Study Protocol

Do smartphones increase linkage to and retention in care in newly diagnosed HIV-positive patients in Johannesburg, South Africa: A multisite randomised controlled trial

Short title: Smartphone Linkage to Care (SmartLtC)

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Helen Joseph Hospital, Perth Road, Rossmore, Johannesburg

Protocol details

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(this protocol is reviewed regularly and updated as new/relevant mobile lab technology & research is released.

Contents

List of abbreviations & definitions

- **Adherence** (to medication) - Following a medicine regimen according to the recommended dosage and frequency.
- **Android** - A free and open-source smartphone operating system created by Google.
- **App** - An application created for a smartphone. An app can be made for Android, iPhone (iOS), BlackBerry or Windows Phone.
- **CD4** - Also known as CD4+ T helper cells, which are an essential part of the human immune system. The number of CD4 cells found per cubic millimetre determines if an HIV-positive individual should be on ARV medication.
- **Linkage (to care)** - Attendance to follow-up HIV care by an HIV-positive patient. In the current study linkage to care is defined as attendance to a follow up clinical visit and laboratory test within 6 months of HIV diagnosis.
- **mHealth** - The use of mobile devices to support health care.
- **Retention (in care)** - Attending to regular follow-up medical visits once receiving HIV care. In the current study, retention in care is defined as continuation of HIV care (regular clinic visits with laboratory tests and/or medicine pickup) after the linkage to care visit.
- **Smartphone** - A mobile phone that runs an operating system that allows the installation of apps. Most phones that cost $50 USD or more are smartphones as are all Android, Apple, and Windows Phone devices.

Rationale & background

South African HIV testing rates are high, with almost 50% of adults knowing their status (Shisana et al, 2014). However, immediate linkage to the next levels of care of newly diagnosed HIV-positive individuals is very low throughout the region (Rosen, 2011). Improved access to point of care CD4 counts, widely anticipated to have improved linkage to care, have yielded disappointingly limited success, suggesting other interventions are required (Larson, 2013; Faal, 2011). Linkage to care and adherence to medication is higher in HIV than in most other chronic illnesses, and this is widely ascribed to widespread HIV patient education programmes within communities; further patient empowerment and involvement in care may additionally improve retention. Current demographic data on those specifically accessing antiretroviral (ART) care, however, suggests that younger people and men are disproportionately less likely to make this link (Takuva et al 2015), again suggesting that these two groups would benefit from more focus.

Previous research has suggested that mobile phones (mHealth) can improve antiretroviral adherence rates in low-resource settings (Lester, 2010; Pop-Eleches, 2011). However, there is a dearth of literature looking at the use of mHealth to encourage patient linkage to care before initiation of ART, and retention through the continuum of care.

A study in Niger tested whether a simple monitoring system, implemented via the mobile phone, can improve student learning as part of an adult education program (Aker & Ksoll, 2015). Using a randomized control trial in 163 villages in Niger, the investigators randomly

assigned half of the villages to a mobile phone monitoring program, whereby teachers, students and the village chief were called on a weekly basis. There was no incentive component to the program. The program dramatically affected student reading and maths test performance already during the first year of the program.

South Africa is a middle-income country that has seen a large increase in mobile phone ownership over the past few years, with significant growth in smartphone ownership. Since early 2014, most phones sold every month in South Africa have been smartphones, due in large part to price drops (currently under R500/<$50 per phone), with sales projected to continue to increase as the prices decrease further (Techcentral, 2014). This proliferation of smartphones in South Africa provides an excellent opportunity to introduce mHealth interventions. Data from a Khayelitsha (a very poor suburb of Cape Town) research project from late 2014 shows regular use of internet (56%), WhatsApp (60%) and e-mail (30%) by health care patients. Anecdotally there has been a significant increase in the use of Smartphones and internet in South Africa over the last year. In one of the study sites the study team noticed a 40-50% use of smartphone during an observation of individuals waiting in line for HIV testing and the phones they were using to pass time.

