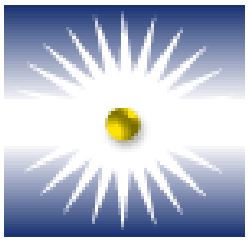


OraSure Technologies, Inc.
220 East First Street
Bethlehem, PA 18015

Clinical Investigation Protocol

A Controlled, Observational Trial of the OraQuick® Rapid HIV Self-Test Performance in Untrained Users

Protocol Number: OQHIV-OF-ST1

Version Date: Version 1, 18 August 2015

SPONSOR SIGNATURE PAGE

Protocol number: OQHIV-OF-ST1

Protocol Title: A Controlled, Observational Trial of the OraQuick® Rapid HIV Self-Test Performance in Untrained Users

Version Date: Version 1, 18 August 2015

The signatures of the representatives below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations stated in the protocol.

M. Roehler — 21 AUG 15
Michele Roehler, Director, Clinical Trials — Date

8/21/15
Graham Yearwood, Ph.D., Director, Research and Development — Date

Tiffany Miller — 24 Aug 2015
Tiffany Miller, Director, Regulatory Affairs — Date

8/24/15
Jose Rosado, Director, Quality Assurance — Date

HA Tempelman MD, MA, CEO Ndlovu Care Group — Date

W Devillé MD, DTMH, PhD, Scientific Coordinator Ndlovu Research Consortium — Date

SPONSOR SIGNATURE PAGE

Protocol number: OQHIV-OF-ST1

Protocol Title: A Controlled, Observational Trial of the OraQuick® Rapid HIV Self-Test Performance in Untrained Users

Version Date: Version 1, 18 August 2015

The signatures of the representatives below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations stated in the protocol.

Michele Roehler
Director, Clinical Trials

Date

Graham Yearwood, Ph.D.
Director,
Research and Development

Date

Tiffany Miller
Director, Regulatory Affairs

Date

Jose Rosado
Director, Quality Assurance

Date

HA Tempelman MD, MA
CEO Ndlovu Care Group

21 August 2015
Date

W Devillé MD, DTMH, PhD
Scientific Coordinator Ndlovu Research Consortium

21 August 2015
Date

INVESTIGATOR SIGNATURE PAGE

Protocol number: OQHIV-OF-ST1

Protocol Title: A Controlled, Observational Trial of the OraQuick® Rapid HIV Self-Test Performance in Untrained Users

Version Date: Version 1, 18 August 2015

The signature of the Principal Investigator, HA Tempelman MD, MA, below constitutes his approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations stated in the protocol.

HA Tempelman MD, MA
CEO Ndlovu Care Group

22 August 2015
Date

TABLE OF CONTENTS

Abbreviations

ADE	Adverse Device Event
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ARC	AIDS Related Complex
ARV	Antiretroviral
CI	Confidence Interval
CRF	Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
ENG	English Language
FDA	Food and Drug Administration
FN	False Negative
FP	False Positive
HCT	HIV Counselling and Testing
HIV	Human Immunodeficiency
ICH	International Conference on Harmonization
ID	Identification
OraSure	OraSure Technologies, Inc.
PrEP	Pre-exposure prophylaxis
RDT	Rapid Diagnostic Test
SA	South Africa
SAE	Serious Adverse Event
SOC	Standard-of-Care
SRS	Software Requirements Specification
STD	Sexually-Transmitted Disease
TN	True Negative
TP	True Positive
UADE	Unexpected Adverse Device Effect
US	United States

OraSure Technologies Inc. Sponsored Observational Trial Study Protocol
Protocol Number: OQHIV-OF-ST1

SPONSOR CONTACTS:

Director, Research and Development	Graham Yearwood, Ph.D. Ph. 1 484 353 1643 Email: gyearwood@orasure.com
Vice President, International Sales	Brian Reid Ph. 44 1491 639464 Email: breid@orasure.com
Director, Clinical Affairs	Michele Roehler Ph. 1 484 353 1658 Email: mroehler@orasure.com
Manager, Clinical Affairs	Mary Donadi Ph. 1 484 353 1663 Email: mdonadi@orasure.com

I. BACKGROUND

A. Summary

Acquired Immune Deficiency Syndrome (AIDS), AIDS related complex (ARC) and pre-AIDS are thought to be caused by the Human Immunodeficiency Virus (HIV). The first AIDS-related virus, HIV-1 (also known as HTLV-III, LAV-1 and ARV) has been isolated from patients with AIDS and from healthy persons at high risk for AIDS. Genetic analysis of HIV-1 isolates has documented the existence of subtypes. To date, eight HIV-1 subtypes (A through H), designated as Group M, have been identified world-wide in addition to the highly divergent HIV-1 isolates from AIDS patients in Cameroon, designated as Group O. A closely related but distinct second type of pathogenic human immunodeficiency retrovirus, designated HIV-2 (formerly LAV-2), has been isolated from West African patients with AIDS. HIV-2 has been shown to share a number of conserved sequences with HIV-1, but serological cross-reactivity between HIV-1 and HIV-2 has been shown to be highly variable from sample to sample.

HIV is known to be transmitted by sexual contact, by exposure to blood (including sharing of contaminated needles and syringes) or by contaminated blood products or it may be transmitted from an infected mother to her fetus during the prenatal period. Individuals infected with HIV produce antibodies against HIV viral proteins. Testing for the presence of antibodies to HIV in bodily fluids (e.g. blood, oral fluid, and urine) is an accurate aid in the diagnosis of HIV infection. However, the implication of seropositivity must be considered in a clinical context. For example, in neonates, the presence of antibodies to HIV is indicative of exposure to HIV, but not necessarily of HIV infection, due to the acquisition of maternal antibodies that may persist for up to eighteen months. Conversely, absence of antibody to HIV cannot be taken as absolute proof that an individual is free of HIV infection or incapable of transmitting the virus. An antibody response to recent exposure may take several months to reach detectable levels. HIV has been isolated from asymptomatic, seronegative individuals presumably before seroconversion following exposure.

The standard HIV testing algorithm used in South Africa consists of a number of approved HIV Rapid Diagnostic tests used in series; i.e.

a screening test, a confirmatory test and a tie breaker. The OraQuick® Rapid HIV-1/2 Antibody Test is a point-of-care test to aid in the diagnosis of infection with HIV-1 and HIV-2. The OraQuick® Rapid HIV-1/2 Antibody Test enables testing outside the clinical setting without producing hazardous medical waste as the test will be performed with oral fluids.

OraSure Technologies, Inc. (OraSure) and Ndlovu Care Group have discussed making the OraQuick® Rapid HIV-1/2 Antibody Test available for self-test. The current protocol "A Controlled, Observational Trial of the OraQuick® HIV Self-Test Performance in Untrained Users" is intended to evaluate the ability of untrained user to use the OraQuick® Rapid HIV-1/2 Antibody Test in a user friendly package called the OraQuick® Rapid HIV Self-Test.

B. Study Overview

The current study will compare results of untrained users who obtain the self-test result as determined by concurrent trained user testing. The main purpose in undertaking this trial is to evaluate the ability of untrained users to conduct the test. The methodology selected for this evaluation is a controlled, observational trial to be conducted in an investigative site that is capable to perform testing with the professional use OraQuick® Rapid HIV-1/2 Antibody Test. All devices in the study will be used from the same manufacturing batch. The comparator is the trained user utilizing the test device from the same batch, but labeled OraQuick® Rapid HIV-1/2 Antibody Test. This study is specifically designed to examine the performance of the OraQuick® Rapid HIV Self-Test when used by untrained users.

This protocol provides for a controlled trial in English, Northern Sotho and Zulu speaking study participants to verify the adequacy of the packaging and labeling for the OraQuick® Rapid HIV Self-Test to direct sample collection, test performance, and reading and interpretation of test results. In this study, up to 2000 untrained users of unknown HIV status will be enrolled. Study participants will be asked to use the OraQuick® Rapid HIV Self-Test product with oral fluid and to interpret their result, after which they will be tested by trained users at the investigative site using the matched batch OraQuick® Rapid HIV-1/2 Antibody Test with oral fluid.

Results of the untrained user will be compared to those of the trained user.

C. Device Description OraQuick® HIV-1/2 Self-Test Packaging and Devices for Study

1. Investigational Device - OraQuick® Rapid HIV-1/2 Self-Test

The OraQuick® Rapid HIV-1/2 Antibody Test is a visually read, qualitative, *in vitro* lateral flow immunoassay for the detection of antibodies to HIV-1 and HIV-2. The device is currently approved for use with oral fluid specimens, whole blood specimens collected either by venipuncture or fingerstick phlebotomy and plasma specimens. The OraQuick® Rapid HIV Self-Test is the same product as the current commercial test - OraQuick® Rapid HIV-1/2 Antibody Test- with an additional users' pamphlet.

OraSure Technologies, Inc. has developed packaging and labeling specifically designed for the OraQuick® Rapid HIV-1/2 Antibody Test in a self-test environment. This packaging is the result of a development effort incorporating investigator feedback and data collected during investigations of self-test accuracy and linkage into care. The package includes a specific step-by-step instructions and a device stand. This is currently referred to as the "OraQuick® Rapid HIV Self-Test". The actual device and developer vial are not different from the current approved device. The difference is in the packaging and labeling which were specifically designed for consumer use. The packaging and labeling of this product configuration is included under the Appendices to this protocol. The prototype packaging, along with the instructions for reading and interpreting the results and all accompanying materials, will be used as the investigational device in this trial.

2. Comparator Method – Matched Batch OraQuick® Rapid HIV-1/2 Antibody Test by Trained User

The comparator method for determination of the investigational product performance will be the same test from the same batch of the OraQuick® Rapid HIV 1/2 Self-Test devices, labeled as OraQuick® Rapid HIV-1/2 Antibody Test, performed by the trained user with oral fluid.

The comparison made is between the untrained and the trained user utilizing the same test from the same batch, in their respective packaging.

D. Summary of Known Benefits and Risk

It is generally accepted that the benefit to the subject of knowledge of their HIV status is high. There is low physical risk associated with the use of the OraQuick® device. Eligible study participants will be those with unknown HIV status in the age group 18 to 49 years. The study is intended to identify 100 evaluable study participants newly diagnosed with HIV infection. In the case of a newly identified preliminary positive HIV result, the benefit to the subject would be in determining their HIV status, and referral into appropriate clinical care, as applicable.

Overall, the primary benefit associated with this study is to gain information to support a self-test approval.

There is no additional risk anticipated to pregnant women or their fetuses.

E. Literature and Data Relevant to the Trial

1. HIV Testing Trends

The percentage of people who tested for HIV in the 12 months preceding the South African National HIV Prevalence, incidence and Behaviour Survey in 2012 (Shisana et al., 2014) had increased compared to 2008. However, sex differences are apparent. Most promisingly, the increase in HIV testing occurred equally as a doubling of numbers for both sexes was observed (from 19.9% in 2008 to 37.5% in 2012 among males and from 28.7% in 2008 to 52.6% in 2012 for females). The observation that more females than males are aware of their HIV status may be due to the additional effect of the PMTCT (Prevention of mother-to-child transmission for HIV) programme. The significant increase in HIV testing can be partly attributed to the HCT national campaign roll-out undertaken by SANAC from April 2010 (UNAIDS, 2013). About 3.5 million people participated in the HIV Counseling and Testing (HCT) campaign. South Africa is among the few countries in the world that has achieved such success with HCT during the past few years. South Africa's neighbour, Botswana, started routine provider-initiated HCT in 2004, and by 2008 had achieved near parity between the two sexes

(with 61.5% for females and 59.0% for males) in terms of testing for HIV and having received the results of such testing in the last 12 months. Although South Africa started provider-initiated HCT four years later and had very low rates of testing in 2008, it is now showing progress as mentioned above: 37.5% among males and 52.6% among females in 2012.

The 2012 survey found that nearly two-thirds of respondents (65.5%) indicated that they had ever been tested for HIV. Two thirds (66.2%) reported that they were tested in the previous 12 months before the survey (Shisana et al., 2014). Both findings show that the country has among the highest levels of HIV testing in any country at national level. The national HCT campaign in South Africa has been largely credited for the success in getting over two million people onto ARV treatment to date (UNAIDS, 2013).

Overall, it was found that there was a large proportion of the general population that believed they were personally at low risk of HIV infection. Perceiving oneself to be at a lower risk of HIV infection is associated with lower HIV testing rates.

F. Study Compliance Statement

This trial will be conducted in compliance with general requirements of / and ethical principles of:

- World Medical Association Declaration of Helsinki
- International Conference on Harmonisation. Guidelines for Good Clinical Practice (ICH GCP)
- Applicable national ethics and regulatory requirements
- Guidelines of Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa

II. STUDY OBJECTIVES

The primary objective of this study is to evaluate the ability of untrained users to correctly interpret their own results using the OraQuick® Rapid HIV Self-Test with oral fluid compared with results obtained by trained users using the matched batch OraQuick® Rapid HIV-1/2 Antibody Test, also with oral fluid. Study participants will be eligible in the age group 18-49 years of age with unknown HIV status selected within the communities of Moutse, Sekhukhune District, Limpopo Province.

