**Study Title:** PHILA: Point of care HIV viral Load testing in a community ART programme

**Internal Reference Number / Short title:** PHILA

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| **Chief Investigators:** | Dr Jienchi Dorward, Nuffield Department of Primary Care Health Sciences, University of Oxford |
| | Dr Nigel Garrett, Centre for the AIDS Programme of Research in South Africa, University of KwaZulu-Natal |
| **Investigators:** | Prof Chris Butler, Nuffield Department of Primary Care Health Sciences, University of Oxford |
| | Mrs Hope Ngobese, eThekwini Municipality Health Unit, eThekwini Municipality |
| | Dr Yukteshwar Sookrajh, eThekwini Municipality Health Unit, eThekwini Municipality |
| | Prof Gail Hayward, Nuffield Department of Primary Care Health Sciences, University of Oxford |
| | Dr Paul Drain, Department of Global Health, University of Washington |
| **Sponsor:** | University of Oxford |
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**Chief Investigator Signature:**

**Conflict of interest statement**

We have no conflicts of interest to declare.

**Confidentiality Statement**

This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from the University of Oxford, the Investigator Team and members of the Oxford Tropical Research Ethics Committee (OxTREC), unless authorised to do so.

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## 1. SYNOPSIS

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|---|---|---|
| **Study Title** | PHILA: Point of care HIV viral Load testing in a community Antiretroviral therapy programme | |
| **Internal ref. no.** | PHILA | |
| **Study Design** | Open label, single-site, randomised implementation trial with qualitative evaluation of implementation processes | |
| **Study Participants** | HIV positive adults (≥18 years) receiving antiretroviral therapy (ART) in the Centralised Chronic Medication Dispensing and Distribution (CCMDD) programme at the Prince Cyril Zulu Clinic in Durban, South Africa. | |
| **Planned Sample Size** | Approximately 200 | |
| **Planned Study Period** | One and a half years | |
| | **Objectives**<br>To compare the effect of point-of-care viral load testing versus standard laboratory viral load testing on: | **Outcome Measures** |
| **Primary** | • Proportion of participants who have their CCMDD prescription renewed | • Proportion of participants with CCMDD prescription renewed by 3 weeks after enrolment |
| **Secondary** | • Time to renewal of CCMDD prescriptions | • Days from enrolment to renewal of CCMDD prescription |
| | • Time to first ART collection in CCMDD | • Days from enrolment to first ART collection recorded in CCMDD system by 16 weeks from enrolment |
| | • Proportion of participants retained in all HIV services (clinic and/or CCMDD) | • Proportion of participants with ART collection recorded in clinic notes or CCMDD system 6-16 weeks from enrolment |
| | • Time to patients receiving viral load results | • Days from enrolment until consultation when viral load results recorded in chart |
| | • Number of clinic visits required for CCMDD renewal | • Number of clinic visits from enrolment until CCMDD renewal |
| | • Cost from the patient perspective to have their CCMDD prescription renewed | • Total cost for the patient (including costs such as transport, time, childcare) to have their CCMDD prescription renewed |
| **Tertiary** | • To evaluate the diagnostic accuracy of the Xpert HIV-1 VL XC at detecting viraemia at a threshold of 50 copies/mL when operated by a nurse in a routine primary care clinic | • Sensitivity and specificity of the Xpert HIV-1 VL XC to detect viral loads ≥50 copies/mL compared to a laboratory reference assay |
| **Qualitative evaluation** | To assess what changes in clinic systems are required to implement point-of-care viral load testing | Staff perspectives regarding implementation of point-of-care viral load testing |