South Africa has a National Health Laboratory System (NHLS) within the state sector, with a sophisticated information infrastructure that can link patient laboratory results across health facilities and provinces. In 2013, the National Department of Health agreed to use a single patient identifier across the country, meaning that individualised longitudinal monitoring of patients will be made easier. The use of the unique number will also increase the confidentiality of patient results as an ID book (or passport/refugee card) will be required to ascertain patient identification.

This study proposes providing individual patient laboratory results to newly-diagnosed HIV-positive smartphone users through a secure application (app) as a method to get them linked to and retained in care, and engage with educational materials purposefully developed to explain their results. Message prompts will also be used to alert patients that their results are ready and provide information on how to link to care, and assistance to relink to care if they fall out of the health system for any reason. Finally, prompts will be sent to patients to remind health care workers if they are due for repeat laboratory monitoring.

NHLS, has begun a similar programme with a TB-app, which allows for clinician TB-patient monitoring and follow-up, launched in December 2014. Early feedback from piloting the TB-app show that clinicians value the ability to have a live database to access patient laboratory results. The app for this intervention will be HIV and patient-focused, but will be created based on the experience of the NHLS. It is expected that patients will also value the ability to monitor their laboratory results and learn more about their condition using their own smartphone.

RHI has been sending SMS-based maternal health messages to pregnant women and new mothers since mid-2012 as part of the MAMA South Africa project. Based on the success of MAMA, starting in August 2014, the National Department of Health (NDoH) launched MomConnect, a national SMS-based maternal health registration and information project. Like MAMA, MomConnect sends stage-based maternal health information to pregnant women and new mothers from their first ANC visit until their baby is one year old and as of

mid-March 2015 over 325,000 women have received maternal health messages through MomConnect. RHI assisted the NDoH with setting up MomConnect and is providing ongoing technical assistance. Recently the NDoH has been investigating sending MomConnect messages using IP-based messaging services (Such as the smartphone apps WhatsApp, WeChat, etc.), which signals a shift to accepting that smartphones could play a role within NDoH activities.

The use of smartphones as a method for patients to receive laboratory results has never been published previously. We hope that this study will show that this method is both acceptable and increases patient engagement. The study uses a patient-centered approach to care and treatment that aims to increase patient empowerment. If this concept of an app increasing linkage to HIV care is proven to work in HIV clients in Johannesburg, it will provide important evidence for potential programmatic roll-out of such an mHealth strategy. Additionally, publishing the findings from this study will encourage other research teams to conduct similar research building on what we have done and learnt.

The decision to use a smartphone-based app for the current study is based on inexpensive data costs (for both provider and patient), the privacy/security of an app, the ability to send immediate and secure notifications and high (and increasing) levels of smartphone ownership in South Africa, particularly among urban dwellers. Even in more rural settings smartphone ownership is expected to reach over 70% in a few years as smartphone prices reach $20 USD each (current smartphone's, such as the MTN Steppe, cost as little as R450 or about $35 USD). Based on learnings from the MomConnect program (described above) an SMS-based strategy is not scalable due to the current (relatively) high cost of sending SMSs in South Africa. Additionally, SMS is not secure or private as they can be read by anyone with access to the phone.

While designing the study, the team was conscious of the limited resources of the potential participants. The app will be installed by the research team using a USB connection, negating the need of data charges to download/install it. Additionally, all of the app's background HIV information and computational logic will be built-in, meaning that any new CD4 count/viral load result sent to the app will only be a few kilobytes each, including the data used for logging into the app. This translates to a maximum cost of R0.02 (or $0.0017 USD) on Vodacom's out-of-bundle data rates (which is currently the most expensive data option, out-of-bundle or in-contract, in South Africa[1]) per laboratory result received. Another option for the study was a secure website which works similarly to the app. Such a website would increase data costs for the patient (since everything on the site would have to be downloaded each time it was visited) and would not allow for notifications. For these reasons, a smartphone app was chosen for the study.