III. STUDY DESIGN

A. Type of Study

This is a controlled study, conducted in two parts, evaluating the performance of the OraQuick® Rapid HIV Self-Test by untrained users through observation (Part 1), and comparing the untrained users' test results to those obtained by clinical staff and trained counselors using the same test, labeled OraQuick® Rapid HIV-1/2 Antibody Test from the same batch with oral fluid (Part 2). Each participant will enroll and complete both parts of the trial in a single day. In Part 1, the proportion of correct performance for each usage step will be evaluated. The comprehension of the use of the device, interpretation of results and reaction will be determined by direct observation along with interview and questionnaire. In Part 2, the proportion of study participants' interpretation of their self-test which is confirmed by the control testing by the trained user will be determined.

B. Populations for Study

1. Study Enrollment Populations

Up to 2000 study participants will be enrolled from the community of Moutse, Sekhukhune District, Limpopo Province in the age group of 18-49 years. Study participants selected are unaware of their HIV Status. The community selected lies in the environment where Ndlovu Care Group has established itself in the early 1990's. It is an area of high HIV prevalence in a rural community.

Disposition of Enrolled Study Participants into Sensitivity and Specificity Analysis Populations

The trained user's oral fluid test result will be the basis for determination of eligibility for inclusion of the study participant's data in either the Sensitivity Analysis Population, or the Specificity Analysis Population. This is fully described in Section VII.C.1. Enrollment will close when 100 evaluable study participants have been newly identified as HIV positive. Because of the estimated prevalence rates of 9.4% and 14.1% in Limpopo and Mupalanga Provinces respectively and response rates under possible HIV+ persons, it is expected that the sample size for the final Sensitivity Analysis and Specificity Analysis Populations will be somewhat

lower than 2000 study participants based upon eligibility for inclusion in those populations

C. Plan of the Study

Up to 2000 study participants of unknown HIV status will be enrolled. Evaluation of product performance for efficacy will be done separately for sensitivity and specificity.

All enrolled study participants will voluntarily provide informed consent and undergo study procedures and provide the specimens required under Study Procedures on the study day (Day 1) for testing with the OraQuick® Rapid HIV Self-Test performed by the untrained participant and compared with the result of the trained counsellor.

In the event of an HIV reactive OraQuick® test, HIV status will be confirmed using the standard RDT testing algorithm in use in the testing centers - ABON™ HIV 1/2/O Tri-Line Human Immunodeficiency Virus Rapid Test. In the event that this confirmatory rapid test is HIV positive as well, the study participant will be referred to a clinical site for further diagnosis, treatment and care. In the event the second rapid test shows a negative result, the HIV status will be considered indeterminate, a blood sample will be drawn and the study participant will be referred to a clinical site for the results of the HIV ELISA test and clinical follow-up. The clinical site connected to the research center is Ndlovu Community Health Centre in Elandsdoorn, Limpopo, a well experienced ARV treatment site with over 3600 HIV patients on treatment.

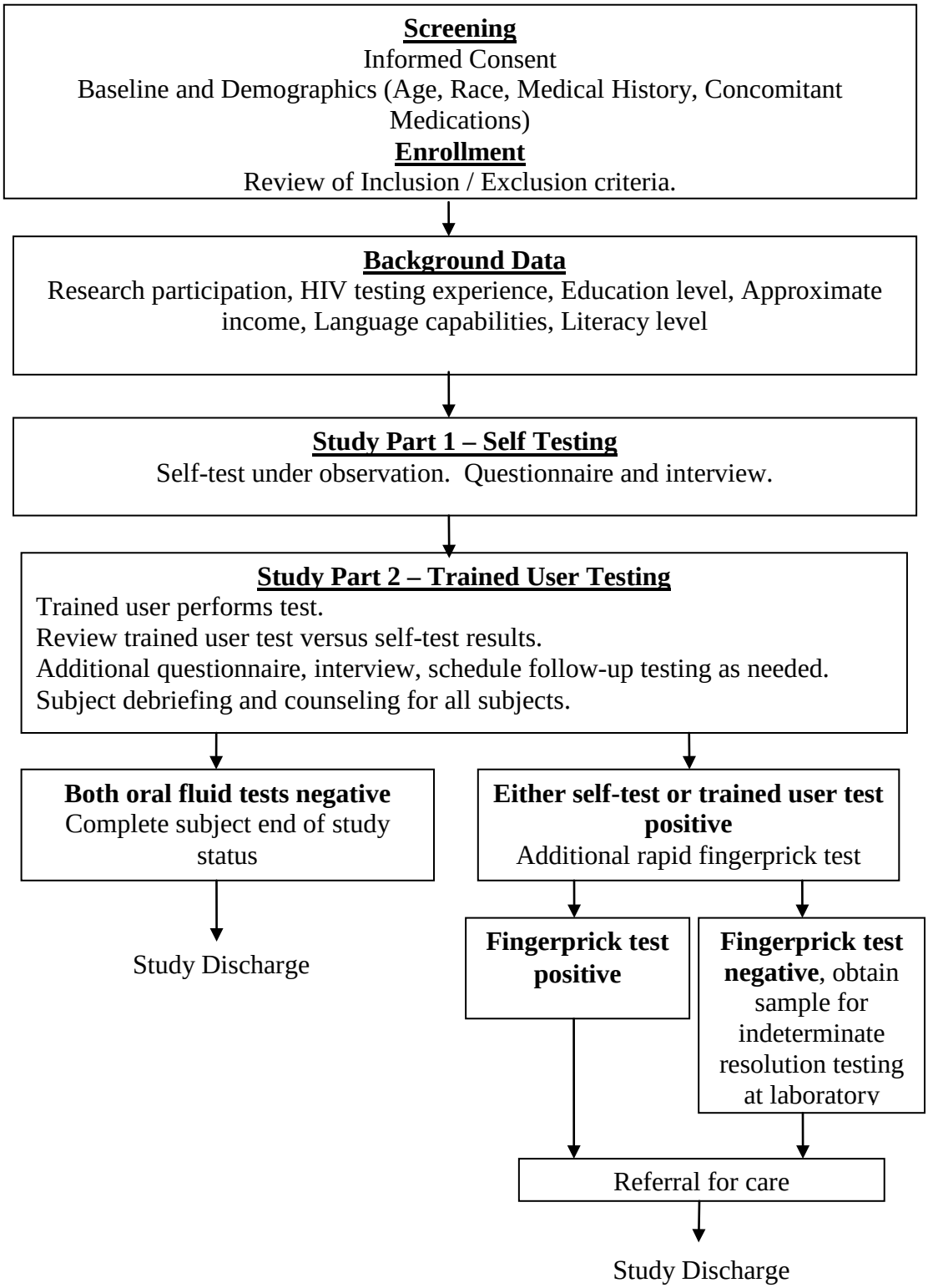
Activities in the plan of study include:

- Screening and informed consent, baseline data
- Enrollment
- Study Part 1: Evaluation of adequacy of proposed labeling and device use as rated by trained observers of study participant self-testing
- Study Part 2: Collection and procession of oral fluid testing by trained user
- Rapid ABON fingerstick test for each participant testing positive by OraQuick® test (participant and/or trained user)
- Subject debriefing / counseling based upon results of rapid testing

- Blood specimen for confirmatory testing, as required and described above
- Counseling (immediate for newly identified preliminary positive study participants) and adequate referral into follow-up care
- Discharge from study

The overall plan of the study is represented in the following figure. Each subject will participate in two parts. Following recruitment, informed consent and review of inclusion and exclusion criteria, study participants may be enrolled in the trial.

Figure III.1. Study Plan Schematic



D. Blinding and Randomization Procedures

This will be a blinded study. Study participants will not be aware of the results of the trained user's testing while they are performing and interpreting their own self-test. In addition, the trained user who reads the current commercial test from the same batch will be blinded to the subject's self-test result. There will be no randomization, as all study participants will have testing with the the same test from the same batch done.

E. Study Sites

Ndlovu Care Group primary serving area, Moutse Sekhukhune District Limpopo Province will serve as the Investigative Site which will direct all study-related procedures that will take place in the field. In an effort to enroll study participants from the enrollment population, the study site makes provision for adequate referral as an adequate high quality community health center (clinic, pharmacy, laboratory, X-ray, etc.) experienced in HIV screening, diagnosis, care and treatment forms part of Ndlovu Care Group's service delivery in Moutse. The Principal Investigator and the staff will have appropriate training and experience in using the currently marketed OraQuick® Rapid HIV-1/2 Antibody Test. The participating site has the ability to comply with all local government requirements for HIV testing and reporting. All oral fluid specimens will be collected under the supervision of the study site Principal Investigator or his/her designee. Collection and testing for the study Part 2 using the current marketed OraQuick® Rapid HIV-1/2 Antibody Test will be performed by trained staff responsible to the Principal Investigator.

A local Principal Investigator will be utilized in this trial. The Investigator responsible for the conduct and oversight of the trial is:

Name Dr HA Tempelman MD, MA
Institution Ndlovu Care Group
Address POBOX 1508 Groblersdal 0470 South Africa

The sponsor has delegated aspects of responsibility to the Principal Investigator in staff training, quality control, data management, statistics, and reporting of results. Protocol design and authorship was collaborative effort between the sponsor and Principal Investigator.

F. Laboratory

Any study participant who has a preliminary positive result (reactive) with either self-testing or with trained user testing will require a second Rapid test to be performed on –site. If this test results in HIV positive as well, the patient will be referred to the clinical site for further management and initiation of treatment and care.
If the results are indeterminate blood will be drawn for HIV ELISA confirmation and the study participant will be referred to the clinical site where counselling and adequate follow up will take place.

The results of the standard laboratory testing will be provided to the Investigative Site and are the sole basis of determination of the study participants' HIV status for clinical follow-up purposes. For study participants with newly-diagnosed HIV infection, referral into clinical follow-up is to be conducted as described under Sections III.L and IV.L of this protocol.

G. Study Endpoints

The study endpoints for this trial are the binomial proportion and the exact 95% confidence interval of the proportion for concordance of study participants' oral fluid self-test results with the trained user oral fluid test results.

H. Selection and Withdrawal of Study participants

Subject's eligibility to enroll will be based upon inclusion and exclusion criteria and the signing of informed consent.

Study participants may voluntarily withdraw participation from the study at any time. Information collected prior to withdrawal from the study may be used for research by the investigator and/or the sponsor unless the study participants provide a written request to limit the use and sharing of their study data. Investigator(s) may separately determine if participation by any subject in this study may be limited or be withdrawn. The sponsor may close the study prematurely for any reasons including administrative decisions.

1. Inclusion/Exclusion Criteria

Study participants for the trial will be recruited from the enrollment populations as described in Section III.B. The requirements for inclusion/exclusion are as follows:

Inclusion Criteria

Study participants considered eligible for inclusion are those who:

1. Are male or female study participants of any race, not proportioned by gender or race.
2. Are of unknown HIV status (have not been tested for HIV in the previous six months).
3. Are at least 18 years of age and no more than 49 years of age.
4. Read and understand English, Northern Sotho or Zulu.
5. Are able to provide Informed Consent in English, Northern Sotho or Zulu.
6. Agree to provide accurate medical history, required specimens of oral fluid, and up to 20 mL of blood by venipuncture if needed.
7. Agree to undergo testing with the OraQuick® tests and an additional HIV Rapid test using capillary blood/finger prick testing.
8. Among the female study participants, pregnant women will be allowed to enroll in the study.

Exclusion Criteria

Study participants considered to be ineligible for participation in the trial are those who meet **any** of the following exclusion criteria:

1. Are known HIV positive
2. Are sponsor or investigator-site employees or immediate family members of sponsor or investigator site.
3. Are trained users with the OraQuick® Rapid HIV-1/2 Antibody Test.
4. Are personnel of HIV outreach or counseling/testing center (or other facilities that perform HIV testing).
5. Have received any experimental HIV vaccine.
6. Are currently on a PrEP regimen or any ARV medication.
7. Have participated in any prior, or concurrent trial of HIV self-tests.
8. Are in the judgment of the investigator unable to complete the study or are unlikely to comply with the study protocol.

2. Withdrawal of Participants

Study participants may withdraw from participation at any time. The investigator will attempt to acquire all study-related information, and the reason for discontinuation (e.g., withdrew consent, adverse event, etc.) will be documented in the subject enrollment log. Information and data collected up to the time of study participant's withdrawal from the study may be used without identifying any personal information, consistent with the informed consent signed for enrollment, unless the study participant provides a written request to limit the use and sharing of their study data.

I. Specimen Collection

All enrolled study participants will be asked to provide specimens as described below:

1. Oral Fluid Specimens (oral mucosal transudate)

Part 1: One oral fluid collection will be self-sampled by the subject using the OraQuick® Rapid HIV Self-Test device. The actual device for the collection is the same as the commercial OraQuick® Rapid HIV-1/2 Antibody Test.

Part 2: One oral fluid sample will be collected from the subject by the trained user using the OraQuick® Rapid HIV-1/2 Antibody Test. This collection is to be done following completion of all study Part 1 procedures.

2. Fingerstick Whole Blood

In the event of a reactive result for an OraQuick® test, an additional rapid test - ABON™ HIV 1/2/O Tri-Line Human Immunodeficiency Virus Rapid Test- will be administered on-site.

