sub-dermal implant and for the HIV prevention field.

2 STUDY SETTING

This post-trial cohort study will be conducted at the CAPRISA eThekwini Clinical Research Site (ECRS) in Durban, KwaZulu-Natal South Africa

3 STUDY OBJECTIVES

3.1 Primary Objective

- To evaluate the severity, duration and resolution of any ongoing implant insertion site reactions including post implant removal local reactions.

3.2 Secondary Objectives

- To assess acceptability of the implant as an HIV prevention option post implant removal
- To assess implant product attribute preferences
- To assess HIV PrEP user/method preferences

- To assess the tenofovir alafenamide (TAF) implant use experience amongst participants and clinical research staff
- *To assess changes in the genital microbiome post implant removal
- *To assess for the presence of TAF resistance mutations, after implant removal
  **Subject to guidance provided in section 5.3*

4 STUDY DESIGN

4.1 Overview

This prospective, cohort study will enrol consenting participants previously enrolled in Group 1 and Group 2 from the CAPRISA 018 trial. After enrolment, participants will attend study visits quarterly and will exit the study at the month 12 visit. Accrual is expected to take between 4 to 6 weeks.

4.1.1 Screening, enrolment, and follow-up standard of care

Participants will be screened telephonically to gauge interest in enrolling in this prospective cohort study. Willing participants will be given an appointment date to visit the study clinic for possible enrolment.

At the enrolment visit, informed consent (Appendix A1: Participant Informed Consent Form) will be obtained first, and relevant procedures will be conducted in accordance with the schedule of evaluations (Appendix B: Schedule of Evaluations). Rapid HIV testing (using 4th generation rapid HIV tests in duplicate) will be conducted at each visit for HIV negative participants. Soft cup vaginal fluid (self-collection is permitted) will be collected at enrolment and at quarterly study visits where permitted (See section 5.3). A 28-day visit window, on either side on the target visit date, is allowed when scheduling participant visits.

A standard package of sexual and reproductive health (SRH) services will be made available to participants should they wish to access these free services for the duration of study participation. Services include, HIV/STI risk reduction counselling messages and condoms (male and female) will be provided by counsellors trained to administer consistent prevention messages, pregnancy testing and syndromic treatment of STIs aligned with national Primary Health Care standard treatment guidelines. Similarly, pregnancy prevention counselling and non-barrier methods of contraception are available at the study clinic and will be provided by trained clinical staff should participants request these services. Emergency post exposure prophylaxis (PEP) may be offered and requests for PrEP or HIV treatment, will be facilitated by referral of participant to an appropriately situated facility. For other medical conditions identified during follow-up procedures, participants will be referred to other sources of care available in their community.

4.2 Implant insertion site assessment

At each study visit, a clinical examination of the implant insertion site located on the inner aspect of the arm will be undertaken. A trained study clinician will assess for implant site reaction (ISR) severity, long term healing and the presence of any ISR related scarring, skin discolouration and any other observations of note, including documenting fully healed insertion sites. An ISR evaluation case report form will be used to document this assessment. For participants who provide consent, photographs of the implant insertion site may be taken at repeated visits to visually capture healing over time.

4.3 Implant acceptability assessments

Structured implant acceptability assessments, similar to that used in CAPRISA 018 to enable comparison, will be conducted at the enrolment, Month 6 and at the study exit visit (Month 12). (Appendix C).

4.4 Product attributes and PrEP preferred method surveys

PrEP implant attribute and PrEP preference surveys will be conducted in HIV negative participants. At both the enrolment and exit visits the TAF implant attribute survey (Appendix D) will assess participant preferences for potential implant modifications and a preferred PrEP use/method survey (Appendix E) will assess HIV negative participants preference for implants compared to oral pills, injectable agents, vaginal rings or vaginal inserts.

4.5 In-depth interviews (IDI) and Focus Group Discussions (FGDs)

Semi-structured one-on-one in-depth-interviews (IDI) and will be conducted with consenting participants at the Month 3 study visit to gain a nuanced understanding of their individual implant use experience. Approximately, 2 participants in each sub-category enrolled in the CAPRISA 018 trial (Table 1) and at least 2 participants should be from the group of 11 participants who had their implants removed earlier than scheduled, will be targeted for interview. A minimum of 10 participants will be targeted for the IDI subset.