[1] For details of Vodacom's out-of-bundle (read: most expensive) data pricing, please see: http://www.vodacom.co.za/vodacom/shopping/data/prepaid-data

Study goals & objectives

Study goal

To determine if a smartphone app that provides laboratory results (CD4 count and viral load) and health information relating to HIV to patients is acceptable to individuals who are newly diagnosed with HIV (will they use it?), increases linkage to and retention in care (do they attend follow up visits at a higher rate?) and can be feasibly implemented in a clinical setting.

Primary objective

To test whether linkage to HIV care is improved by providing clients with access to a smartphone-enabled application (app) when compared to standard of care around 6 months post-diagnosis.

Secondary objectives

1. To compare ART initiation rates between intervention and control arms.
2. To assess the feasibility and acceptability of receiving laboratory results to a personal smartphone.
3. To assess secondary effects from improved patient information, including return rates after falling out of care (assessed through routine patient record reviews), patient satisfaction (through face-to-face surveys at the 6-month follow-up visit and end of the study), and rates of additional blood tests (especially CD4 count, viral load).
4. To assess patient knowledge levels of their laboratory results.
5. To specifically look at 2 subgroups – men and young adults (18 to 25 years of age), who would particularly benefit from improved linkage to care.
6. To assess the performance of the app in clients with different levels of education and standard of living, and see if there are differences in clinical and usage outcomes
7. To evaluate differences in linkage-to-care, HIV-knowledge, adherence to medication (treatment patients only) and reported quality of life between wellness and treatment patients.
8. To assess the financial and economic costs of providing the SmatLtC smartphone app.
9. To determine the incremental cost, and cost-effectiveness of ART initiation link to the smartphone app (receiving laboratory results and linkage-to-care) as compared to the standard ART initiation.

Study design

Population

The study was designed to take place in two high-volume HIV testing sites in Johannesburg, South Africa. To ensure a sufficient sample size for the study results to be statistically significant, the study sites required a minimum of 1000 new HIV-positive patients per month. According to the District Health Information System, there are three possible sites within the province of Gauteng, where Johannesburg is situated; Chris Hani Baragwanath Hospital, Hillbrow Community Health Centre (CHC), and Helen Joseph Hospital. The study team selected Hillbrow CHC and Helen Joseph Hospital due to their proximity to each other, ease of access and the fact that no similar research activities are ongoing in either site.

Hillbrow CHC is an inner-city clinical site which provides primary, HIV, antenatal care (ANC) and postnatal care (PNC) care to patients. Johannesburg's inner-city is characterised by high density living, a large immigrant population and high rates of poverty and unemployment. While official population estimates cite Johannesburg's population as 400,000 individuals, unofficial population estimates suggest that over 900,000 individuals currently live in the area (O'Connor et al, 2011). The official catchment population for Hillbrow CHC is approximately 220,000 from around Hillbrow and surrounding neighbourhoods. Despite the poverty, smartphone ownership for those attending care at Hillbrow CHC is approximately 40-50%. HIV prevalence levels are approximately 22%.

Helen Joseph Hospital is approximately 4 km west of Johannesburg's inner-city in the suburb of Auckland Park. As a tertiary clinical site, the hospital provides a number of clinical services including HIV, ANC, PNC, and specialised care services to patients and has a connection with the University of Witwatersrand's Department of Medicine. The area surrounding Helen Joseph Hospital is comprised of mostly black South African middle-income families living in single unit residential dwellings. Helen Joseph Hospital has a catchment population of around 250,000 and an HIV prevelence of approximately 15-20%.

Linkage-to-care rates for all newly diagnosed HIV-positive individuals in both sites are 50-55%. Women have slightly higher linkage rates, at 60%, while men have slightly lower rates, close to 45%. Exact linkage-to-care figures for young adults, those aged between 18 and 25, in this area are unknown. However, previous research has suggested linkage rates for young adults to be 40-45% (Takuva et al 2015). Due to South African laws that protect exploitation of children and the resulting difficulty in including them in research studies, all participants will be 18 years of age or older.