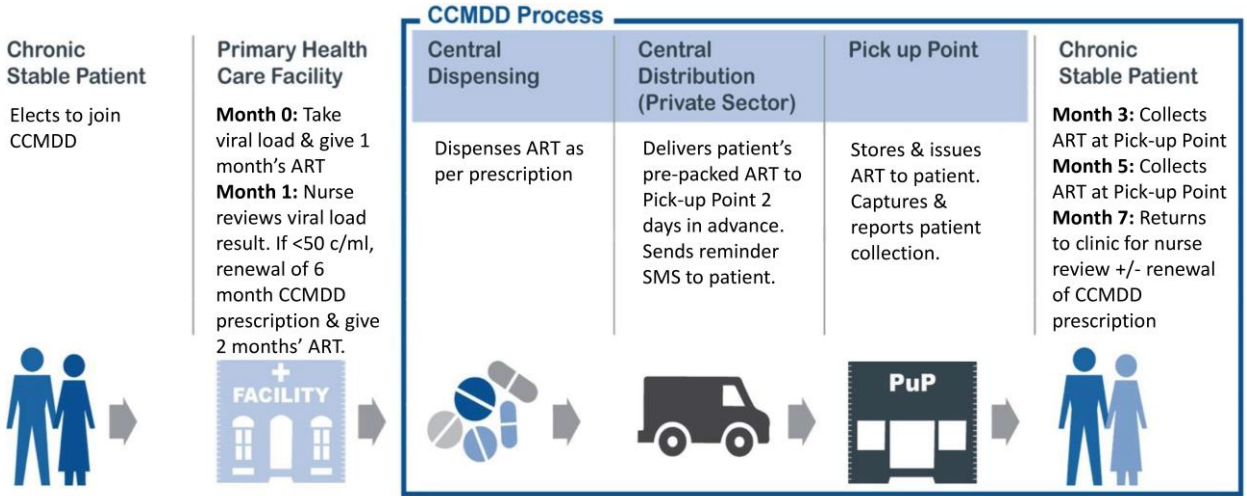
## 2. ABBREVIATIONS

| | |
|---|---|
| ART | Antiretroviral Therapy |
| BREC | Biomedical Research Ethics Committee |
| CAPRISA | Centre for the AIDS Programme of Research in South Africa |
| CI | Chief Investigator |
| CCMDD | Centralised Chronic Medication Dispensing and Distribution system |
| CRF | Case Report Form |
| eGFR | Estimated glomerular filtration rate |
| GCP | Good Clinical Practice |
| HIV | Human Immunodeficiency Virus |
| ICF | Informed Consent Form |
| LMIC | Low- and middle-income country |
| MDRD | Modification of Diet in Renal Disease |
| NHLS | National Health Laboratory Service |
| OxTREC | Oxford Tropical Research Ethics Committee |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| SOP | Standard Operating Procedure |
| WHO | World Health Organization |

## 3. BACKGROUND AND RATIONALE

To provide life-saving antiretroviral therapy (ART) for all of its 7.9 million people with HIV[1], the South African government has developed a community ART delivery programme known as the Centralised

**Figure 1: CCMDD flow diagram (adapted from[2])**



Chronic Medication Dispensing and Distribution system (CCMDD).[2] CCMDD can benefit patients by allowing ART collection at pick-up points (churches, community groups, pharmacies) that are nearer, have longer opening hours and are less congested than clinics. This can improve adherence and retention in care.[3–5] However, only stable patients with a suppressed annual HIV viral load <50 copies/mL are eligible for CCMDD. Currently, taking blood and reviewing the viral load result requires two clinic visits over 7-28 days (Figure 1), as samples are sent away for testing in specialist central laboratories. Patients can struggle to attend both these visits and samples and results often get lost.[6] Without an annual viral load result, patients cannot be re-enrolled in CCMDD, so they either miss treatment or must continue collecting from crowded clinics far from home. Currently, ~300,000 of the 1 million patients in CCMDD are in this situation (so-called 'dormant'), meaning their repeat prescription has been delayed by ≥3 weeks (personal communication, Roma Ramphal, CCMDD Co-ordinator for KwaZulu-Natal).

**Figure 2: GeneXpert® System & Xpert® HIV-1 viral load cartridge.**

We hypothesise that using a point-of-care viral load test, to provide results in one clinic visit, could expedite CCMDD prescription renewal, reduce clinic visits and decrease the number of 'dormant' patients. The World Health Organization (WHO) recently approved the Xpert® HIV-1 (Cepheid®, Sunnyvale, USA), which can provide a viral load at the point-of-care in <2 hours (Figure 2) from 1 mL of plasma.[7,8] The assay has been validated in multiple settings, including the proposed clinical site,[9] with good correlation and accuracy in a recent meta-analysis (see Box 1, section 7.5).[10] Of note, the assay uses the fully automated molecular GeneXpert® platform, which is already widely used in low- and middle-income countries (LMICs) for diagnosing tuberculosis.[11] In 2017, an estimated 9,449 GeneXpert® instruments had been procured in 130 countries.[12] If the Xpert HIV-1 VL assay can be implemented in routine services, it could become a vital tool for HIV programmes across LMICs, particularly in Southern Africa. Recently, Cepheid has launched a newer, CE-IVD approved, dual target version, the Xpert HIV-1 VL XC, which utilises the same GeneXpert platform, and has been successfully validated in the study clinic (n = 164, Pearson correlation co-efficient 0.97 (95% CI 0.95, 0.99), mean bias -0.10 log copies/mL, (-0.54 to 0.34), specificity at viral load threshold of 50 copies/mL = 0.96 (0.91, 0.99), sensitivity = 0.93 (0.82, 0.98), manuscript in draft). The m-PIMA HIV-1/2 VL (Abbott, Chicago, USA), a similar point-of-care viral load assay, has also received WHO approval.

We performed the first pilot randomized trial of the Xpert HIV-1,[13] which demonstrated that in a research clinic amongst people recently initiated on ART, point-of-care testing increased retention in care, viral suppression, and earlier first referral into CCMDD.[14] However, we do not know whether these benefits apply in routine, non-research primary care clinics, and amongst people who need longer term viral load monitoring for renewal of CCMDD prescriptions. Implementation of point-of-care viral load testing may not be feasible in non-research settings, as it requires multiple steps including centrifuging samples, assay maintenance, quality assurance and reorganisation of clinic flow, to ensure that results are delivered and managed appropriately.

Therefore, we aim to implement point-of-care viral load testing in a routine HIV primary care clinic in South Africa, and assess whether it can improve access to ART by improving renewal of CCMDD prescriptions.