3. Blood Specimens (venous blood)

Whole blood will be obtained by the study site personnel for HIV confirmatory testing at the laboratory from study participants in the event of indeterminate HIV status from rapid testing. A maximum of 20 mL of blood may be drawn.

J. Specimen Handling and Analysis

Oral fluid specimens will be handled according to the information included in the packaging and information for both the self-test and current professional use products. Whole blood specimens will be handled and transported according to the instructions provided by the clinical laboratory.

K. Informed Consent Form

Informed Consent must be obtained before study participants are allowed to participate in the trial. This Informed Consent form must contain the required elements according to ICH E6 4.8 and be approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

The Principal Investigator or his/her designated staff will provide the Informed Consent for participation in this study to the subject or subject's legally acceptable representatives, explain the nature of the study, and answer any questions that might arise. The Informed Consent will contain general information about the study as well as specific information regarding the samples to be collected. Study participants will be consented prior to conducting any study-related procedures. The last page of the Informed Consent will have the appropriate signature lines that need to be filled out to complete the Informed Consent process, facilitating enrollment. Study participants will be instructed that they may stop the specimen collection procedure and withdraw from the study at any time.

L. Follow-up for Unexpected Results

Any preliminary positive test result in a subject by either the trained user or the study subject (as confirmed by a trained user) and confirmed by the second rapid fingerprick test, will be treated as a clinically positive result. The study staff will provide counseling to the subject at study prior to the subject leaving the site. For any subject with a preliminary positive result from any test, the study staff will provide counseling to the subject regarding the meaning of their result, in accordance with current guidelines. The sample for HIV status resolution will be obtained, and the referral into follow-up is to be scheduled to occur as soon as possible. Referral into clinical follow-up based upon the results of this testing is the responsibility of the site Principal Investigator. The site Principal

Investigator is also responsible to comply with all local regulations regarding the reporting of newly-identified HIV positive individuals.

M. Confidentiality

Study participants' study data will be maintained in a confidential manner at the study site to protect the privacy of the study participants. The informed consent form will indicate that all participant names and personal contact information will be kept confidential and that any data reported to the Sponsor or the Ministry of Health will be linked to a participant number and their initials, and date of birth.

IV. STUDY PROCEDURES

Following a screening period which may occur earlier, all study evaluations for a given study participant will take place on a single day. Under the controlled observational setting, their ability to read the device will be evaluated and their interpretation of results recorded. Questionnaire and interview techniques will be used to further assess comprehension and performance. Following this, the trained user at the study site will perform oral fluid testing. Table IV.1 provides details of the study procedures.

Table IV.1 Schedule of Study Procedures and Events			
Study Activity / Procedure	Study Day Activities		
	Enrollment	Self-Testing Period Under Observation	Trained User Testing
Informed consent	X		
Enrollment questionnaire	X		
Demographic data	X		
Background data	X		
Medical history	X		
Concomitant medications	X		
Dispense test device		X	
Study participant self-testing		X	
Participant self-reported outcomes questionnaire		X	
Observational ratings of participant self-test performance		X	
Trained user interpretation of participant's self-test			X
Trained user collection of oral fluid and independent trained user running and interpreting the sample (trained user result)[†]			X
Comparison and documentation of trained user and self-test results			X
ABON rapid test (fingerprick) in event of reactive test result by participant and/or trained user			X
Debriefing / counseling of study participants based on rapid test results.			X
Venous blood sample for confirmatory laboratory testing in the event of indeterminate rapid tests.			X
Refer HIV positive and HIV indeterminate into clinical care and follow-up			X
Adverse event reporting		X	X
Discharge from study			X
Administrative follow-up for newly detected infection, based on governing requirements for health authority reporting [‡]			X
Complete end-of-study status			X

[†] The trained user collecting this sample will be the user interfacing with the study participant. The test will be run and read by an independent trained user who is blinded as to the results of the study participant's self-test.

[‡] Follow-up for compliance with mandatory reporting

A. Recruitment

Participants for this study will be recruited in using several methods. Study participants will be recruited from the study center conducting HIV screening in this high prevalence population (9 – 14%) covered by the Ndlovu Medical Clinic with a radius of 30km, Recruitment will involve in-person screening. Additional recruitment methods will be utilized as outreach activities within the community at community events and at the local Mall, where will be tested on the spot. A mobile unit is available with two testing compartments Recruitment materials, including potential advertising, will be approved by the IRB/IEC prior to use. If qualified and interested, these participants can also be scheduled and directed to the clinical research site.

B. Informed Consent

This study is subject to ICH E6 GCP regulations, Guidelines of Good Practice in the conduct of Clinical Trials in Human Participants in South Africa and informed consent is required. All study participants must provide informed consent in order to participate in the trial. The informed consent will include that the subject will be performing an HIV test on themselves, and that a trained person will also be performing the same test on them. Because of this, the informed consent process will disclose the type of test and the testing to be performed. The informed consent will be available in English, Zulu and Northern-Sotho/Sepedi.

C. Enrollment Questionnaire - Review of Inclusions / Exclusion Criteria

An enrollment questionnaire will be administered to each subject to determine whether or not they meet the inclusion/exclusion criteria, and therefore, qualify for participation in the study. This will also serve as the source of data for some demographic variables. All questionnaires will be available in English, Zulu and Northern-Sotho/Sepedi. The enrollment questionnaire will gather information on:

- Age
- Experience with HIV testing
- Education level
- Race and ethnicity
- Visual status

- Reading impairment
- Language capabilities
- HIV Status

Upon satisfaction of inclusion / exclusion criteria and informed consent, each subject will be assigned a unique study ID number (study participant number). The enrollment information including subject initials, date of birth, date of informed consent, subject study number, and date of enrollment will be documented on a screening and enrollment log. Study participants not meeting inclusion / exclusion criteria after providing informed consent will be considered to be screening failures.

D. Demographic Data

For all study participants meeting inclusion / exclusion criteria, demographic data to be documented at will include:

- Initials
- Date of birth (age will be computed)
- Race: Zulu, Ndebele, other
- Gender: Male, Female

E. Background Data

For all study participants meeting inclusion / exclusion criteria, background data to be documented will include:

- Experience with HIV testing
  - Date of last HIV test (approx.)
- Education level
  - None
  - Completed Primary School
  - Completed Matric
  - Completed College / Technician
  - University
- Language capabilities
  - Claimed ability to read, speak and understand English
  - Claimed ability to read, speak and understand Zulu
  - Claimed ability to read, speak and understand Northern-Sotho/Sepedi
- Health Literacy
  - Inadequate
  - Marginal

- Adequate

F. Medical History / Oral Health

For all study participants meeting inclusion / exclusion criteria, their self-reported medical history will be obtained and documented. In addition to any self-reported medical conditions, specific medical conditions will be queried, in particular the study participant's HIV status. Data to be documented will include:

Medical History

- Self-reported HIV status.
  - Unknown, never tested
  - Unknown, previously tested negative at least six months prior. The date and location of testing along with the type of test is to be recorded, if known.
  - HIV positive.
- Self-reported medical conditions (e.g. diabetes, etc.).
  - Any medical condition that the subject currently reports, and the date of diagnosis. Study participants' self-report will serve as the source of these data and verification in medical records is not required.
- Pregnancy status for female study participants.
  - Pregnant, not pregnant
- Self-reported Ocular health / visual impairment.
  - Requirement for, and current use of, glasses or contacts
  - Any condition that specifically affects vision (besides the need of glasses or contacts, (e.g. macular degeneration, etc.))

Oral Health

- Responses to specific oral health questions.
  - Specific presence or absence of oral health conditions
    - Cavities and/or fillings
    - Braces
    - Periodontal disease and/or bleeding gums
    - Oral fixtures; full or partial dentures
  - Specific last use of oral products, food and drink
    - Last food and/or beverage consumption
    - Tooth paste
    - Mouthwash or oral rinse
    - Smoking or smokeless tobacco

G. Concomitant Medications

For all study participants meeting inclusion / exclusion criteria, their self-reported current concomitant medications will be obtained and documented. Data to be documented throughout the study will include:

- General concomitant medications, and herbal or dietary supplements, including the product name, dosage, and duration of use over the previous one year.
- Vaccines, including the product name if known, the reason for the vaccination (e.g. influenza).
- Immunotherapy (e.g. allergen injections).

H. Dispensing and Return of the Investigational Device

One OraQuick® Rapid HIV Self-Test will be provided to each subject who qualifies for self-testing. At the conclusion of all testing (both self-testing and trained user testing), the used devices will be collected by the study staff and discarded in accordance with local requirements at the site.

I. Subject Self Testing

Study participants will be instructed to perform the self-testing using the OraQuick® Rapid HIV Self-Test. The self-testing is to be completed under the direct observation of the study staff. The study staff will verbally instruct the subject as follows;

"*This is the part of the study in which you will be asked to use the study product. With this product and the instructions provided, you can perform the test yourself. I will not be able to answer any questions or talk to you while you are using the product, but I will be looking to see how you use it. When you are finished, we would like you to tell us what you think the test result is. I will then collect another sample and another staff person will perform the same type of test we use in the clinic to see if your self-testing result is correct or not.*"

The subject will then be permitted to perform the self-test.

J. Observations and Verification of Subject Self-Testing

The subject self-testing will be performed in an environment that is conducive to self-testing and provides privacy. Study participants must self-test singly, without the ability to see or hear another

subject either prior to or during the test. The room for subject self-testing must minimally provide for the following:

- Privacy from other study participants, or study staff other than the staff performing observations
- Seating
- Counter, desk, or other space to place the test kit
- Adequate lighting, with the ability for the subject to control lighting
- An obvious manner to measure time (wall clock, desk clock)

Dependent upon the study sites' physical layout, the clinical staff observing the study participant may or may not be visible to the subject. In any case, the staff is not to interact with the subject during testing, unless intervention is required for a study participants' wellbeing or privacy. During the study participant self-testing, the study staff will collect the following observational data for correct performance of the test. These ratings will be collected as the Observational Ratings of Self-Test Performance. In addition, questionnaire and interview-based data will be collected. Data that will be collected are described in this section.

1. Observational Ratings of Study Participant-Self Test Performance

- Did the study participant read the information sheet?
- Was it difficult for the study participant to remove the contents of the test pack?
- Was the study participant able to find the test tube packet?
- Did the study participant remove the test tube from the packet?
- Did the study participant remove the cap from the test tube?
- Did the study participant place the test tube in the holder?
- Did the study participant have any difficulty with the test tube (specify if "yes")
- Was the study participant able to find the test stick packet?
- Did the study participant remove the test stick from the packet?
- Did the study participant touch the flat pad?
- Did the study participant collect the sample correctly (1x upper and lower swab)? If no, specify

- Did the study participant place the test stick in the test tube correctly? If not, specify
- Record test developing start time.
- Record time of study participant reading test.
- Record time study participant concludes they have completed the test.
- Study participant's apparent level of distress:
    - Calm
    - Appears anxious
    - Verbally communicates distress
    - Staff intervention required

After the study participant has completed the self-testing they will be requested to provide their result to the staff. This will be followed by a staff interview.

2. Trained User's Interpretation of Study Participant's Self-Test Result and Interview Questions

Following the completion of the study participant's self-testing interpretation, one trained user will make their own interpretation of the study participant's test result. This should be the trained user who observed the study participant's self-test. Data to be collected are:

- The trained user's interpretation of the study participant's self-test.

The trained user's interpretation of the study participant's self-test is intended to serve two purposes. The primary reason is to determine if confirmatory testing is warranted based upon the result of the study participant self-test. The need for confirmatory testing for clinical resolution is based on the trained user's interpretation of either the study participant's self-test or the trained user's test being positive. Secondarily, this will allow for review of the data regarding study participants' potential failure to obtain a result versus incorrect interpretation of the result they do obtain. In the case of a truly invalid test by the study participant, the test will not be repeated. The trained user who observes the study participant and interprets their self-test will be independent from the trained user who will interpret the reference result by the current commercial matched batch OraQuick Rapid HIV-1/2 Antibody Test in Part 2 of the study. An independent trained user who is unaware

of the study participant's self-test result or their HIV status will interpret the testing to establish the independent trained user result as described under Part 2 of the Plan of the Study (Section III C.)

In study Part 1 the observing trained user will also review the study participant's interpretation of their test. Any ambiguous answer will have one attempt made to clarify it. The trained user will question the study participant, as follows:

"I am not sure what you think your test result is. According to the product instructions, can you please tell me what you think the result of your test is?"

The study participant's response will be interpreted by a check box with five possible selections;

- Do not have HIV / negative
- May have HIV / preliminary positive
- Test not working / invalid
- Not sure / don't know
- Refused or ambiguous answer

K. Trained User Testing

An independent trained user, who is blinded to the study participant's self-test result, will repeat testing using the current commercial matched batch OraQuick® Rapid HIV-1/2 Antibody Test, according to the current package insert. In order to maintain blinding, the first trained user who observed the study participant self-testing will collect the oral fluid sample. The independent trained user will interpret this test. In the event that the trained user obtains an invalid result, they may repeat the test once.