Intervention

This is a multi-site randomised controlled trial in which newly diagnosed HIV-positive patients, fulfilling all inclusion criteria, will be randomised to either receive the intervention (installation of a password-protected laboratory result and HIV-information app on their smartphone) or the standard of care. All patients will be provided with their unique identifier, to present to the clinic, and asked for permission to access their results on the computer, as a means to assess follow up, to phone them and ask them about their experience of HIV care (at the end of the study) and to verify their clinic attendance throughout the study. Participants will be able to provide feedback about the study to the study team by phone or SMS at any time. In return for their time all study participants will receive a R50 study participation allowance, in the form of a mobile phone credit voucher, at the end of their recruitment visit. Participants will be informed that no additional funds will be provided for subsequent appointments.

Patients randomised to the intervention arm will be assisted with downloading and installing the app, and setting up their accounts with a username, password and PIN. How to use the app including accessing laboratory data and HIV support information will also be explained. All patients will be recruited at first CD4 count test as the classification into 'wellness' or 'treatment' will not occur until their return to the clinic. As standard of care, both wellness and treatment patients are requested to return after 6 months for a follow-up phlebotomy and CD4 count (for wellness patients) or viral load (for patients on ART) testing. All study

participants will be assumed to be linked to care if they attend for the follow up laboratory tests by the end of the 8th month after joining the study. The study team is aware that some patients will need ART bloods at 3 months, and some will need a follow-up VL due to not being suppressed at 6 months. With this in mind, the app will notify the study participant to go for an appointment 6 and 12 months after recruitment irrespective of their initial CD4 count (both wellness and treatment groups). To provide additional support to study participants in the treatment arm, the app will monitor the first viral load result and notify participants with a viral load of >1000 copies/mm^3 to go to the clinic in two months, while notifying participants with a viral load of <1000 copies/mm^3 to go to the clinic after six months. This logic will be built into the app and is per current South African HIV Guidelines published 24 December 2014 by the National Department of Health.

The intervention arm will not receive additional or different individualised or real time care, other than at the installation and use of the app; we want to demonstrate the performance of the app in as 'real-world' an environment as possible. Any appointment reminder message sent to the patient will be automated and based on algorithms developed from national guidelines. Use of the app by patients is expected to add to their understanding of HIV and the role of laboratory tests (specifically CD4 counts and viral loads) and ARV medicine as the treatment ensuring their wellbeing. If visits are missed, or monitoring protocols are not followed, this will be noted when the final data are analysed. The team will also monitor use of the app by patients throughout the study to get an understanding which parts of the app were regularly used and how long patients spent reviewing their results or reading other information within the app.

Inclusion criteria

- Newly diagnosed HIV-positive, clients presenting at selected public health facilities, irrespective of CD4 count
- Access to an Android smartphone with data (estimated to be 40-50% of current Hillbrow Community Health Centre (CHC) population)
- Willing to pay the (small) cost to access their laboratory result
- Age – 18 years and older
- Proof of ID/passport/refugee number (for identification/security, and to confirm the single patient identifier)
- Can read English or Zulu
- Ability and willingness to sign informed consent

Exclusion criteria

- Clients presenting for ANC services, as these women will be enrolled in the national MomConnect program
- Refusal to participate

Note that success of the primary objective is not ART initiation, but linkage to care as defined above i.e. *attending for a CD4 count measurement PLUS one other HIV-related NHLS test within 8 months of HIV diagnosis*. This allows the study team to assess linkage to care of patients who are both eligible and not eligible for ART. Traditionally, non-ART eligible patients have been disproportionately lost to follow up and have therefore been included in

this study.