## 4. OBJECTIVES AND OUTCOME MEASURES

| Objectives | Outcome Measures | Timepoint(s) of evaluation of this outcome measure |
|---|---|---|
| **Primary Objective**<br>To compare the effect of point-of-care viral load testing versus standard laboratory viral load testing on the proportion of participants who have their CCMDD prescription renewed | **Primary Outcome:**<br>Proportion of participants in each arm with renewal of CCMDD prescription recorded within CCMDD database (binary) | 3 weeks post enrolment |
| **Secondary Objectives**<br>To compare the effect of point-of-care viral load testing versus standard laboratory viral load testing on: | | |
| a) Time to renewal of CCMDD prescriptions | a) Days from enrolment to renewal of prescription in CCMDD database | a) Up to 16 weeks post enrolment |
| b) Time to first ART collection in CCMDD | b) Days from enrolment to first ART collection recorded in CCMDD database | b) Up to 16 weeks post enrolment |
| c) The proportion of participants retained in all HIV services (clinic and/or CCMDD) | c) Proportion of participants in each arm with ART collection recorded in clinic notes or CCMDD system | b) 6 - 16 weeks post enrolment |
| d) Time to patients receiving viral load results | d) Days from enrolment until consultation when viral load results recorded in chart | d) Up to 16 weeks post enrolment |
| e) The number of clinic visits required for CCMDD renewal | e) Number of clinic visits from enrolment until CCMDD renewal | e) Up to 16 weeks post enrolment |
| f) Cost from the patient perspective to have their CCMDD prescription renewed | f) Total cost for the patient (including costs such as transport, time, childcare) to have their CCMDD prescription renewed | f) At enrolment and subsequent visits up to and including CCMDD renewal |
| **Tertiary Objectives**<br>To evaluate the diagnostic accuracy of the Xpert HIV-1 VL XC (or similar point-of-care viral load assay) at detecting viraemia at a threshold of 50 copies/mL when operated by a nurse in a routine clinic | Sensitivity and specificity of the Xpert HIV-1 VL XC (or similar assay) to detect viral loads ≥50 copies/mL compared to a laboratory reference assay | At enrolment |
| **Qualitative Study Objectives:** | | During enrolment when point-of-care |

| | | |
|---|---|---|
| To assess what changes in clinic systems are required to implement point-of-care viral load testing? | Staff perspectives regarding implementation of point-of-care viral load testing in a routine clinic | testing is being implemented, and after study conclusion |

We hypothesise that POC VL testing will lead to faster renewal of CCMDD prescriptions due to results being available more rapidly. We have chosen to assess the primary outcome of CCMDD renewal at 3 weeks as the interval currently used within the CCMDD programme to define 'dormant' patients is not having a CCMDD prescription renewed by 3 weeks after expiration of the current prescription. Our trial primary outcome therefore aligns well with programmatic outcomes that are important to CCMDD policy makers and health system managers .

## 5. STUDY DESIGN

This will be a single-site, open label, individually randomised, implementation trial comparing point-of-care viral load testing with standard laboratory based viral load testing within CCMDD (Appendix A). Study implementation will be assessed using in-depth staff interviews and focus groups.

HIV positive adults who are receiving ART in CCMDD will be recruited when they are due a repeat HIV viral load to guide renewal of their CCMDD prescription. After screening, eligible, consenting participants will be enrolled and randomized 1:1 to the point-of-care intervention arm, or standard-of-care. Participants in the standard of care arm will have standard laboratory viral load and creatinine testing performed by the National Health Laboratory service. Participants in the point-of-care arm will have point-of-care viral load testing (Xpert® HIV-1 VL XC, Cepheid, Sunnyvale, CA, or similar assay) and point-of-care creatinine testing (Statsensor Xpress-I, Nova Biomedical, Waltham, MA, US, or similar assay) (Table 1). Point-of-care results will be provided in the same clinical visit, where possible. If point-of-care results are not available in the same visit, the participant will be asked to return for the result on a date scheduled at the staff and participant's discretion (normally between 1 and 28 days). In the standard-of-care arm, participants will need to return after 7-28 days to receive their results, as results may not be available before 7 days. All patients with a viral load <50 copies/mL will be given 8-12 weeks of ART and have their CCMDD prescription renewed for subsequent ART collection after 8 or 12 weeks at their community pick-up point. All prescriptions and ART collections are routinely captured electronically and recorded in a central CCMDD database, while viral load results, clinic visits and clinic ART prescriptions are documented in clinical charts and routinely captured in the clinic's TIER.net database. The research team will monitor the CCMDD and TIER.net databases, as well as clinical charts, to record all viral load results prescriptions and ART collections for each participant until 16 weeks post-enrolment (Appendix B).

During implementation of point-of-care viral load testing and after the study ends, a research assistant will perform in depth interviews and focus group discussions with clinic staff, using topic guides informed by Normalisation Process Theory to explore implementation of point-of-care testing and barriers to CCMDD prescription renewal (see section 11). Interviews and focus groups will be audio recorded, transcribed and analysed using Framework analysis.

## 6. STUDY SETTING

The study will take place at the Prince Cyril Zulu Clinic with support from the adjacent CAPRISA eThekwini Clinical Research Site. The Prince Cyril Zulu Clinic is a large public clinic situated next to the main transport hub in central Durban and provides HIV, tuberculosis sexual health and primary care services to a large, diverse, urban population. In 2016 the Prince Cyril Zulu Clinic was one of the first clinics to implement the CCMDD programme in Durban, and now cares for approximately 10,000 people living with HIV. However, if necessary to complete enrolment timeously, participants can be recruited from another HIV clinic or from CAPRISA's clinical research site in Vulindlela.