Table 1: Targeted IDI minimum sample size selection

Group 1 (1 implant)	N=2
Group 2 A/B Placebo (1 implant)	N=2
Group 2A/ B Active (1 implant)	N=2
Group 2B/C Placebo (2 implants)	N=2
Group 2 B/C Active (2 implants)	N=2

For participants who agree to participate in FGDs – groups of 3 to 6 participants will be scheduled to join a FGD at either their Months 3, 6 or 9 visit. Depending on uptake, approximately 3 to 5 FGDs may conducted in this study and this number will depend on uptake. Participants may choose to participate in either a FGD or IDI or both or may opt out of either.

The IDI/FGD guided discussion template (Appendix F: Participant IDI/FGD discussion guide) will ascertain participants experiences with the TAF implant, with a focus on insertion and removal procedure experiences, implant tolerability and acceptability challenges. The guide may be adapted, depending on what information the researchers find during the conduct of the initial IDIs or FGD, to remain responsive to the purpose of the research objectives. In-depth interviews and FGDs are anticipated to last between 60-120 minutes.

IDI techniques will also be used to interview consenting (Appendix A2: Research staff informed consent form) clinical research staff (doctors and nurses) from the CAPRISA 018 trial who will be invited to share their experiences with the implant insertion and removal processes as well as managing ISRs (Appendix G: IDI guide for research staff).

5 STUDY POPULATION

Up to 36 eligible participants may be enrolled. This corresponds to the total number of participants enrolled in the CAPRISA 018 trial. The following eligibility criteria will be applied.

5.1 Inclusion Criteria

- Previous participant in the CAPRISA 018 trial
- Able and willing to provide written informed consent
- Able and willing to provide adequate locator information for study retention

5.2 Exclusion Criteria

- Participants who are unwilling or unable to comply with required study assessments, or where study participation may be deemed to be unsafe in the opinion of the study investigators may be excluded from study participation.

5.3 Co-Enrolment Guidelines

Participants in this study may take part in other concurrent research studies, provided participation does not interfere with the objectives of either study and the appropriate study approvals are obtained. Approved co-enrolment in other concurrent protocols will be documented in participant records and on the SA MRC biomedical co-enrolment prevention system (BCEPS) record.

If a participant tests HIV positive in CAPRISA 097 and is known to be co-enrolled in another study where ARVs are being tested, genital and storage samples will not be collected, no blood will be drawn for HIV resistance testing and no further rapid HIV testing will be conducted in the CAPRISA 097 study.

5.4 Participant Retention

The target retention rate is 90% over the 12-month follow-up period. Once a participant is enrolled in the study, every reasonable effort will be made to retain her in follow-up. This may include obtaining and checking locator data, conducting off-site visits, issuing telephone and in-person reminders of scheduled visits, and maintaining a scheduler of enrolled participants as part of a strategy to achieve the retention target.

5.5 Participant Withdrawal

Participants may voluntarily withdraw from the study for any reason and at any time. The Principal Investigator or designee may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Continued participation in the study may also be terminated by the Principal Investigator or designee based on advice from the Study Sponsor and/or the University of KwaZulu-Natal's (UKZN) Biomedical Research Ethics Committee (BREC).

6 DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS

6.1 Data management

All participants will be assigned a study PID to maintain the confidentiality of the data. Clinical, laboratory and survey data will be collected on case report forms (CRFs) that have been developed by the study team. If data entered on the CRFs are taken from an external source (e.g., laboratory reports, patient records), the source documents will be maintained in the participant's medical chart or study file at the site and will be available for review. The CRFs will be faxed into the central CAPRISA database management system (DataFax Discover database) running on SuSe Linux V11. Data Encoders will verify all data by cross-checking the faxed version with what is entered into the database. Queries arising during validation of the data will be recorded in quality control (QC) reports sent to the sites on a regular basis. Database files will be password-protected and access to the files will be limited to authorised study staff. All data will be backed up at regular intervals The original CRFs and the DataFax version of the CRFs and related documents will be stored securely at the sites for both during and after the completion of the study. At all sites, the forms will be stored in locked cupboards in a secure room with restricted access. Upon completion, and finalisation of the database for analysis, the original forms will be bound and kept for long-term storage.