L. Additional Procedures and Testing for Study participants with New Preliminary Positive Results

Any study participant who has a preliminary positive OraQuick® result, as determined by the trained user's interpretation of either the study participant's self-test or the independent trained user test, and/or confirmed by the 2nd rapid test will be counseled by the appropriate study staff regarding the meaning of their result. In case of indeterminate HIV status from discordant rapid test results, the study participant will have whole blood collected for additional clinical testing for serostatus resolution at the laboratory. The study participant will be requested to go to the clinical site to receive their

confirmatory testing results, post-test counseling and follow-up care, as applicable. This post-test counseling is to be conducted consistent with current guidelines. The investigator will refer into clinical follow-up for all newly-diagnosed HIV study participants. The site Principal Investigator will also be responsible for compliance with all local requirements regarding the reporting of newly-identified HIV positive individuals. In addition, the Principal Investigator may institute any additional precautions which are in their judgment warranted based upon individual study participant safety.

M. Additional Procedures for Study Participants with Negative Results

1. Post-Test Counseling

Any study participant who has a negative OraQuick® result, as determined by the trained user's interpretation of both the study participant's self-test and the independent trained user test, will be counseled by the appropriate study staff regarding the meaning of their result. Study participants will be questioned regarding their intention for future testing.

2. Intention Questionnaire

Three questions will be used to gain information on the study participant's expectations for HIV testing and potential for use of a self-test if available. Each question will be answered using a scale of 1 to 4, with 1 "not at all likely" to 4 "definitely"

- How likely are you to get tested for HIV again, at a clinic or other center?
- When a rapid HIV home test becomes available as a self-test, how likely are you to use it to test yourself?
- When a rapid HIV home test becomes available as a self-test, how likely are you to use it to screen sexual partners?

V. QUALITY CONTROL AND QUALITY ASSURANCE

A. Trained User Responsibilities

Identified "trained user" personnel will perform the testing using the OraQuick® Rapid HIV-1/2 Antibody Test as well as interpret the results of the subject's self-test using the OraQuick® Rapid HIV Self-Test. The site will provide trained technicians who will be responsible for running, interpreting, and documenting the results of the

OraQuick® Rapid HIV-1/2 Antibody Test for trained user testing and for interpreting the study participants' self-test results. During the study conduct, the trained user who runs and interprets any given study participant's trained user test must be independent of the study participant's self-testing procedures and results. In this manner the trained user result is blinded from the study participant's own result or the study participant's reaction to that result. All trained technicians will have received appropriate training that covers study procedures as well as instructions for performing the test before the study begins. The training will include a pilot tryout of testing a participant. OraSure Technologies, Inc. will provide all test kits for use in this study. Investigators are responsible to ensure correct use of devices and interpretation of results. Per the study protocol, commercial kit controls as per package instructions and local requirements.

B. Study Monitoring

The study will be monitored by Clinical Trials Department personnel at OraSure Technologies, Inc or a Sponsor delegate. The monitor will routinely visit the site to assess study status and review study procedures and applicable documents. Applicable documents may include subject clinical records. The study will be monitored according to and in accordance with ICH E6: Guidelines for Good Clinical Practice.

The teams of counsellors will also be monitored weekly by the principal investigator/project manager through a (bi-)weekly joint meeting to discuss progress and to resolve possible problems encountered. The quality of the data collection and data entry will be monitored weekly by the project manager/data capturer on the informed consent forms, collected source documents and the database. Each team will be monitored for compliance during the first days of their implementation of the research and by regular unannounced visits.

VI. CHANGES IN PLANNED STUDY CONDUCT

Protocol modifications (amendments) must be prepared by the Principal Investigator responsible for the study reviewed and approved according to local authorities and IRB/IEC. With the exception of administrative changes, any modifications or additions to this clinical study protocol require a justified, written protocol

amendment that must be approved by the Principal Investigator, local authorities, and IRB/IEC. Amendments potentially affecting the safety of study participants, the scope of the investigation or the scientific quality of the study, as require approval. A copy of the written approval must be maintained by the Principal Investigator.

Examples of amendments requiring such approval are:

- A significant change in the study design.
- An addition or deletion of a test procedure for safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or the sponsor in the interests of preserving the safety of all study participants included in the trial. If an immediate change to the protocol is deemed necessary by the investigator and is implemented by him/her for safety reasons, the study Principal Investigator should be notified and the IRB/IEC should be informed within ten (10) working days.

VII. DATA MANAGEMENT AND STATISTICAL ANALYSES

A. Data Management

Data management will be provided by Ndlovu Care Group
Data will be collected on paper (questionnaires, observations, interview, test results, safety forms) and daily transmitted to the Ndlovu Research Centre. A data capturer will enter the data within a week in a electronic database developed by the Ndlovu Care Group. Data quality control will be performed bi-weekly by the epidemiologist.

B. Data Reporting

Data analysis and reporting will be performed by the epidemiologist. A research report will describe the study area, the study population, the execution of the research, and present the study results as mentioned under VII.C. Statistics. The report will discuss the outcomes of the study.

C. Statistics

1. Populations for Analyses

The analyses of safety and effectiveness will be conducted on distinct populations described below. If a study participant is excluded from an analysis population, the reason for exclusion will be described.

Primary Safety Population

The Primary Safety Population for analyses is all study participants enrolled. Adverse events will be captured and line listings provided. Any Serious Adverse Event or Adverse Device Event which may occur in a subject from this population will be reported.

Sensitivity Analysis Population

The primary Sensitivity Population is expected to result from study participants who have positive trained user results for the current OraQuick® Rapid HIV-1/2 Antibody Test using oral fluid. Study participants of unknown HIV status, with a confirmed positive self-test (by 2nd rapid finger prick test), but a false negative trained user test result will be excluded from the Sensitivity Analysis Population.

In a secondary analysis the Sensitivity Population is considered to result from study participants who have a positive 2nd rapid test result with ABON™ HIV 1/2/O Tri-Line Human Immunodeficiency Virus Rapid Test.

Specificity Analysis Population

The primary Specificity Population is expected to result from the disposition of study participants who have negative trained user results for the current OraQuick® Rapid HIV-1/2 Antibody Test using oral fluid. Study participants who have a postive self-test (indicating the need for confirmatory testing) and a negative trained user test result which is not confirmed (by 2nd rapid finger prick testing) will be excluded from the Specificity Analysis Population.

In a secondary analysis the Specificity Population is considered to result from study participants who have a negative 2nd rapid test result with ABON™ HIV 1/2/O Tri-Line Human Immunodeficiency Virus Rapid Test, or a negative untrained user result for the OraQuick® Rapid HIV Self-Test and a negative trained user result for the current OraQuick® Rapid HIV-1/2 Antibody Test using oral fluid, In case both the untrained or trained user results are positive while the 2nd rapid test is negative, the result is considered indeterminate and excluded from the specificity analysis.

The algorithms for inclusion of study participants in the primary Sensitivity Analysis Population and the primary Specificity Analysis Population based upon trained user test and confirmatory testing (if appropriate) are included in the following table.

Table VII.2 Algorithm for Inclusion in the primary Sensitivity Analysis and Specificity Analyses

Testing and Results	**Enrollment Populations**						
OraQuick® Rapid HIV Self-Test Study Participant interpretation	**Pos.**	**Neg.**	*Pos.*	**Pos.**	**Neg.**	**Pos.**	**Neg.**
OraQuick® Rapid HIV-1/2 AntibodyTest Trained user result	**Pos.**	**Pos.**	*Neg.*	**Pos.**	**Pos.**	**Neg.**	**Neg.**
Confirmatory testing result (2nd rapid test)	**Pos.**	**Pos.**	*Pos.*	**Neg.**	**Neg.**	**Neg.**	--
Inclusion in Sensitivity Analysis Population	**Yes**	**Yes**	*No*	**Yes**	**Yes**	No	No
Result for Sensitivity Analysis	**True Positive**	**False Negative**	*Excluded*	**True Positive**	**False Negative**	--	--

Testing and Results	**Enrollment Populations**						
Inclusion in Specificity Analysis Population	No	No	*No*	No	No	**Yes**	**Yes**
Result for Specificity Analysis	--	--	*Excluded*	--	--	**False Positive**	**True Negative**
Count as newly detected HIV infection criteria	Yes	Yes	*Yes*	No	No	No	No

2. Safety Analyses

The type and incidence of adverse events associated with the test or study procedures will be reported for the Safety Population. Adverse events may include adverse psychological events associated with the study procedures. Serious adverse events will be reported for all study participants enrolled. Newly identified infections, as such part of the data for analysis, would not be considered AEs. Follow-up information for study SAEs, will be documented as permitted by the Principal Investigator and the study participant's other medical care providers, within the constraints which safeguard the privacy of the study participants' medical information.

3. Efficacy Analyses

Primary Efficacy Analyses

The primary efficacy analyses will be separate analyses of sensitivity and specificity of study participants' self-test results with the OraQuick® Rapid HIV Self-Test versus the result obtained by the trained user with the matched batch OraQuick® Rapid HIV—1/2 Antibody Test using oral fluid. The proportion of study participants' interpretation of their self-test which is confirmed by the trained users' oral fluid testing, and thereby considered "true," will be determined following determination of study participant's data evaluability for inclusion in either the Sensitivity Analysis Population or the Specificity Analysis Population as described previously. The overall lower 95% confidence interval will be determined when:

- Sensitivity = [TP / (TP + FN)] x 100, where
  - TP (true positive) is positive oral fluid self-test in agreement with trained user positive oral fluid test, and
  - FN (false negative) is negative oral fluid self-test discordant with trained user positive oral fluid test.
- Specificity = [TN / (TN + FP)] x100, where
  - TN (true negative) is negative oral fluid self-test in agreement with trained user negative oral fluid test, and
  - FP (false positive) is positive oral fluid self-test discordant with trained user negative oral fluid test.

Secondary Efficacy Analyses

Secondary efficacy analysis will include descriptive statistics of the sensitivity and specificity analyses among various subgroups of each of the Specificity Analysis Population and the Specificity Analysis Population, including the following factors:

- Age.
  - 18 to 35 years
  - 35 years and above
- Language capabilities (self-reported).
  - English reading and speaking
  - Nothern-Sotho/Sepedi reading and speaking
  - Zulu reading and speaking
- Educational level.
  - Less than High School
  - Completed High School
  - Completed Matric
  - Completed College / Technical School
  - Completed University
- Literacy level
  - Inadequate
  - Marginal
  - Adequate
- Ocular health.
  - Need for glasses or contacts, or reported vision impairment
  - No reported vision impairment

Additional secondary efficacy analyses will include the descriptive statistics of the following:

- Observational Ratings of Study Participant Self-Test Performance (Section IV.M.1)
- Trained User's Interpretation of Study Participants Self-Test Result (Section IV.M.3)

These data will be summarized for all enrolled study participants and for the Sensitivity Analysis Population and the Specificity Analysis Population separately.

The rates of invalid tests will be evaluated in the untrained versus the trained users, as well as the rate at which the untrained users were unable to perform the test.

4. Demographics

The following will be summarized for aggregate enrollment population and for the Sensitivity Analysis Population and the Specificity Analysis Population separately.

- Demographic Data (Section IV.D)
- Background Data (Section IV.E)
- Medical History (Section IV.F)

VIII. SAMPLE SIZE

Enrollment will close when 100 evaluable study participants have been newly identified as HIV positive. Because of the estimated prevalence rates between 9.4% and 14.1% in Limpopo and Mupalanga Provinces respectively, and possible response rates under possible HIV+ persons, it is expected that the sample size for the final Sensitivity Analysis and Specificity Analysis Populations will be somewhat lower than 2000 based upon eligibility for inclusion in those populations.

IX. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE AND INFORMED CONSENT

A. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

This protocol, and any subsequent changes that may affect the safety, health or welfare of study participants, must be reviewed and approved by a properly constituted IRB/IEC prior to the initiation of the program. Review and approval by the IRB/IEC for continuation of the program must take place at least once a year.

B. Informed Consent

ICH GCP regulations require that a written, IRB/ICE-approved, Informed Consent Form must be read by and explained to all study participants. If a study participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. The witness should sign and date the consent form after the study participant. Prior to entering a research study, each study participant must sign and receive a dated copy of the Informed Consent Form. A copy of the signed, dated Informed Consent Form must be maintained with the study participant's records. The Informed Consent Form, and any subsequent changes that may affect the safety, health or welfare of study participants, must be reviewed and approved by a properly-constituted IRB/IEC prior to initiation of the study.

X. OBLIGATIONS OF THE INVESTIGATOR

A. Retention of Documents

Following completion of any study, copies of all study-pertinent records must be retained by the Principal Investigator for 15 years according national rules after the later of the following two dates: the date on which formal discontinuation of the clinical development has been discontinued, or there are no pending on contemplated marketing applications in an ICH region. After a two year period, investigative site records will be stored in the Clinical Trials Department of OraSure Technologies, Inc.

B. Device Accountability

The Principal Investigator or his/her designees will maintain accurate records of all investigational assays/devices used in each study performed under this protocol. Damaged, dropped, or otherwise destroyed devices will be noted and documented on the device accountability form provided by the sponsor.