## 7. PARTICIPANT IDENTIFICATION AND RECRUITMENT

### 7.1. Study Participants

HIV positive adults (≥18 years old) receiving ART in CCMDD and who are due a viral load test for renewal of their CCMDD prescription.

### 7.2. Inclusion Criteria

The participant may enter the study if ALL of the following apply:

- Participant is willing and able to give informed consent for participation in the study.
- HIV positive adult, Male or Female, aged ≥18 years.
- Receiving ART in CCMDD and willing to continue in CCMDD
- Due a renewal of their prescription in CCMDD
- Requires an HIV viral load test for renewal of their CCMDD prescription

### 7.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Not eligible for CCMDD as per South African Department of Health criteria:
    - Known to be pregnant or breast feeding
    - Current tuberculosis
    - Known to have diabetes and with blood glucose >7.0mmol/L
    - Known to have hypertension with blood pressure ≥140/90 mmHg
    - Other medical condition requiring regular clinical consultations

## 8. STUDY PROCEDURES

### 8.1. Recruitment

HIV-positive patients who are in CCMDD and due viral load testing for renewal of their prescription will be identified by clinic staff and offered referral to the study team.

## 8.2. Informed Consent

A research assistant or research nurse will approach patients at the clinic who have been identified as awaiting CCMDD renewal. The research assistant or research nurse will describe the study, address any questions and ask for voluntary participation. If the participant is willing, they will be invited to a private room in the clinic where the research assistant or research nurse will present written and verbal versions of the Participant Information and Informed Consent detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent will be offered to the participant. The original signed form will be retained at the study site.

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

## 8.3. Screening and Eligibility Assessment

After informed consent has been obtained, a research nurse will review the study inclusion/exclusion criteria with the patient. Demographics and a brief medical history will be taken. The patients clinical and laboratory record will be reviewed, and blood pressure will be measured. Pregnancy testing will be performed for all women aged 18-55 who report possible pregnancy and who have not yet had a pregnancy test on that clinic visit. Patients known to have diabetes will have a random finger prick capillary blood glucose measurement. Patients deemed eligible for the study will be enrolled on the same day as screening.

## 8.4. Randomisation, blinding and code-breaking

A CAPRISA statistician will generate the allocation sequence using random numbers generated in a statistical software program such as STATA 14.0 (Statacorp, Texas, USA) or SAS 9.4 (SAS Institute Inc., Cary, USA). The allocation sequence will contain variable block sizes, with participants randomised in a 1:1 ratio to the intervention or standard of care arm. The allocation sequence will be programmed into the REDCap (Vanderbilt University, Nashville, USA) enrolment electronic case report form (eCRF). All study staff apart from the statistician and data manager will be blinded to the allocation sequence. At enrolment, the research assistant or research nurse will complete the enrolment eCRF, which will automatically assign the intervention allocation and generate a unique participant identification number (PID). As this is an open label study, study staff, clinic staff and participants will not be blinded to intervention allocation.

## 8.5. Study enrolment visit

### 8.5.1 Baseline demographics and medical history

At enrolment, a research assistant or research nurse will ask participants to provide information on their demographic, social and medical history.

### 8.5.2 Laboratory testing

In both arms, participants will have viral load and creatinine testing to assess eligibility for CCMDD (see Table 1). Creatinine results will be used to calculate the estimated glomerular filtration rate (eGFR), using the Modification of Diet in Renal Disease (MDRD) formula.

For participants randomised to the point-of-care arm, a phlebotomist or nurse will draw venous blood for point-of-care viral load testing in the clinic. Results should be available in approximately two hours. The nurse or phlebotomist will also take a capillary finger-prick sample to perform point-of-care creatinine testing on the Statsensor Xpress-i (or similar assay), which provides a result in 90 seconds.

In the standard-of-care arm, venous blood will be drawn by a nurse or trained phlebotomist for laboratory HIV viral load and laboratory serum creatinine, and sent to the standard of care National Health Laboratory Service (NHLS) for testing as per routine clinic procedures.

### 8.5.3 Management of results and CCMDD prescription renewal

In both arms, clinic staff will be encouraged to act on results as soon as possible. In the point-of-care arm, results could be available in the same visit, or if not available or the client cannot wait, they will be available at the next clinic visit scheduled at staff and patient's discretion. In the standard of care arm, laboratory viral load results are normally available after 7 days, and clients typically return after 7 -28 days for results, depending on their availability, ART supply and clinic schedules.

Participants who are eligible for CCMDD with viral load <50 copies/mL and eGFR >50 mL/min/1.73 $m^2$ will have their prescription renewed by a nurse using the standard Department of Health CCMDD electronic prescribing form. If the electronic system is offline or unavailable, the standard Department of Health paper prescribing form will be used. The renewed prescription will allow the participant to collect their ART after 8 and 16 weeks at their community pick up point. Pick up dates will be recorded in their hand held CCMDD card. The nurse will also supply the client with ART to cover the 8 week period up to their next CCMDD pickup.