The data management systems used at CAPRISA are all hosted on the secure CAPRISA network, which is firewalled, and access controlled, with the servers backed up daily to a secure off-site facility. CAPRISA backup and restorations are done in line with the CAPRISA IT Disaster Recovery and Business Continuity

IDI and FDG notes, and audio recordings will be used by a trained, impartial interviewer to capture discussions with participants and research staff. Following each session, the recorded interviews will be transferred from the audio recorder to a password-protected, secure, and backed-up computer. All written data extracted from the interviews including the transcripts and notes will be kept in a locked and secure filing cabinet, and digital data will be stored in a password-protected computer database.

For research staff IDIs, a tracking log will be prepared by the interviewer which will include personal identifying information that links the IDI data to the staff member. This will be stored separately in a password-protected file. However, to maintain confidentiality when the data is being analysed and presented, each category of research staff, will be identified by their designation and the order in which they are interviewed e.g., *Clinician 1, Nurse 2*.

6.2 Statistical considerations

This is a prospective study that will utilise structured clinical assessments of the implant insertion site, in addition to quantitative methods (structured questionnaires) and qualitative methods (in-depth interviews [IDIs] and focus group discussions [FGDs]).

The time from initial ISR presentation to complete healing (no evidence of ISRs) will be calculated in days and illustrated using a Kaplan-Meier analysis. If the date of complete healing is unknown, then mid-point between the last visit at which ISRs were present and the first visit at which all ISRs were absent will be used to approximate the healing time. Those who did not fully heal during study follow-up will be censored at their last visit. The proportion of those with ISRs documented at study end, overall and by ISR type, will be calculated, with 95% Wilson (score) confidence intervals. Results will be presented for the full cohort and split by number (1 or 2) and type (active/placebo) of implants received and the duration of use in the CAPRISA 018 trial.

For the analysis of implant acceptability, implant attribute preferences and HIV PrEP user/method preferences, categorical variables will be summarised using frequencies and percentages and continuous variables will be summarised using medians and interquartile ranges (IQRs).

6.3 Qualitative data analysis

The data collected from the IDI and FGD interview transcripts, as well as the observational notes, will be analysed using the Grounded Theory Approach. This theoretical framework operates through data collection and the creation of categories to help with the analysis of data and the building of a hypothesis. It is an inductive method which provides guidelines for gathering, synthesizing, analysing, and conceptualizing qualitative data. Data will be analysed through systematic coding and identifying categories which demonstrate actions, interactions, relationships and processes (26).

7 HUMAN SUBJECTS CONSIDERATIONS

7.1 Ethics Oversight

The study will be conducted under the oversight of the University of KwaZulu-Natal (UKZN) Biomedical Research Ethics Committee (BREC) in Durban, South Africa.

7.2 Informed Consent

In accordance with South African GCP and ICH GCP guidelines, written informed consent will be obtained from each study participant in English or isiZulu prior to enrolment (Appendix A1 and A2), Standard methods will be used for document translation that ensure comparability to the original English. All translated materials will be submitted to the ethics committee for approval prior to use. Participants will be offered a copy of the informed consent form.

7.3 Risks

- There is a very low volume of blood drawn in this study. However, some participants may feel dizzy or faint, and/or develop a bruise, swelling, or infection where the needle is inserted.
- There may be discomfort associated with the soft cup insertion for vaginal fluid collection.
- Participants may become embarrassed, worried, or anxious when receiving HIV counselling. They also may become worried or anxious while waiting for their HIV test results or after receiving HIV-positive test results. Trained study staff will be available to assist participants.
- Additionally, while study personnel will make every effort to protect participant privacy and confidentiality in individual interactions, it is not always possible to assure complete confidentiality in FGD settings.
- If participants disclose their HIV status to non-study participants, they could be treated unfairly or discriminated against.