C. Adverse Events and Adverse Device Events Reporting

1. Adverse events

Assessment of adverse events (AE) will be carried out during all parts of the study. An AE is defined as any untoward medical occurrence in a study participant using the device under this protocol which does not necessarily have a causal relationship with

this use. An AE, therefore, can be any unfavourable and unintended sign, symptom, or medical condition temporally associated with the use of the study product, even if the event is not considered to be related to the study product.

Adverse events will be collected from the time the informed consent signed until the completion of the all study procedures. Information about all AEs, whether volunteered by the study participant, discovered by investigator questioning, or detected through physical examination or other means, will be collected and recorded on the Adverse Event Form and followed as appropriate.

A positive HIV result, as determined by the laboratory testing, will not be documented as an AE if HIV positive status was previously unknown, as HIV results are part of the endpoint evaluation of the study. This will be reported to the IRB/IEC, however.

As much as possible, each AE will also be described by:

1. Its duration (start and end dates).
2. The severity grade (mild, moderate, severe).
3. Its relationship to the study product (definite, probably, possibly, unrelated).
4. The action(s) taken.
5. Its relevance to the outcome.

2. Severity of Adverse Events

The investigator is to classify the severity of an AE according to the following definitions:

Mild: The study participant is aware of signs or symptoms, which are easily tolerated.

Moderate: The signs and symptoms are sufficient to restrict, but not prevent, usual activity.

Severe: The study participant is unable to perform usual activity.

The maximum intensity of an AE (mild, moderate, or severe) will be assessed at each visit taking into account the possible range of intensity of the symptom(s).

3. Relationship of Adverse Events to the Device

The investigator is to classify the relationship of an AE to the investigational product according to the definitions outlined below.

Association	Definition
None (unrelated)	(1) The existence of a clear alternative explanation or (2) non-plausibility (e.g., the subject is struck by an automobile or develops cancer a few days after product use).
Possible	A clinical event with a reasonable time sequence to product use, but which could also be explained by concurrent disease or other agents.
Probable	A clinical event with a reasonable time sequence to product use, unlikely to be attributed to concurrent disease or other agents, and which follows a clinically reasonable response on withdrawal.
Definite	The properties of the study device and the course of the AE after treatment indicated involvement of the study product in the occurrence/worsening of the AE and no indication of other causes existed.

4. Serious Adverse Events

The ICH Guideline E2A, entitled "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" defines a **serious adverse event (SAE)/experience** or reaction as being any untoward medical occurrence which:

- Is fatal or life-threatening.
- Requires or prolongs hospitalization.
- Results in persistent or significant disability/incapacity
- Is medically significant, may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above, or
- Is a congenital anomaly/birth defect.

Events **not** considered to be serious adverse events are hospitalizations for the:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen, and/or
- Treatment on an emergency, on subject basis for an event **not** fulfilling any of the definitions of serious given above and **not** resulting in hospital admission.

To ensure subject safety each SAE must also be reported to the manufacturer **within 48 hours of learning of the occurrence.** The following guidelines are for reporting to Research Ethics Committee, University of Pretoria:

Report within 7 calendar days after first knowledge. The initial notification should be followed by as complete a report as possible within an additional 8 calendar days

- All deaths
- Serious, unexpected, adverse drug reactions which are fatal or life threatening

Report as soon as possible and not later than 15 calendar days after first knowledge

- Serious, unexpected, adverse drug reactions which are not fatal or life threatening

Report as part of the 6-monthly progress reports

- All Serious Adverse Events
- Non-serious unexpected adverse drug reactions

5. Adverse Device Events (ADE)

An Adverse Device Event (ADE) is any AE that occurs to the subject as a result of using the device (.i.e.; is Possible, Probable or Definite in relationship).

Unanticipated Adverse Device Effects (UADEs)

An Unanticipated Adverse Device Effect is any adverse event that the Principal Investigator determines to be attributable to an investigational oral specimen collection device that is serious or

not previously identified in nature, severity or degree of incidence in the current protocol or the commercial product's labeling.

XI. CONFIDENTIALITY OF SUBJECT SPECIMENS AND INFORMATION

Study participant names will appear only on the Informed Consent and the study source documents including the subject-ID code roster or database that will be kept in a secure fashion. Study participants will be identified in the study by their participant number and initials. Testing records and laboratory specimens will be coded to protect the participants' confidentiality. Study participant confidentiality will be carefully maintained.

XII. COMMUNICATION AND PUBLICATION OF RESULTS

OraSure Technologies, Inc. must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). OraSure Technologies, Inc. will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being divulged, and provide any relevant supplementary information. Any presentation or publication of data from this study is at the discretion of the OraSure Technologies Inc., and requires the written approval. All results will become publically available

XIII. AUDITS AND INSPECTIONS

Key documents for this study will be made available to appropriately qualified personnel or designee(s) from the local OraSure Technologies, Inc. and to the FDA. Participating investigative sites may be audited by qualified personnel or designee(s) for OraSure Technologies, Inc. and may be inspected by the FDA.

XIV. References

Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Zungu N, Labadarios D, Onoya D et al. (2014) *South African National HIV Prevalence, Incidence and Behaviour Survey, 2012.* Cape Town: HSRC Press.
UNAIDS (2013) South Africa: country data; http://aidsinfo.unaids.org

UNAIDS (2013) *2013 Regional report: Getting to Zero:HIV in Eastern and Southern Africa.* Geneva: UNAIDS

XV. APPENDICIES AND RELATED DOCUMENTS

Appendices

1.1 OraQuick® Rapid HIV-1/2 Antibody Test Package Insert

1.2 OraQuick® Rapid HIV Self -Test Package Configuration for Study

1.2.1 Product Package

1.2.2 Instruction Sheet

1.3 Related Documents

1.3.1 Informed Consent Form

1.3.2. Enrollment Questionnaire

1.3.3. Baseline Questionnaire

1.1 OraQuick® Rapid HIV-1/2 Antibody Test Package Insert

OraQuick® Rapid Antibody Test HIV-1/2

For Outside USA Use Only
***In Vitro* Diagnostic Use • Do Not Reuse**

Read this product insert completely before using the product. Follow the instructions carefully. Not doing so may give inaccurate test results. Not approved by the US Food and Drug Administration. For outside USA use only.

NAME AND INTENDED USE

OraQuick® HIV-1/2 is a qualitative, *in vitro* immunoassay. It detects antibodies to the human immunodeficiency virus types 1 and 2 (HIV-1/2) in human oral fluid, whole blood, serum or plasma. The assay is read visually, and is intended for the detection of such antibodies from individuals infected by HIV-1 or HIV-2.

SUMMARY AND EXPLANATION OF THE TEST

HIV-1 and HIV-2 are etiologic agents of the acquired immunodeficiency syndrome (AIDS) and related conditions. HIV has been isolated from patients with AIDS, AIDS related complex (ARC) and from healthy individuals at high risk for AIDS.[1-3] Clinical evidence of HIV infection may be obtained by testing for HIV antibodies in blood or oral fluid of individuals who may be at risk for HIV infection.[4-6] OraQuick® HIV-1/2 detects antibodies to HIV-1 and HIV-2 present in oral fluid, whole blood, serum or plasma.

BIOLOGICAL PRINCIPLES OF THE TEST

OraQuick® HIV-1/2 is a visually read, qualitative immunochromatographic test for the detection of antibodies to HIV-1 and HIV-2. The flat pad that contacts the gums (see below) is treated with a mild surfactant, and no materials of viral origin are used in the manufacture of the test. One cannot become infected with HIV by taking this test.

The device (see figure below) is placed into the subject's mouth, so that the flat pad is between the cheek and the outer gums, then swabbed across the outer gum line (see oral fluid TEST PROCEDURE, below). The device is then placed into a vial containing a premeasured amount of developer solution, and allowed to develop. Use only the stand provided to hold the developer vial. Fluid from the surface of the gums enters the device through the flat pad, then flows onto a test strip. As it migrates across the strip, it hydrates and mixes with a red-colored reagent (protein A bound to colloidal gold). IgG antibodies in the specimen bind to the reagent. If in turn the bound IgG antibody recognizes synthetic HIV-1 or HIV-2 antigen immobilized on the strip enclosed in the housing, a colored line forms in the 'T' (test) area of the result window. If not, no line forms there.

Further up the strip, the colored reagent encounters an immobilized biochemical that recognizes human antibodies. The line that forms in this 'C' area of the result window is the control line. It demonstrates assay validity, indicating that the oral fluid contains IgG, that the strip is functioning properly, and that fluid is migrating appropriately through the device.

Alternatively, a whole blood, serum or plasma specimen can be collected using a loop. The loop is immersed into the developer and stirred to mix. See the test procedure for whole blood, serum or plasma below.

Kit controls for OraQuick® HIV-1/2 are available separately. These serve to demonstrate that the test is maintaining adequate performance (see Kit Control insert).

CONTENTS

OraQuick® HIV-1/2
500 tests, 20 test stands, 25 loops, 1 product insert.
100 tests, 10 test stands, 5 loops, 1 product insert.

Also available separately are:

Loop
Catalog number 1001-0144; package of 5.
Catalog number 1001-0145; package of 25.

Test Stand
Catalog number 004-0002; package of 5.

ACCESSORIES

No accessories are required to run the oral fluid test. However, a timer or watch is needed to determine when to read the result.

When performing the test on a fingerstick whole blood specimen, an alcohol wipe and lancet (not supplied) are required.

WARNINGS AND PRECAUTIONS For *In Vitro* Diagnostic Use

- Handle specimens and materials contacting specimens as if potentially infectious biological materials in accordance with "Universal Precautions for Prevention of Transmission of Human Immunodeficiency Virus, Hepatitis B Virus, and other Blood-borne Pathogens in Health-Care Settings" (CDC, MMWR, June 24, 1988).[7] It has been reported that infectious HIV can be isolated from the oral fluid of some infected patients. When detectable in oral fluid, infectious virus is present at low levels compared with blood and may be inactivated by salivary inhibitors.
- Clean and disinfect any oral fluid- or blood-containing spills. Use a 0.5% sodium hypochlorite (1:10 household bleach) solution, or other appropriate disinfectant.[8]
- Dispose of all potentially contaminated materials in accordance with local regulations for disposal of biohazardous materials.
- If an oral fluid test must be repeated (following the gum-swab procedure), start the process over using a new test device, and use the blood test procedure.
- Use adequate lighting to visually check a test result. If two lines are present at any visible intensity, the test result is interpreted as reactive (see Interpretation of Results section).
- Do not cover or otherwise obstruct the two small holes on the back of the test device. The flow of fluid can be impaired.
- Individuals infected with HIV-1 and/or HIV-2 who are receiving highly active antiretroviral therapy (HAART) may produce false negative results.
- Do not use the test beyond the expiration date printed on the Divided Pouch. Always check expiration date prior to testing.

STORAGE

- Store unused OraQuick® HIV-1/2 tests unopened at 2-30 ºC. Do not open the foil pouch until you are ready to perform a test.
- This test should be performed at temperatures in the range of (15-37 ºC, 59-99 ºF). If stored refrigerated, ensure that the Divided Pouch is brought to operating temperature (15-37 ºC, 59-99 ºF) before performing Testing.
- If the test kit is stored at temperatures outside of ambient temperature (2-27 ºC, 36-80 ºF), or used outside of the operating temperature (15-37 ºC, 59-99 ºF), use the Kit Controls to ensure performance of the test.

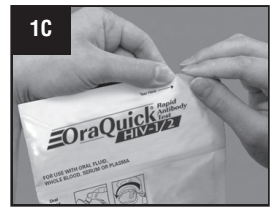
SPECIMEN COLLECTION and TEST PROCEDURE (oral fluid)

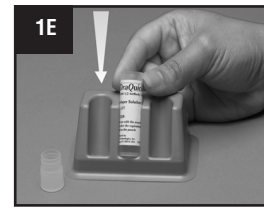
The administrator of the test should first instruct the subject about the test and how to collect an oral fluid sample. The test device is then offered to the subject. Instruct the subject to collect a sample, as outlined below.

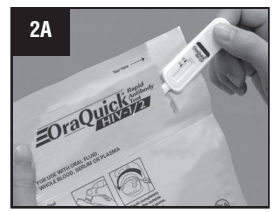
1. A) Ensure prior to testing that the subject has not had anything to eat, drink or has chewed gum for at least 15 minutes. Have the subject wait for at least 30 minutes prior to testing if they have used any oral care products.
   B) Set the reusable stand on a flat, level surface.
   C) Tear open the foil pouch containing the test device and developer vial. Remove the developer vial.
   D) Carefully uncap the vial by gently rocking the cap back and forth.
   E) Place the uncapped vial into the stand.

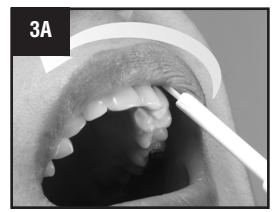
2. A) Have the subject grasp the test device and remove it from the foil pouch without touching the collection pad. **Check to see if absorbent packet is present. If no absorbent packet is present, discard the unit.**

3. A) Instruct the subject to swab completely around the **outer** gums with the test device, by gently wiping the **flat pad** completely across the **upper** and **lower** gums, one time around.