Patients with viral load ≥50 copies/mL or eGFR <50 mL/min/1.73 $m^2$ will not be eligible for CCMDD prescription renewal (Table 1). Participants in both arms with an eGFR of <50 mL/min/1.73 $m^2$ will have a repeat laboratory creatinine sample taken and will be referred to the clinic physician for assessment with the result, as is standard practice in the clinic. Participants in both arms with a detectable viral load ≥50 copies/mL will be referred to a counsellor for enhanced adherence counselling and will continue ART collection at the clinic as per South African HIV guidelines.[15,16]

**Table 1: Viral load and eGFR results and CCMDD eligibility**

| Test | Result | CCMDD eligibility | Action |
|---|---|---|---|
| HIV Viral load | < 50 copies/mL | Potentially eligible | Renew CCMDD prescription if eGFR >50 mL/min/1.73 $m^2$ |

| | | | |
|---|---|---|---|
| | ≥50 copies/mL | Not eligible | Refer to counsellor for enhanced adherence counselling |
| eGFR | >50 mL/min/1.73 $m^2$ | Potentially eligible | Renew CCMDD prescription if viral load normal |
| | ≤50 mL/min/1.73 $m^2$ | Not eligible | Take laboratory creatinine test and refer to clinician with result |

## 8.6. Follow up and outcome assessment

Assessment of study outcomes such as subsequent CCMDD prescriptions, clinic visits, CCMDD ART pick-ups and time to availability of viral load results will be captured by the study team at 0, 8 and 16 weeks by reviewing participants routine clinical charts, laboratory results and the CCMDD electronic database (Appendix B). If no CCMDD renewal prescription is found in the CCMDD electronic database, and no ART collection is found in the clinical chart, we will follow up with the CCMDD hotline for healthcare providers to establish whether any referral was received. Between 16 and 18 weeks, any participant with no CCMDD renewal and no record of ART collection at the clinic will be contacted by the research team to establish the reason for not collecting in CCMDD. This is in accordance with standard South African guidelines for tracking patients on ART who have missed clinic appointments.

## 8.7. Extended follow up of routine data

For participants who agree, research staff may access routine medical records, prescription data and laboratory results for up to five years after the study exit visit, in order to determine longer term retention in care, ART adherence and viral load results. For participants who are lost to follow up, and who provided consent at enrolment, the participants vital status may be checked on the South African National Population Register.

## 8.8. Sample Handling

### 8.8.1 Point-of-care testing

Point-of-care viral load testing will be performed by a nurse, phlebotomist or technician in the clinic, who will have received comprehensive training on all aspects of performing point-of-care viral load testing and been assessed as competent by the CAPRISA laboratory site manager. All point-of-care viral load testing procedures will be performed in a specially prepared room in the clinic, using a small centrifuge and the Xpert HIV-1 VL XC assay on the GeneXpert platform, or a similar validated point-of-care assay (e.g. the m-PIMA HIV-1/2 VL). Testing will be performed following manufacturer instructions, using approximately 4 mLs of venous blood, drawn using aseptic technique. The sample will be centrifuged to separate approximately 1 mL of plasma which will be pipetted into the assay cartridge. The cartridge will be placed in the fully automated assay platform, with results available after approximately 90 minutes. In the case of an invalid result, a repeat blood sample may need to be drawn for point-of-care testing. If repeat point-of-care testing is not possible (e.g. machine failure) the repeat sample will be sent for standard laboratory

testing. Error codes will be checked regularly and reported to the CAPRISA laboratory staff and manufacturer to identify and correct sample processing or machine errors.

Point-of-care creatinine testing will be performed by a nurse or phlebotomist using the Statsensor Xpress-i, a small hand-held device similar to a glucometer that measures creatinine levels in 90 seconds. The nurse or phlebotomist will use a standard, single-use lancet to obtain a finger-prick sample of capillary whole blood, under aseptic technique, and apply it to the Statsensor test strip. Prior to use, each new lot of Statsensor® strips will be tested using manufacturer supplied linearity controls. Creatinine values will be used to calculate eGFR with a standard, validated MDRD eGFR calculator app (e.g. "eGFR Calculators" by National Kidney Foundation).

**8.8.2 Standard laboratory testing**

Laboratory viral load and creatinine testing will be performed by a nurse or phlebotomist in the clinic according to standard clinic procedures. In brief, approximately 9 mLs of venous blood (4 mLs for viral load testing, 5 mLs for creatinine testing) will be drawn using aseptic technique and transported on the same day to the National Health Laboratory Service for testing using their routine laboratory assays. Currently, the National Health Service performs creatinine testing on the Dimension® EXLTM 200 (Siemens Healthcare, Erlangen, Germany) at Addington Hospital, and viral load tests on either the Realtime m2000 assay (Abbott, Chicago, USA) at the Addington Hospital Laboratory, or the Cobas 6800/8800 assay (Roche, Basel, Switzerland) at the Inkosi Albert Luthuli Hospital Laboratory, depending on machine availability and capacity.

**8.8.3 Storage blood**

Participants who provide additional consent may also have 4 mLs of venous blood drawn for storage and retrospective ART drug level and HIV viral load and drug resistance testing. At enrolment, 5 mLs of urine will also be taken for storage and ART drug level testing. Samples will be stored in the CAPRISA biorepository according to Good Clinical Laboratory Practice for up to ten years and will be made available to the study team or other approved investigators who have obtained ethical approval for additional projects. After ten years, remaining stored samples will be disposed of.**8.8.4 Potential evaluation of newer point-of-care assays**

If new point-of-care viral load assays become available, we may use samples from this study to compare results from the new assay to the laboratory reference assay. The new assay results would be for validation purposes only and would not be used to guide clinical management.