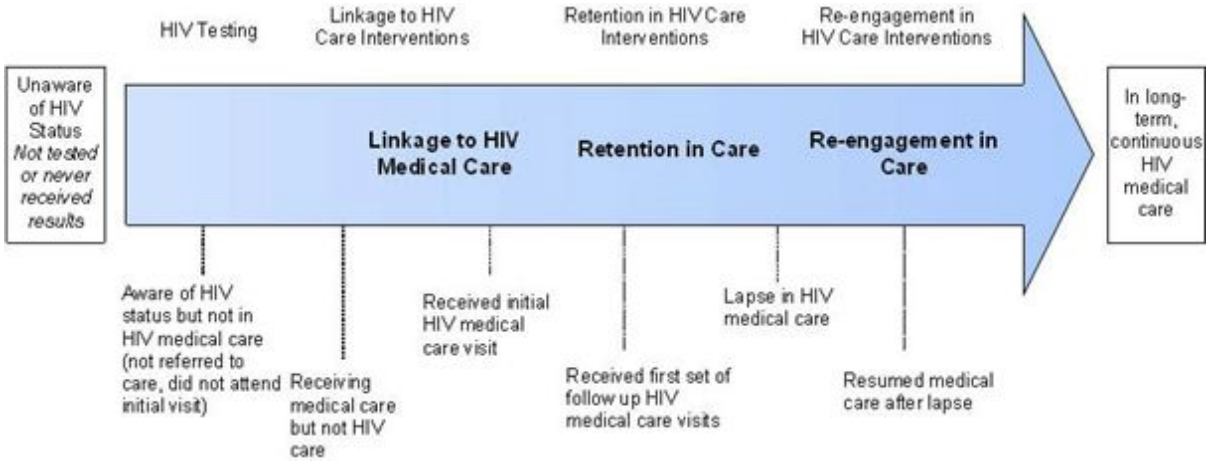


Figure 1: Adapted from Health Resources and Services Administration, HIV/AIDS Bureau. Continuum of engagement in HIV care. Cheever LW. Engaging HIV-infected patients in care: their lives depend on it. Clin Infect Dis 2007;44(11):1500-02. Available from http://www.cdc.gov/hiv/prevention/programs/pwp/linkage.html

Methodology

Pre-recruitment

Prior to recruitment the study team will test study feasibility through potential user one-on-one interviews and focus groups to test the usability and language of the app, the information contained within it, the informed consent document and an HIV quiz to ensure these tools are understandable by potential study participants. Additionally, the study team will host a meeting with Wits RHI's HIV-positive Community Advisory Group (CAG) to garner feedback, gauge interest in the app and test usability. This qualitative feedback on app use and interpretation of data will be used to improve the app design and client information. Due to the proof-of-concept nature of the study, we will not conduct a pilot, but we will monitor and review progress regularly, and act on any feedback received from app users.

Recruitment

Study participants will be recruited at HIV clinics after receiving a confirmatory HIV test and following the drawing of CD4 count bloods. A trained and GCP-certified research staff member will approach patients and inform them about the study, and invite them to get pre-screened for participating in the study. The study team is aware this can be a traumatic time for individuals, but previous research has provided RHI staff with useful experience to ensure that the research staff are appropriately sensitive to the patient's feelings and needs. The recruitment site will be organised for efficient flow of potential participants which will include a private space for consenting to the study, collecting patient information and app installation/training. Two recruiters will work at each site, minimising the waiting time for potential participants.

If interest is shown, the study recruiter will first inquire about their age and pregnancy status as the study only allows those who are 18 years of age and older and not currently pregnant. Upon finding individuals who are under 18 or are pregnant the recruiter will inform them they are not eligible, thank them for their time, and record the reason for non-participation in the study database. For individuals who are 18 or older and are not pregnant, the recruiter will invite them to a private space where they will be asked (non-identifying) demographic and socioeconomic questions. The demographic and socioeconomic questions asked to all potential participants will allow the study team to perform a comparison later to determine what differences there are between smartphone owners and non-owners, and how generalisable the results are. Following the demographic and socioeconomic questions will be a number of inclusion and exclusion criteria questions to confirm the remaining eligibility criteria (smartphone ownership, literacy, photo proof of identification, willingness to participate). If an individual is found to be ineligible the recruiter will inform them they are not eligible, thank them for their time, and record the reason for non-participation in the study database. If the reason for exclusion is that they do not own an Android phone with data, the type of phone will also be noted.