7.4 Benefits

There may be no direct benefits to participants in this study. However, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may contribute to the development of a safe and acceptable sub-dermal implant that prevents HIV infection.

Study participants will be made aware that they have access to a full package of Sexual and Reproductive Health (SRH) services aligned with the standard of care in the public health sector in South Africa, should they wish to access this. Standard services include HIV counselling and testing, syndromic management of STIs and provision condoms and contraception. Emergency post exposure prophylaxis (PEP) may be offered and requests for PrEP or HIV treatment, will be facilitated by referral of participant to an appropriate facility. For other medical conditions identified during follow-up procedures, participants will be referred to other sources of care available in their community.

Participants will be reimbursed for their time, transport costs and inconvenience for each scheduled visit and refreshments will be provided at the clinic.

7.5 Community involvement and consultation

Regular study updates, on progress with accrual and any challenges experienced with retention or other issues, will be communicated to the Community Advisory Board by study leadership at the bi-monthly community team meetings.

7.6 Confidentiality

Study-related information will be stored securely at the study site. All participant information will be stored in lockable file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, and other reports will be identified by PID only, to maintain participant

confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records.

All databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link PID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Participants' study data, as identified by PID number only, will not be released without their written permission, except as necessary for review and monitoring by regulatory agencies.

Where participants provide consent for photography to document post-removal implant insertion site healing, photography will be limited to the arm and no other physically identifiable features of participants will be photographed. Study personnel will make every effort to protect participant privacy and confidentiality.

7.7 Use of data and publications policy

On study completion, the study team will disseminate the results from this research as broadly as possible. The results from this research will be disseminated through presentations at scientific meetings and peer reviewed publications. All peer reviewed publications will be uploaded to the UKZN publication repository. The findings will also be shared with the study participants, all stakeholders including the general public.

Requests to access the data can be made through the CAPRISA website (www.caprisa.org) on study completion and following publication of the primary outcomes from this study.

8 REFERENCES

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9 APPENDICES

9.1 Appendix A1: Participant Informed Consent Form

9.2 Appendix A2: Research Staff Informed Consent Form

(Attached and version controlled as separate documents)

9.3 Appendix B: CAPRISA 097 Schedule of evaluations

Study Month	0 Enrolment	3	6	9	12 Study exit
Administrative and Regulatory Procedures					
Informed consent process	X				
PID assignment and cross link to CAP018	X				
Demographic data	X				
Locator information update	X	X	X	X	X
*HIV pre- and post-test counselling	X	X	X	X	X
Clinical assessments, surveys, and interviews					
Concomitant ARV use verification	X	(X)	(X)	(X)	X
Implant insertion site examination	X	X	X	X	X
Implant insertion site photography	X	(X)	X	(X)	X
Post removal implant acceptability	X		X		X
Implant product attribute survey	X				X
*HIV PrEP user preference survey	X				X
In-depth interview (participant)		X			
In-depth interview (research staff)	X				
Focus group discussions		X	X	X	
Clinic laboratory tests					
*#Rapid HIV testing	X	X	X	X	X
Soft cup genital fluid collection	X	X	X	X	X
**HIV Resistance test	(X)	(X)	(X)	(X)	(X)
***Storage blood sample	X	X	X	X	X

(X) – if clinically indicated

*** Conducted in presumed HIV negative participants only**

 # 4th generation HIV rapid tests are preferred

****A single 4ml EDTA blood sample, taken at the visit corresponding to first positive rapid HIV test, if it is clinically appropriate, and the participant is not co-enrolled in another interventional trial (see section 5.3) and was in the active arm of the CAPRISA 018 trial.**

*****Collect 4ml EDTA**

9.4 Appendix C: Post removal implant acceptability assessment

9.5 Appendix D: PrEP Implant attribute survey

9.6 Appendix E: PrEP User Preference Survey

9.7 Appendix F: Participant In-depth interview (IDI)/Focus Group Discussion (FGD) interview Guide

9.8 Appendix G: Research Staff In-depth interview (IDI)

(Attached and version controlled as separate documents)