## 8.9. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent

Participants who withdraw from the study will not be replaced. Data for participants who withdraw will be included in intention to treat analysis. The reason for withdrawal will be recorded in the Case Report Form.

## 8.10. Definition of End of Study

The end of study is the date 18 weeks after enrolment of the last participant.

# 9. SAFETY REPORTING

This study does not involve an investigational medicinal product or intervention that affects physiology, and therefore will not require serious adverse event reporting. However, for completeness we will report all cases of mortality in the study to the University of KwaZulu-Natal's Biomedical Research Ethics Committee (BREC).

# 10. STATISTICS AND ANALYSIS

## 10.1. Description of Statistical Methods

At the conclusion of the study, we will test the hypothesis that point-of-care viral load testing is superior to standard laboratory testing by calculating the absolute differences in the proportion achieving study outcomes between the two arms, using intention to treat analysis.

## 10.2. Analysis of Outcome Measures

### 10.2.1 Primary outcome

We will present the absolute difference between the two arms in proportions achieving the binary primary outcome of CCMDD prescription renewal by 3 weeks. We will present 95% confidence intervals calculated using Newcombe Wilson method, and test the null hypothesis of no difference between the two arms using the chi-squared test. All participants enrolled in each arm will be included in the primary intention to treat analysis.

### 10.2.2 Secondary outcomes

We will use Cox proportional hazard models to compare time to receipt of viral load results, time to renewal of CCMDD prescriptions and time to first ART collection in CCMDD between the two arms. If a high proportion of events occur on days 0 to 1 post-enrolment, then a Cox model may not be suitable, and we will instead compare proportions achieving the outcome of interest at 2, 4, 8, 12 and 16 weeks post enrolment, using chi-squared tests and Newcombe Wilson 95% confidence intervals. Retention in HIV services will be defined as collecting ART from either the clinic or CCMDD between 6 and 16 weeks post enrolment. We will compare the proportion retained in HIV services between the two arms using chi-squared tests and Newcombe Wilson 95% confidence intervals. Amongst those with CCMDD renewals, we will compare the mean number of clinic visits from enrolment until CCMDD prescription renewal, and the mean total cost to the participant to attend these clinic visits, using Students t-Test. All participants enrolled in both arms will be included in intention to treat analyses of the above secondary outcomes.

#### 10.2.3 Tertiary Objectives

We will calculate the sensitivity and specificity, with 95% confidence intervals, of the point-of-care assay to detect viral loads ≥50 copies/mL compared to a laboratory reference assay. All enrolment point-of-care viral load results will be compared to a laboratory reference viral load assay (e.g. the Cobas 6800/8800 assay (Roche, Basel, Switzerland)) using storage blood taken at the same time point.

### 10.3. The Number of Participants

Based on current clinic performance, we assume that 75% of patients in the standard of care arm will achieve the primary outcome of CCMDD renewal by 3 weeks. Assuming a 15% improvement in the point-of-care arm, a sample size of 100 participants per arm will have 80% power to demonstrate superiority with a two-sided alpha of 95% (Table 2). As all enrolled participants will be included in the final intention to treat analysis, we have not adjusted for loss to follow up or potential withdrawals.

**Table 2: Sample size and power estimates**

| Proportion achieving the primary outcome | Power (beta) | Estimated total sample size |
|---|---|---|
| POC 90% vs lab 70% | 80% | 124 |
| POC 85% vs lab 65% | 80% | 146 |
| POC 80% vs lab 60% | 80% | 164 |
| **POC 90% vs lab 75%** | **80%** | **200** |
| POC 90% vs lab 80% | 80% | 398 |
| POC 80% vs lab 70% | 80% | 588 |

## 11. DATA MANAGEMENT

### 11.1. Access to Data

Direct access will be granted to authorised representatives from the University of Oxford and CAPRISA for monitoring and/or audit of the study to ensure compliance with regulations.

### 11.2. Data Handling and Record Keeping

The research team will capture study data using standardised electronic CRFs in REDCap. All data entry will undergo three stages of quality control including pre-programmed data validity checks in electronic CRFs, immediate source document review, and weekly quality reports generated by REDCap. The participants will be identified by a unique study specific number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file.

## 12. QUALITATIVE STUDY

### 12.1. Background

Point-of-care diagnostics have been used widely in healthcare systems in many low and middle income countries.[17] In HIV programmes, some tests such as rapid, lateral flow assays for diagnosis of HIV, have been evaluated, endorsed and incorporated into guidelines by the World Health Organization and successfully adopted in many settings.[18] However, other assays, such as more complex molecular polymerase chain reaction technologies for tuberculosis, have remained as laboratory tests despite being marketed as point-of-care assays.[17] A large systematic review of barriers to point-of-care HIV diagnostic implementation in low and middle income countries found that in 132 studies, integration of the point-of-care test into clinical work flows was the most commonly identified challenge to test utilisation.[19] However, there are few published implementation projects that have used a theory-based approach to assess implementation of point-of-care tests in healthcare systems, particularly in LMICs. One theory that has been widely used to assess implementation of new technologies in healthcare is Normalisation Process Theory. Normalisation Process Theory aims to identify what is needed to 'normalise' use of a technology in a healthcare system.