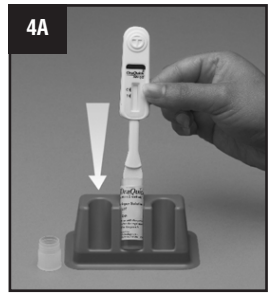






4. A) When the subject has finished swabbing the gums, have the subject insert the **pad end** of the test device all the way down into the vial.
   B) Be sure the result window faces **forward** so it can be read.
   C) Start the timer, or note the time.

5. A) **Read test result in 20 to 40 minutes.** Record the test result seen in the result window (refer to Interpretation of Results and Limitations of the Procedure, below), then dispose of the device and vial in a biohazardous waste container.



SPECIMEN COLLECTION and TEST PROCEDURE (whole blood, serum, plasma)

Please observe Universal Precautions[7] when performing the fingerstick and blood testing procedures.

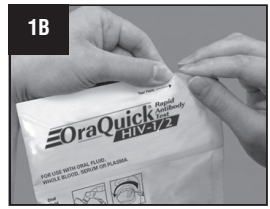
1. A) Set the reusable stand on a flat, level surface.
   B) Tear open the foil pouch containing the test device and developer solution vial. Remove the vial.
   C) Carefully uncap the vial by gently rocking the cap back and forth.
   D) Place the uncapped vial into the stand.

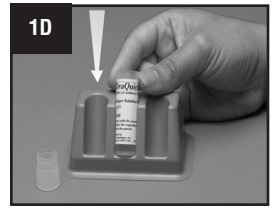
2. A) Cleanse the subject's finger with an antiseptic wipe, let it air dry, then use a lancet to puncture the finger.
   B) Express a small amount of blood.

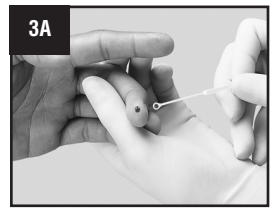
3. A) Touch a loop to the blood droplet.
   B) Transfer the droplet of blood to the vial.

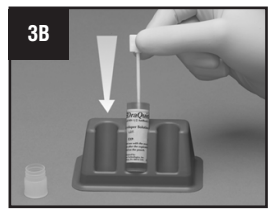
   Note: If you are testing venipuncture blood, a serum or plasma sample, or kit controls, use a loop, or a 5 microliter sample volume transferred with a micropipet.

4. A) Use the loop to gently stir the sample in the vial of developer solution.
   B) Discard the loop as biohazardous waste.









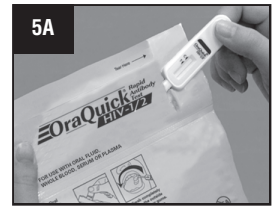
5. A) Have the subject grasp the test device and remove it from the foil pouch without touching the collection pad. **Check to see if absorbent packet is present. If no absorbent packet is present, discard the unit.**

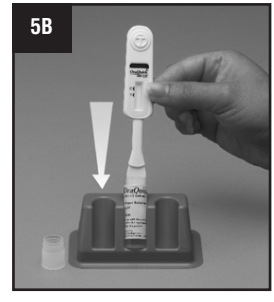
   B) Insert the **pad end** all the way down into the vial.

   C) Be sure the result window faces **forward** so it can be read.

   D) Start the timer, or note the time.

6. A) **Read test result in 20 to 40 minutes.** Record the test result seen in the result window (refer to Interpretation of Results and Limitations of the Procedure, below), then dispose of the device and vial in a biohazardous waste container.





QUALITY CONTROL

A control line in the 'C' area of the result window indicates a valid result. A valid result indicates a suitable sample was collected and the test functioned properly. The control line will appear on all valid tests, whether or not the result is reactive. (Refer to Interpretation of Results, below).

Kit control reagents are available separately. These are used to verify adequate test performance. Kit controls should be run once per shift by the test administrator, and whenever changing to a different lot of tests. Refer to the Kit Control product insert when using these reagents.

INTERPRETATION OF RESULTS – Refer to the result window

NON-REACTIVE – only the control line appears
If a single line appears on the test strip in the area adjacent to the triangle labeled 'C', the result is **non-reactive**. The diagram at the right shows a non-reactive result. It suggests the **absence** of anti-HIV antibodies in the specimen.

Note: using the **Negative Kit Control** gives this result (see insert for OraQuick *ADVANCE*® HIV-1/2 Kit Controls).

NON-REACTIVE

REACTIVE – two lines appear
If two lines appear on the test strip, adjacent to the 'T' and 'C' triangles, respectively, the result is considered **reactive**. One of these lines may be darker than the other. At the right are examples of reactive results, which suggest the **presence** of anti-HIV antibodies in the specimen.

Note: using the **HIV-1 Kit Control** or **HIV-2 Kit Control** gives a result like the one shown in the center panel (see insert for OraQuick *ADVANCE*® HIV-1/2 Kit Controls).

REACTIVE REACTIVE REACTIVE

INVALID – no line present in 'C' area of window

If there is no line in the area labeled 'C', the result is **invalid**. An invalid test should be repeated with a new test device. If the invalid test was obtained with an oral fluid specimen, use the blood test procedure for repeat testing. At the right are examples of invalid results.

INVALID INVALID INVALID

LIMITATIONS OF THE PROCEDURE

1. The OraQuick® HIV-1/2 test kit must be used in accordance with these instructions to obtain an accurate result.
2. Oral fluid specimens for OraQuick® HIV-1/2 testing must be freshly collected, as detailed in the procedure. For blood-based testing, aged specimens or specimens which have undergone repeated freeze-thaw cycles may give incorrect results.
3. Blood-based specimens that have been heat or chemically inactivated may not give accurate results.
4. The test is not for use with body fluids not specified here, with oral fluid collected by other methods or with other commercially available oral fluid collectors, or with pooled specimens.
5. Clinical data has not been collected to demonstrate the performance of OraQuick® HIV-1/2 in persons under 13 years of age.
6. Do not use this test as the sole basis for a diagnosis of AIDS, ARC or HIV infection. Any reactive result should be confirmed.
7. For a reactive result, the intensity of the test line does not necessarily correlate to the titer of antibody in the specimen.
8. A non-reactive result does not preclude the possibility of exposure to HIV or infection by HIV. An antibody response to recent exposure may take some time to reach detectable levels.
9. If a red background in the result window makes it difficult to read the test at 20 minutes, wait until the background clears to read the result (but not more than 40 minutes total time).

PERFORMANCE CHARACTERISTICS

SPECIFICITY

Serostatus	Number tested	Non-reactive by OraQuick®	Non-reactive by reference test(s)[1]
Seronegative (Thailand)[2]	779	778/779 (99.87%)	779

SENSITIVITY

Serostatus	Number tested	Reactive by OraQuick®	Reactive by reference test(s)[1]
Seropositive (Thailand)[2]	219	219/219 (100%)	219[3]

1 The reference tests for the study were Genelavia Mixt ELISA and Western Blot.

2 Matched oral fluid, whole blood and plasma.

3 In addition, two subjects had repeat reactive ELISA and Western Blot indeterminate results. OraQuick® and PCR results were reactive for one subject. For the second subject, NucliSens RNA PCR and OraQuick® HIV-1/2 were non-reactive, and Roche Amplicor PCR was reactive. It is likely that this subject may be early in the seroconversion process.

BIBLIOGRAPHY

1. Gallo RC, Salahuddin SZ, Popovic M, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV III) from patients with AIDS and at risk for AIDS. *Science* 1984; 224:500-3.
2. Curran JW, Morgan WM, Hardy AM, et al. The epidemiology of AIDS: current status and future prospects. *Science* 1985; 229:1352-7.
3. Clavel F, Guetard D, Brun-Vezinet F, et al. Isolation of a new human retrovirus from West African patients with AIDS. *Science* 1986; 233:343-6.
4. Archibald DW, Zon LI, Groopman JE, et al. Salivary antibodies as a means of detecting human T cell lymphotropic virus type III/ lymphadenopathy-associated virus infection. *J Clin Microbiol* 1986; 24:873-5.
5. Parry JV, Perry KR and Mortimer PP. Sensitive assays for viral antibodies in saliva: an alternative to tests on serum. *Lancet* 1987; 2:72-5.
6. Major CJ, Read SE, Coates RA, et al. Comparison of saliva and blood for human immunodeficiency virus prevalence testing. *J Infect Dis* 1991; 163:699-702.
7. CDC. Universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. *MMWR* 1988; 37(24):377-388.
8. Sehulster LM, Hollinger FB, Dreesman GR, and Melnick JL. Immunological and biophysical alteration of hepatitis B virus antigens by sodium hypochlorite disinfection. *Appl Env Microbiol* 1981; 42:762-7.

EXPLANATION OF SYMBOLS

This Way Up	Not for Sale in USA	Caution, Consult Accompanying Documents
Avoid Prolonged Exposure to Sunlight	Not for Retail Sale	TESTS — Tests
Fragile, Handle With Care	Temperature Limitation	PN — Part Number
Keep Dry	REF — Catalog Number	CONTENTS — Contents
LOT — Batch Code	5µL SPEC COLLECT LOOP — 5µL Specimen Collection Loop	
IVD — *In Vitro* Diagnostic Medical Device	Do Not Reuse	

Manufactured in Thailand for

OraSure Technologies, Inc.

220 East First Steet
Bethlehem, PA 18015 USA
(001) 610-882-1820
www. OraSure.com

PN 204-7052 rev. 04/15

OraQuick ADVANCE® Rapid Antibody Test HIV-1/2

Kit Controls

Read this package insert and the OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test Kit package insert completely before using the product. Follow the instructions carefully. Not doing so may result in inaccurate test results. Before performing testing, all operators MUST read and become familiar with Universal Precautions for Prevention of Transmission of Human Immunodeficiency Virus, Hepatitis B Virus, and other Blood-borne Pathogens in Health-Care Settings.[1,2]

NAME AND INTENDED USE

The OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test Kit Controls are quality control reagents for use only with the OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test.

Run the Kit Controls under the following circumstances:

- each new operator prior to performing testing on patient specimens,
- when opening a new test kit lot,
- whenever a new shipment of test kits is received,
- if the temperature of the test kit storage area falls outside of 2°- 27°C (36°- 80°F),
- if the temperature of the testing area falls outside of 15°- 37°C (59°- 99°F), and
- at periodic intervals as dictated by the user facility.

It is the responsibility of each laboratory using the OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test to establish an adequate quality assurance program to ensure the performance of the device under its specific locations and conditions of use.

SUMMARY AND EXPLANATION OF THE KIT CONTROLS

OraQuick *ADVANCE*® Kit Controls are human plasma-based reagents. The Kit Controls are specifically formulated and manufactured to ensure performance of the Test, and are used to verify your ability to properly perform the test and interpret the results. The HIV-1 and HIV-2 Positive Controls will produce a Reactive test result and have been manufactured to produce a very faint Test ("T") line. The Negative Control will produce a non-reactive test result. Use of kit control reagents manufactured by any other source may not produce the required results and, therefore, will not meet the requirements for an adequate quality assurance program for OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test.

MATERIALS PROVIDED

OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test Kit Controls

Each Kit Control box contains a package insert and three vials (one HIV-1 positive control, one HIV-2 positive control and one negative control) as described below:

HIV-1 Positive Control

One black-capped vial containing 0.2 mL of photochemically inactivated human plasma positive for antibodies to HIV-1, diluted in a defibrinated pool of normal human plasma. Preservative: 2-methyl-4-isothiazolin-3-one. Negative for Hepatitis B surface antigen and Hepatitis C antibody.

HIV-2 Positive Control

One red-capped vial containing 0.2 mL of photochemically inactivated human plasma positive for antibodies to HIV-2, diluted in a defibrinated pool of normal human plasma. Preservative: 2-methyl-4-isothiazolin-3-one. Negative for Hepatitis B surface antigen and Hepatitis C antibody.

Negative Control

One white-capped vial containing 0.2 mL of defibrinated pool of normal human plasma negative for antibodies to HIV-1 and HIV-2. Preservative: 2-methyl-4-isothiazolin-3-one. Negative for Hepatitis B surface antigen and Hepatitis C antibody.