Patients who fit the study eligibility criteria will be invited to participate, provided a broad overview of the study, explained the randomisation, read the informed consent documentation, and asked to sign it after being told that participating requires them to allow the study team to monitor their laboratory results throughout the study and contact them with a follow-up questionnaire about their experiences of the study and HIV care they received. At any time, if an individual decides they do not want to participate, the recruiter will thank them for their time, and record the reason for non-participation in the study database.

Upon signing informed consent, their personal details including name, surname, ID number, and a baseline survey which consists of a HIV/CD4 count knowledge questionnaire (all tools listed in appendix II) will be recorded into REDCap (Harris et al, 2009), an electronic data capture tool hosted at Wits University[2], using a tablet device by trained research staff. At the end of the recruitment process all patients will be provided their R50 participation allowance. Patients in both study arms will be encouraged to return to the clinic as per the clinic guidelines to receive their CD4 result and attend wellness or HIV care follow-up.

REDCap will randomise the participant to the standard of care or intervention arm through the device without informing the participant. Participants randomised to the standard of care arm will be provided with a copy of their signed informed consent document and thanked for their time.

Participants randomised to the intervention arm will be told about the smartphone app and told how it works. The study staff member will install the app on the participant's phone and assist the participant in setting up an account with a username, password and PIN number and provide an overview of how the app and notification system works. Participants will be

[2] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

informed that they are welcome to use the app at any time, and it will notify them when a laboratory result has arrived. As mentioned above, the cost per laboratory result received is approximately R0.02. Patients will be informed of this cost prior to participating.

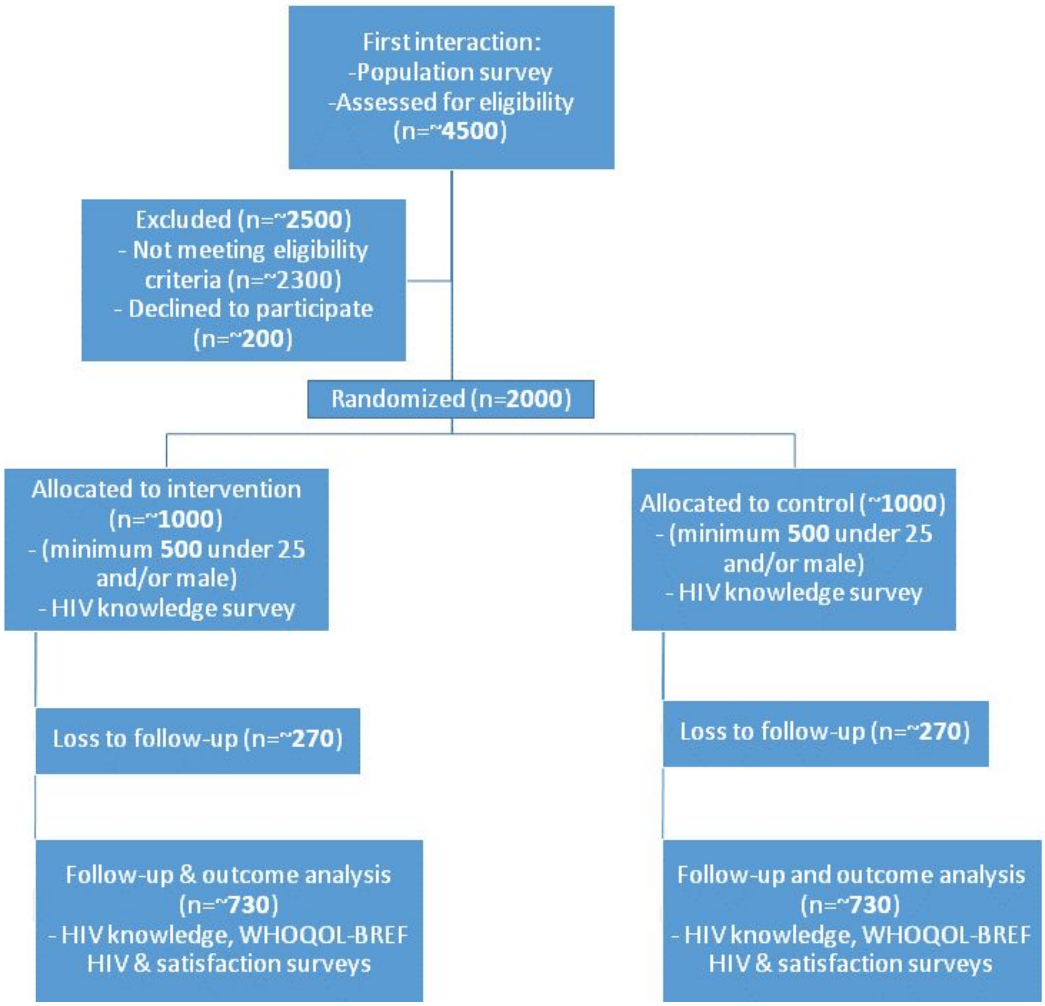
The aim of the study is to show that smartphone apps work for that proportion of the population that currently have Android smartphones, not that it works for the general population. Smartphone purchase is rapidly increasing in South Africa, with 75% of new cell phones sold in South Africa currently being smart phones. We expect that randomization and a large sample size will enable us to have a reasonable balance between the arms, unless participants randomized to the control group request study withdrawal due to not getting the app.