## 12.2. Aim

We aim to assess staff perspectives on implementation of point-of-care viral load testing as part of the CCMDD programme.

## 12.3. Study design

During trial enrolment when implementation of point-of-care viral load testing is taking place, a trained research assistant with experience of qualitative research will perform the first round of semi-structured interviews with approximately 8-10 staff, and a focus group with approximately 8-10 staff. After completion of enrolment, we will perform a second round of interviews and focus group, to assess perspectives on implementation of point-of-care viral load testing and integration with CCMDD.

## 12.4. Participants

Approximately 10-15 staff involved in viral load testing and CCMDD will be approached to participate in this qualitative study. Staff will include counsellors, phlebotomists, nurses, pharmacy staff, laboratory staff, doctors and health service managers. Focus groups and in-depth interviews may consist of the same or different staff members. However, we will endeavour to include the same staff members in the first and second round of interviews and focus groups.

## 12.5. Procedures

### 12.5.1. Informed consent

A trained research assistant will approach staff in the clinic, explain the nature of the project and offer participation. Should the staff member be interested, they will be taken to a private space and provided with written and verbal versions of the Qualitative Study Participant Information and Informed Consent. The research assistant or other study team member will answer any questions that the staff member may have, and it will be clearly stated that staff are able to refuse to participate without adverse consequences

for their working life. Once written informed consent has been provided, a copy will be offered to staff participant, and the original will remain with the research team.

#### 12.5.2. Interviews and focus groups

Once the Informed Consent Form has been signed, the research assistant will use predetermined topic guides to conduct interviews and/or focus groups in a private room at the study clinic, or if necessary, at another suitable private venue of the participant's choice. Interviews will last approximately 30-60 minutes, and focus groups 45-75 minutes. We will make an audio recording of interviews and focus group discussions. If a participant does not consent to audio recording, we will take a written recording of the interview or focus group.

#### 12.5.3. Analysis

Audio and written recordings will be anonymised and translated from isiZulu (when necessary) and transcribed. Data will be analysed using thematic analysis as described by Attride-Stirling and reported accordingly.[20]

## 13. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

Study documentation including participant information sheets, informed consent forms, regulatory files, standard operating procedures, source documentation and electronic CRFs will be subject to internal quality audits by the CAPRISA Quality Assurance team, in accordance with CAPRISA standard operating procedures. CAPRISA routinely measure quality control and retention rates on all studies. The study will be conducted in accordance with relevant regulations and standard operating procedures.

## 14. ETHICAL AND REGULATORY CONSIDERATIONS

### 14.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

### 14.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

### 14.3. Approvals

The protocol, participant information sheet and informed consent form, topic guides and any proposed advertising material will be submitted to OxTREC and BREC for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all amendments to the original approved documents.

## 14.4. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database. All documents will be stored in a secure cabinet in the locked research office, and will only be accessible by study staff and authorised personnel. The electronic data will be stored in REDCap, which is a password protected data management service. All computers with access to the data will be password protected. The study will comply with the General Data Protection Regulation (GDPR), which requires that personal data must not be kept as identifiable data for longer than necessary for the purposes concerned.

For the qualitative evaluation of implementation processes, interviews and focus group discussions will take place in a private room. We will make a written record during the focus group or interview, or from the recorded audio, but we will not write down any information that might identify participants or others. For example, if the participant mentions names of colleagues, we will not write those names down. The recording and notes from interviews and focus group discussions will be stored in a locked cabinet and only the staff working on this study will be able to use them. We will destroy the recordings when the research is completed. Data will never be reported in a way that could potentially reveal a single participant's identity. If during interviews or focus groups a staff member reveals practice which is not in line with professional standards and may cause harm to patients, we will discuss this with the staff member and the clinic manager.

## 14.5. Expenses and Benefits

Patient participants will be reimbursed ZAR150 (approximately £8.00) after the enrolment visit for their participation in the research. This is in accordance with CAPRISA Policy on Study Participant Compensation, which adhere to the Department of Health and SAPHRA guidelines, and will consider time of visits, inconvenience of study procedures, and transport expenses.[21] Reasonable travel expenses for any visits additional to normal care will be reimbursed.

Staff participants will not be reimbursed as interviews or focus groups will take place during working hours, at a mutually convenient time that has been agreed with the clinic manager.

## 14.6. Reporting

The CI shall submit an Annual Progress Report to OxTREC and BREC on the anniversary of the date of approval of the study. In addition, the CI shall submit an End of Study Report to OxTREC and BREC within 12 months of completion of the study. If we extend follow up of routinely collected clinic and laboratory data, for up to five years after the last study exit visit, the study will remain under annual review by OxTREC and BREC while those data are being collected.

## 14.7. Other Ethical Considerations

All study participants will be HIV-positive and may face HIV-related stigma. Therefore, maintaining confidentiality is particularly important in this study (see section 13.4).

For staff interviews and focus groups, there is the possibility that they will feel unable to refuse participation, or that they will feel challenged at being interviewed about aspects of their work. While every effort will be made to maintain staff confidentiality, due to the small numbers of staff participating in the study it may be possible for superiors and colleagues to infer their identity indirectly. Therefore, the option to refuse participation without implications in their work will be made clear in the informed consent process. We will also warn staff about the risk of colleagues and superiors being able to infer their identity indirectly. Staff will not be asked questions which could threaten their work position or personal questions about their lives. Questions will focus work-related issues that are already likely to have been discussed in other settings, as the clinic team have implemented point-of-care viral load testing and CCMDD.