MATERIALS REQUIRED AND PROVIDED in the OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test Kit

Divided Pouches, each containing a Test Device, an Absorbent Packet, and a Developer Solution Vial
Reusable Test Stands
Specimen Collection Loops
Subject Information Pamphlets
OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test Package Insert with Customer Letter

MATERIALS REQUIRED BUT NOT PROVIDED

Timer or watch capable of timing 20 to 40 minutes
Latex, vinyl or nitrile disposable gloves
Biohazard waste container
Clean, disposable, absorbent workspace cover

WARNINGS AND PRECAUTIONS

For *in vitro* Diagnostic Use

1. Read this package insert and the OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test package insert completely before using the product. Follow the instructions carefully. Not doing so may result in inaccurate test results.
2. Handle specimens, and materials contacting specimens, as if potentially infectious biological materials in accordance with "Universal Precautions for Prevention of Transmission of Human Immunodeficiency Virus, Hepatitis B Virus, and Other Blood-borne Pathogens in Health-Care Settings".[1,2]
3. Handle the Kit Controls, and materials contacting the Kit Controls, as if capable of transmitting infectious agents.
4. Do not drink, eat, or smoke in areas where the Kit Controls are being handled.
5. Wear disposable gloves while handling specimens. Wash hands thoroughly after performing each test. Dispose of gloves in a biohazard waste container after use.
6. Dispose of all Kit Controls and materials used in the test procedure in a biohazard waste container. The recommended method of disposal of biohazard waste is autoclaving for a minimum of 1 hour at 121°C. Disposable materials may be incinerated. Liquid wastes may be mixed with appropriate chemical disinfectants. A freshly prepared solution of 10% bleach (0.5% solution of sodium hypochlorite) is recommended. Allow 60 minutes for effective decontamination. **NOTE: Do not autoclave solutions that contain bleach.** For additional information on biosafety, refer to "Universal Precautions for Prevention of Transmission of Human Immunodeficiency Virus, Hepatitis B Virus, and Other Blood-borne Pathogens in Health-Care Settings".[1,2]
7. Wipe all spills thoroughly with a freshly prepared solution of 10% bleach or other appropriate disinfectant.[3]
8. Use of kit control reagents manufactured by any other source may not produce the required results, and therefore, will not meet the requirements for an adequate quality assurance program for the OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test.

STORAGE INSTRUCTIONS

Store the OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test Kit Controls at 2°- 8°C (36°- 46°F). Do not use Kit Controls beyond the expiration date printed on the outer carton. Open the Kit Control vials only when you are performing tests. Recap and store the vials in their original container at 2°- 8°C (36°- 46°F) after use.

Dispose of unused portions of opened Kit Control vials after eight weeks.

DIRECTIONS FOR USE

General Test Preparation

Perform procedures indicated in the *Set-Up Your Workspace* and *General Test Preparation* sections of the OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test package insert.

TEST PROCEDURE

1. Open a Kit Control vial containing the control reagent.
2. Insert the round end of an unused Specimen Collection Loop into the vial of control reagent. Visually inspect the loop to make sure that it is completely filled with the control reagent. **Use separate unused Specimen Collection Loops for each control reagent.**
   NOTE: The Kit Control reagents are clear to straw-colored. Do not use if the reagent appears visually cloudy or discolored.
3. Immediately immerse the control-reagent-filled Specimen Collection Loop in the developer solution inside the Developer Solution Vial. Use the Specimen Collection Loop to stir the specimen in the developer solution. Remove the Specimen Collection Loop from the Developer Solution Vial and discard the used loop in a biohazard waste container.
4. Remove the Test Device from the Divided Pouch without touching the flat pad. Insert the Test Device, flat pad first, into the Developer Solution Vial containing the specimen. **Be sure that the result window faces forward and the flat pad touches the bottom of the Developer Solution Vial**.
5. Leave the Test Device in the Developer Solution Vial and start a timer. **Do not remove the Test Device from the vial until you have read the results.** Read the results after 20 minutes but not more than 40 minutes in a fully lighted area. Read the results as described in the *Test Result* and *Interpretation of Test Result* sections of the OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test Kit product insert.
6. Dispose of the used Developer Solution Vial and the Test Device in a biohazard waste container.
7. Reseal the Kit Control reagent vials and store them in their original container at 2°- 8°C (36°- 46°F).

EXPECTED RESULTS

Negative Control:
The Negative Control will produce a Non-Reactive test result. A line should be present in the Result Window in the area adjacent to only the triangle labeled "C." This indicates a Non-Reactive test result.

HIV-1 Positive Control:
The HIV-1Positive Control will produce a Reactive test result and has been manufactured to produce a very faint Test ("T") line. A line should be present in the Result Window in the area adjacent to the triangle labeled "C" **and** a line should appear in the area adjacent to the triangle labeled "T." This indicates a Reactive test result. The lines will not necessarily be the same intensity.

HIV-2 Positive Control:
The HIV-2 Positive Control will produce a Reactive test result and has been manufactured to produce a very faint Test ("T") line. A line should be present in the Result Window in the area adjacent to the triangle labeled "C" **and** a line should appear in the area adjacent to the triangle labeled "T." This indicates a Reactive test result. The lines will not necessarily be the same intensity.

NOTE: If the test result for either the Negative Control or the HIV-1 Positive Control or the HIV-2 Positive Control is not as expected, the test should be repeated using a new Test Device, Developer Solution Vial and control specimen. If the test result for any of the controls is not as expected upon repeat testing, discontinue testing and contact OraSure Technologies Customer Service.

LIMITATIONS
The OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test Kit Controls are quality control reagents for use only with the OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test.

BIBLIOGRAPHY

1. CDC. Universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. *MMWR* 1988; 37(24):377-388.
2. CDC. Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. *HICPAC* 2007; 12-93.
3. Sehulster LM, Hollinger FB, Dreesman GR, and Melnick JL. Immunological and biophysical alteration of hepatitis B virus antigens by sodium hypochlorite disinfection. *Appl Env Microbiol* 1981; 42:762-7.

EXPLANATION OF SYMBOLS

LOT Batch Code	IVD *In Vitro* Diagnostic Medical Device
REF Catalog Number	Manufacturer
Caution, Consult Accompanying Documents	Temperature Limitation
HIV CONTROL – HIV Negative Control	Use By
HIV-1 CONTROL + HIV-1 Positive Control	HIV-2 CONTROL + HIV-2 Positive Control
CONTENTS Contents	KIT CTRLS Kit Controls

OraSure Technologies, Inc.

220 East First Street
Bethlehem, PA 18015 USA
(800) ORASURE (1-800-672-7873)
(610) 882-1820
www.orasure.com

Item# 3001-1202 rev. 04/13

1.2 OraQuick® Rapid HIV Self -Test Package Configuration for Study

1.2.1 Product Package

1.2.2 Instruction Sheet

OraQuick® Rapid Antibody Test HIV-1/2

OraQuick® Rapid HIV Self-Test

FOR INVESTIGATIONAL USE ONLY

IVD

Manufactured in Thailand for:

OraSure Technologies, Inc.

220 East First St.
Bethlehem, PA 18015 USA
www.OraSure.com

LOT: HIVCO-####

EXP: DDMMYYYY

PN 5X4-0003 OF

Avery Label #5168 (5" x 3.5")
rev. 05/15

Tear Here

OraQuick® Rapid Antibody Test HIV-1/2

30 °C
2 °C

FOR INVESTIGATIONAL USE ONLY

IVD PN 5X4-0003 ST

LOT
EXP FPO

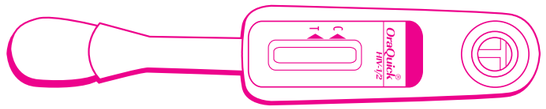
Item# 3001-2343 rev. 08/12

Manufactured in Thailand for:

OraSure Technologies, Inc.
220 East First St.
Bethlehem, PA 18015 USA
www.orasure.com

Tear Here

OraQuick® Rapid Antibody Test HIV-1/2



USA
RETAIL

FOR INVESTIGATIONAL USE ONLY

FOR EXPORT ONLY
FOR *IN VITRO* DIAGNOSTIC USE

6.5" Cutoff

1.5"

12"

Item# 3001-2343-70
rev. 08/12

Thai_Self Test (PSI rev. 04/15)

FOR INVESTIGATIONAL USE ONLY ▪ DIRECTIONS FOR USE

You must follow the test directions carefully to get an accurate result. Do not eat, drink or use oral care products (mouthwash, toothpaste) 15 minutes before you start the test.

WARNING: If you are HIV-positive and on HIV treatment (ARVs) you may get a false negative result.

THIS KIT CONTAINS

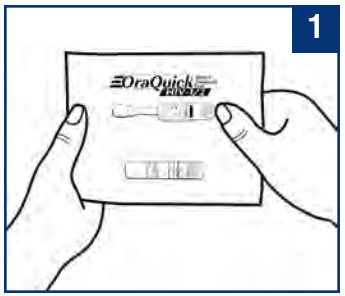

Test Device Stick


Test Tube


Tube Holder

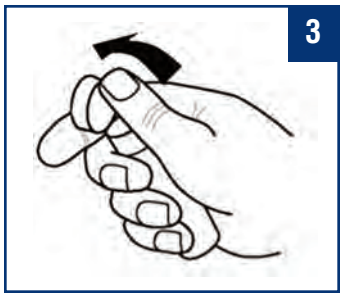

Preservative
(not needed for the test)

PERFORMING THE TEST

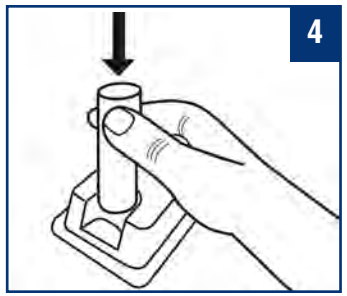


Tear open the packet.

Locate and remove the **test tube**.

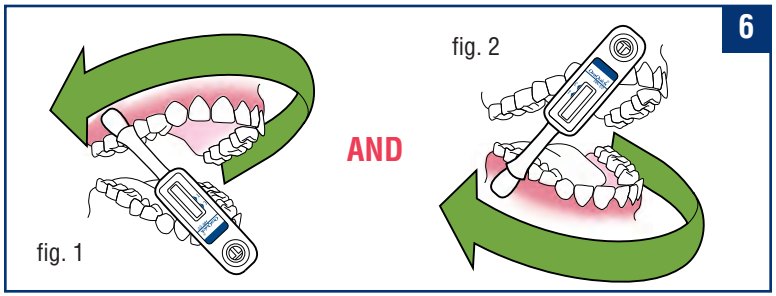


Remove the cap.

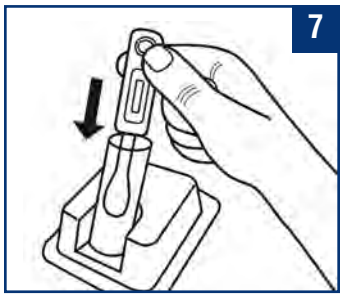


Place tube in the tube holder.

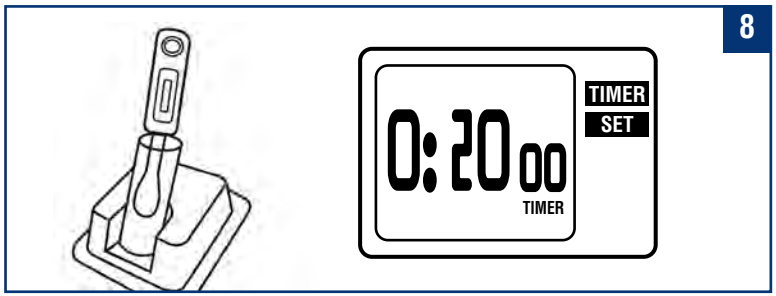
Locate and remove the **test stick**. **DO NOT** touch the pad with your fingers.



Press the pad firmly against your gum and swipe it along your **upper gum once** (fig. 1) and **your lower gum once** (fig. 2).



Place test stick into tube.

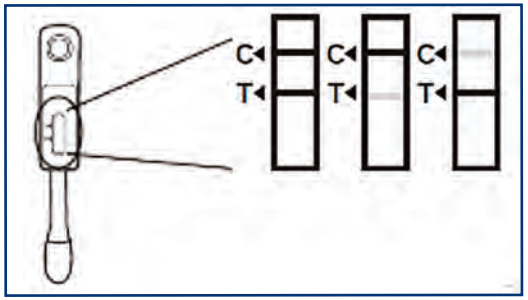


WAIT 20 MINUTES. You can read the results after 20 minutes but you must read the result before 40 minutes. DO NOT read the result after 40 minutes.

OraQuick® Rapid Antibody Test HIV-1/2

READING THE RESULTS

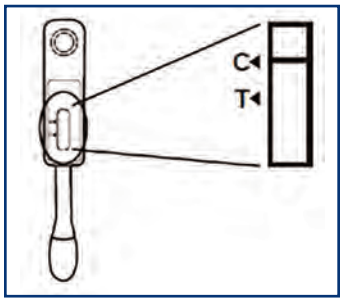
POSITIVE RESULT



If there are TWO LINES, one next to the “C” and one next to the “T” – EVEN A VERY FAINT ONE, you may have HIV.

IF YOU HAVE A POSITIVE RESULT, YOU SHOULD NOW CONTACT YOUR CLOSEST HEALTHCARE CLINIC OR NURSE. THEY WILL BE ABLE TO GIVE YOU ADVICE ON THE NEXT STEPS TO ENSURE YOU REMAIN HEALTHY.

NEGATIVE RESULT



If there is ONE LINE next to the “C” and NO line next to the “T”, your result is negative.

If you have been exposed to HIV recently, seek repeat testing in 3 months.

INVALID RESULT

If there is no line next to the “C” or a red background makes it impossible to read the test, the test is not working and should be repeated.

You will need to obtain another test.

DISPOSE

Remove the test stick, put the cap on the test tube and throw away all contents in the normal trash.

Manufactured in Thailand for:

OraSure Technologies, Inc.

220 East First Street
Bethlehem, PA 18015
01+610-882-1820
www.OraSure.com

Item# 3001-2822 rev. 05/15

1.3 Related Documents

1.3.1 Informed Consent Form

1.3.2. Enrollment Questionnaire

1.3.3. Baseline Questionnaire

Ndlovu Oraquick Self-test PARTICIPANT INFORMATION SHEET: ENROLMENT

What is the name of this study?
Ndlovu Oraquick Self-test

Who is doing this study?
The study is being conducted by the Ndlovu Research Centre (NRC) of the Ndlovu Care Group, Elandsdoorn (South Africa).

Why is this study being done?
This is a diagnostic study that is researching if a new oral HIV-test can easily be used and understood as a self-test by people in a rural area in South-Africa.

How can you join the study?
This Participant Information Sheet gives you information to help you decide if you want to join the study. If you decide to be part of the study, we will ask you to sign and date your permission in an Informed Consent Form. By signing the Informed Consent Form you agree to test yourself for HIV, to have some blood taken for confirmation of the first test-results in case of a positive test-result, and for you to answer a small questionnaire. The Informed Consent Form says that you and I have discussed everything you need to know about the study. If you sign the Informed Consent Form, it means that you understand what the study is all about and that you agree to join the study. We will give you a copy of the Participant Information Sheet and Informed Consent Form to keep.

Before you decide if you want to join this study, we want to explain the studyto you, its risks, its potential benefits, and what you will be asked to do. You may ask questions as we discuss the study. It is important you know the following things:

- To be part of the study is your decision and not up to anyone else.
- You will not lose any of your usual medical care benefits if you decide not to join the study.
- You may join the study and then change your mind and leave the study at any time.

Who will be in the study?
Approximately 2000 men and women, 18 years and older from the Moutse area, Limpopo Province, South Africa. If you are pregnant you may also participate in this study if you would like to.

What does the study require you to do?
First we will check if you are suitable to enter the study by asking you a few questions.

Before you will test yourself you will receive pre-test counselling to make sure that you understand the procedure and its consequences. You may refuse to participate without penalty to you.

If you then agree to be tested, we will give you an oral HIV test with instructions on how to use it and how to read the results. After you have tested yourself, a counsellor or nurse will repeat the test using the same kit to check the result independently from your first test.

If your result is negative you will receive post-test counselling on how to stay HIV negative and you will be encouraged to be tested again after three months and regularly thereafter. If one of the two oral test results is positive, you will get another test done using a different type of test to make sure the first test was

correct. This test will require us to prick your finger to get a few drops of blood.. If the finger-prick test is also positive you will receive post-test counselling, after which you will be referred to the Ndlovu Medical Centre or a clinic of your choice for a CD4 count and further management and treatment, as necessary.

If the finger-prick test is negative, the result is indeterminate and the nurse will draw blood to have it tested at the Ndlovu Medical Centre.

If you want your results, you can wait for your results. If you do not want your test result, you do not have to wait for the results. You can however get your results at any time, if you decide afterwards that you want your results.

Finally you will be asked a short questionnaire that will enquire about your general and oral health, the medication you might take, your vision, and literacy.

What are the benefits of this study?
This study will be of direct benefit to you by providing you with HIV counselling and testing, referring you to health care if needed and providing information about how to protect yourself from HIV and sexually transmitted infections. On the other hand knowing your HIV-status can also result in mental stress. You or others may also benefit in the future from what we learn from this study about the use of this new oral self-test in South-Africa. By participating in this study, you will receive more information about HIV and treatment at the Clinic.

Will you find out the results of the study?
You will be told when the results of the study are available, and how to learn about this.

Do you have options other than joining this study?
You can choose not to join this study at all.

Is there any cost for you to be in this study?
There is no cost to you for taking part in the study.

Who will see your personal and medical information?
We will do everything we can to protect your privacy. You will get a code number which will be used instead of your name. This code number will be used on all information collected about you in this study. If you sign the informed consent form, you or your representative give us permission to use your information.

What if you have questions or problems?
If you have any questions, you can contact a member of the research centre staff on 013 9800014

This study has been reviewed and approved by the Research Ethics Committee of the University of Pretoria**.** This committee ensures that the rights and safety of all participants in the study are protected and that the study is conducted according to strict guidelines. If at any time you have any questions regarding your rights as a participant in a study, you may contact:

The Chairperson of Research Ethics Committee of the University of Pretoria
Tel: 012 3541330

E-mail: manda@med.up.ac.za and/or deepeka.behari@up.ac.za

Are you ready to join the study?

If you want to join the study, the next step is for us is to check if you are suitable to join this study before you sign the informed consent form. You should only sign the form if you understand everything the study requires. This is why you should ask questions to make sure you understand. You will also be asked some questions to make sure everything has been explained to you. When you sign the form, you will be enrolled into the study. "Enrolled" means you have joined the study.

To join this study you need to be literate, so you will be asked to please read the following text. If you are not able to read it, you unfortunately cannot join the study:

"I want to join this study voluntarily. Everything was well explained to me and I understand that this study is about the use of a new oral HIV self-test. I will perform the test myself. If I join the study I will receive counselling before and after the test. If necessary, blood will be drawn to confirm a positive test result. First I will have to answer some questions so that it can be decided if I can join the study"

ENROLMENT INFORMED CONSENT

Before you sign this consent form, make sure of the following:

- You have had the participant information sheet read to you.
- You have been given a copy of the enrolment participant information sheet dated 13 August 2015
- This study has been explained to you.
- The positive and negative effects of knowing your HIV status have been explained to you (if your HIV status is not known).
- You have had your questions answered.
- You understand you can ask more questions at any time.
- You understand your study records will be available to the research centre staff and other groups of people.
- You agree to join the study.

PARTICIPANT CONSENT FOR HIV TESTING (if HIV status not known)

My signature below confirms that I agree to an HIV test as described in the participant information sheet. I understand that I will be informed of the results of the tests in confidence, and that I will be advised about further counselling and care.		
Participant's Name	Participant's Signature	Date

PARTICIPANT CONSENT FOR TO JOIN THE STUDY

My signature below confirms that I freely agree to JOIN the Ndlovu Oraquick Self-test Study.		
Participant's Name	Participant's Signature	Date

INVESTIGATOR

As investigator, or properly delegated by the investigator, I have fully informed the participant of all aspects of the study.		
Investigator/Designee Name	Signature	Date

Date of visit ☐☐ ☐☐ ☐☐☐☐ Initials Investigator ☐☐☐☐

Participant Initials ☐☐☐☐ Participant ID **ORA** ☐☐☐☐

ENROLLMENT FORM

Demographics		
Q1	Race	☐ Zulu ☐ Ndebele ☐ Caucasian ☐ Other: _____
Q2	Date of Birth	DD/MM/YYYY: ☐☐ ☐☐ ☐☐☐☐
Q3	Education	☐ None ☐ Primary school completed ☐ Secondary school completed ☐ Matric ☐ Technicon/ College ☐ University
Q4	Reading and understanding language	☐ Zulu ☐ Sepedi / Northern Soto ☐ English
Q5	Relationship Ndlovu Care Group (clinic, HCT programme, Ndlovu Research Centre)	☐ Employee > EXCLUDED ☐ Family of employee > EXCLUDED ☐ None
HIV Testing		
Q6	Have you ever had an HIV test?	☐ Yes, within the past 6 months > EXCLUDED ☐ Yes, more than 6 months ago ☐ Refuse > EXCLUDED
Q7	Date of last HIV-test (approximative)	DD/MM/YYYY: ☐☐ ☐☐ ☐☐☐☐
Q8	Where were you tested?	
Q9	What is your HIV-status?	☐ Unknown ☐ Negative ☐ Positive > EXCLUDED ☐ Refuse > EXCLUDED
Q10	Were you ever trained to use the OraQuick® Rapid HIV-1/2 Antibody Test?	☐ No ☐ Yes > EXCLUDED
Q11	Have you ever received any experimental HIV vaccine?	☐ No ☐ Yes > EXCLUDED
Q12	Are you currently on a Pre-exposure HIV Prophylaxis regimen?	☐ No ☐ Yes > EXCLUDED
Q13	Have you ever participated in any prior, or concurrent trial of HIV self-tests?	☐ No ☐ Yes > EXCLUDED
According judgment counsellor:		
Q14	Candidate is unable to complete the study or is unlikely to comply with the study protocol	☐ Yes > EXCLUDED ☐ No > ENROLL

****GO FOR INFORMED CONSENT****

Date of visit ☐☐ ☐☐ ☐☐☐☐ Initials Investigator ☐☐☐☐

Participant Initials ☐☐☐☐ Participant ID **ORA** ☐☐☐☐

BASELINE ASSESSMENT FORM

General health

Q1	How would you rate your health today?	☐ Very good ☐ Good ☐ Bad ☐ Very bad
Q2	Are you pregnant?	☐ Yes ☐ No ☐ N/A (male)
Q3	Do you suffer from any illnesses or injuries?	☐ Yes ☐ No → **Go to Q7** ☐ Don't know
Q4	Did you consult a health worker such as a nurse, doctor or traditional healer as a result of this illness or injury?	☐ Yes ☐ No ☐ Don't know

Q5 Have you been informed by a medical practitioner or nurse that you suffer from any of the following illnesses or conditions or other?

Asthma?	☐ Yes	☐ No
Diabetes?	☐ Yes	☐ No
Cancer?	☐ Yes	☐ No
TB?	☐ Yes	☐ No
Hypertension/high blood pressure?	☐ Yes	☐ No
Arthritis?	☐ Yes	☐ No
Other?	(specify: _____)	

Q6	If "yes" for question Q3, are you taking medication for these illness(es)? (select all that apply)	☐ Asthma? ☐ Diabetes? ☐ Cancer? ☐ Hypertension/high blood pressure? ☐ Arthritis? ☐ Other? (specify: _____)

☐ Don't know

Visual impairment		
Q7	Do you have difficulty in seeing (even with glasses if you wear them)?	☐ No difficulty ☐ Some difficulty ☐ A lot of difficulty ☐ Unable to do ☐ Don't know ☐ Cannot yet be determined
Q8	Do you use of glasses or contacts?	☐ Yes ☐ No
Q9	Any condition that specifically affects vision (besides the need of glasses or contacts	☐ Yes ☐ No

Oral health		
Q10	Do you have any of the following oral health conditions?	
	Cavities and/or fillings?	☐ Yes ☐ No
	Braces?	☐ Yes ☐ No
	Periodontal disease and/or bleeding gums?	☐ Yes ☐ No
	Oral fixtures; full or partial dentures?	☐ Yes ☐ No
Q11	What have you been eating or drinking the past hour?	_____ _____
Q12	Did you use tooth paste today?	☐ Yes ☐ No
Q13	Did you use mouthwash or oral rinse today?	☐ Yes ☐ No
Q14	Have you been smoking or using smokeless tobacco today ?	☐ Yes ☐ No

Date of visit ☐☐ ☐☐ ☐☐☐☐ Initials Investigator ☐☐☐☐

Participant Initials ☐☐☐☐ Participant ID **ORA** ☐☐☐☐

Relevant medical history			
Diagnosis	Start date (MM/YYY)	Stop date (MM/YYY)	Ongoing
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o
	_____ /_____	_____ /_____	o

Date of visit |__|__| |__|__| |__|__|__|__| Initials Investigator |__|__|__|__|

Participant Initials |__|__|__|__| Participant ID **ORA** |__|__|__|__|

Medication use (including contraceptives , herbal and traditional medication, recent vaccines and immunotherapy)

Name	Characteristics
	Start date: _____/______/__________ (DD/MM/YYYY) Stop date: _____/______/__________ (DD/MM/YYYY) Dosage: Frequency: Route:
	Start date: _____/______/__________ (DD/MM/YYYY) Stop date: _____/______/__________ (DD/MM/YYYY) Dosage: Frequency: Route:
	Start date: _____/______/__________ (DD/MM/YYYY) Stop date: _____/______/__________ (DD/MM/YYYY) Dosage: Frequency: Route:
	Start date: _____/______/__________ (DD/MM/YYYY) Stop date: _____/______/__________ (DD/MM/YYYY) Dosage: Frequency: Route:
	Start date: _____/______/__________ (DD/MM/YYYY) Stop date: _____/______/__________ (DD/MM/YYYY) Dosage: Frequency: Route:
	Start date: _____/______/__________ (DD/MM/YYYY) Stop date: _____/______/__________ (DD/MM/YYYY) Dosage: Frequency: Route:

Date of visit ☐☐ ☐☐ ☐☐☐☐ Initials Investigator ☐☐☐☐

Participant Initials ☐☐☐☐ Participant ID **ORA** ☐☐☐☐

Health Literacy (DBSQ and BEHKA-HIV)						
		Allways	Often	Sometimes	Occasionally	Never
Q15	How often do you have problems learning about your medical condition because of difficulty understanding written information?	☐	☐	☐	☐	☐
Q16	How often do you have someone (like family member, friend or caregiver) help you read hospital materials?	☐	☐	☐	☐	☐
Q17	We would like to know how familiar you are with a HIV term: did you ever hear about a CD4 count? Do you know what it means?	☐ Correct ☐ Not correct ☐ Do not know _____				
Q18	If a HIV-patient is treated is the CD4 count expected to go up or down	☐ Up ☐ Down ☐ Do not know				

Remarks: _____

****END QUESTIONNAIRE****