## 15. FINANCE AND INSURANCE

### 15.1. Funding

This study is funded by a fellowship from Wellcome Trust PhD Programme for Primary Care Clinicians and the Countess Dowager Eleanor Peel Trust Medical Grants Scheme.

### 15.2. Insurance

The University of Oxford has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

## 16. PUBLICATION POLICY

Findings from this study will be presented at academic conferences and submitted to peer reviewed journals for Open Access publication in accordance with Wellcome Trust policies for Wellcome Trust funded research. Authorship and acknowledgements will follow the International Committee of Medical Journal Editors guidelines. Author accepted manuscripts will be posted on the investigators' institutional websites.

## 17. REFERENCES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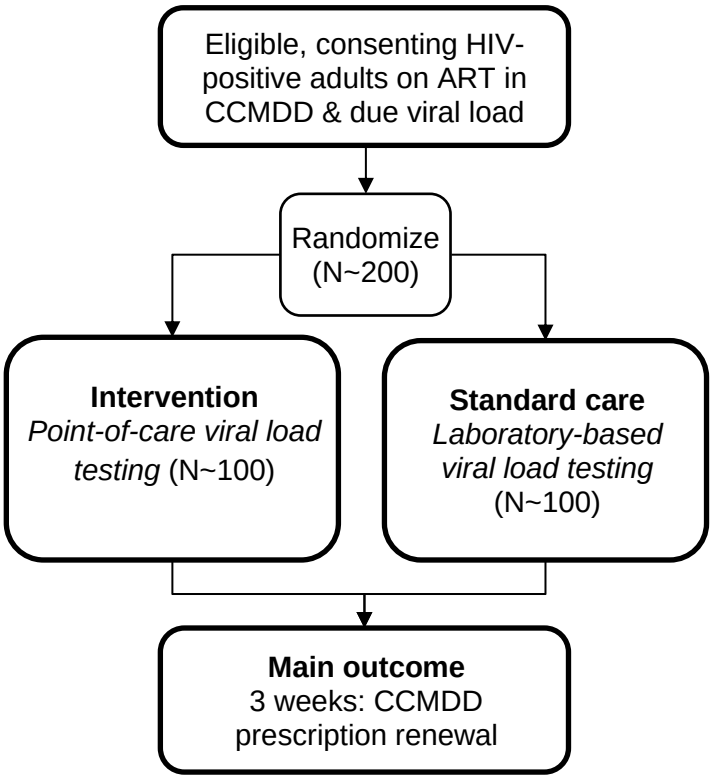
## 18. APPENDIX A: STUDY FLOW CHART



## 19. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

| | | Enroll | Outcome assessment | |
|---|---|---|---|---|
| **Weeks in study** | | 0 | 8 | 16 |
| **Informed consent** | | X | | |
| **Socio-demographics** | | X | | |
| **Medical History** | | X | | |
| **Vital signs +/- urine pregnancy test** | | X | | |
| **Eligibility screen** | | X | | |
| **Randomization** | | X | | |
| **POC Arm** | **POC viral load (4 mLs venous blood) & creatinine (1.2 µL finger-prick capillary blood)** | X | | |
| **SOC Arm** | **Lab viral load & creatinine (9 mL venous blood)** | X | | |
| **Optional storage blood and urine** | | X | | |
| **See clinic nurse for ART** | | X | | |
| **Outcome: Electronic CCMDD prescription renewal** | | | X | X |

POC: point-of-care, SOC: standard of care, ART: antiretroviral therapy

## 20. APPENDIX C: AMENDMENT HISTORY

| Amendment No. | Protocol Version No. | Date issued | Author(s) of changes | Details of Changes made |
|---|---|---|---|---|
| 1. | 1.1 | 10th November 2019 | Jienchi Dorward | Addition of Mrs Hope Ngobese and Dr Yukteshwar Sookrajh as co-investigators; addition of alternative, approved point-of-care assays that could be used in the study, instead of the Xpert HIV-1 VL; addition of optional extended follow up of participants routinely collected clinic data and vital status in the South African National Population Register; simplification of the description of procedures for invalid point-of-care results; change in the duration of blood storage from 2 to 10 years; addition of the potential evaluation of new point-of-care assays |

| | | | | |
|---|---|---|---|---|
| 2. | 2.0 | 10th November 2021 | Jienchi Dorward | Change of planned sample size to 'approximately 200'; change of primary outcome from CCMDD renewal at 12 to 3 weeks; change of assessment of secondary outcomes from 12 to 16 weeks to reflect changes in CCMDD; addition of time to ART collection in CCMDD as secondary outcome; replacement of patient flow outcome with cost of CCMDD renewal from patient perspective outcome; addition of the novel Xpert HIV-1 VL XC instead of the Xpert HIV-1 VL; addition of potential to use another site if necessary to complete recruitment; change in inclusion criteria to allow non-annual viral loads to be used; change in exclusion criteria to 'known pregnancy'; amendment of optional stored samples at enrolment to include urine, and to allow ART drug level, and HIV drug resistance testing. |