Sample Size

Based on a primary endpoint of a second HIV-linked laboratory test (CD4, viral load) being performed at a clinical facility, within 8 months after the HIV-positive result, suggesting successful attendance and entry into HIV care, we anticipate at least 1000 patients in each arm will be needed. The study team expects to see a 20% difference in linkage to care levels through the app (using a second HIV-linked laboratory test as an indicator for linkage to care). The sample size is calculated based on 80% power, 0.05 significance with a loss-to-follow-up rate of approximately 27% (Hillbrow CHC data). Both ART and pre-ART patients will be expected to return for a follow-up laboratory test around 6 months after diagnosis; ART patients for a viral load, and pre-ART for a follow-up CD4 count.

In South Africa, both younger and male clients have lower linkage to care rates than females and individuals over 25. In order to conduct subgroup analysis on these higher-risk populations (young people and men), there will be an over-sampling of male patients and those between the ages of 18 (the age of majority) and 25 for both the intervention and control arms given that it has been shown that these groups are less likely to access health services efficiently (Kranzer, 2010). These populations will be recruited until 250 of these individuals are included in both arms to ensure the study is powered to analyse the effect in these key subgroups. Based on a 20% difference in linkage to care for the intervention/app arm with an 80% power, a significance level of 0.05 and a loss-to-follow-up rate of 40% a sample size of 97 per arm is required. Again, the study team will over-sample based on the proof-of-concept nature of the study.

Figure 2: *Recruitment flow chart*



App specifications

The application will be able to be quickly installed by the study staff, at no cost to the patient, and once installed, will consume minimal network data, as patients are very conscious of cost of data bundles. For the study the app will be available on Android only (the type of phone potential participants with non-Android smartphones have will be recorded). The app icon and name on the phone will be non-descript and not suggestive of a health application. Username, password and PIN requirements will prevent any unauthorized access to this data. App-based push-notification reminders will notify patient when a new result is present by stating "*There is updated information for you. Please use the app to access it*". The notification will give no detail about the nature of the information, ensuring all detail is only displayed within the password-protected section of the app.

Within the app, laboratory result data will be presented clearly, with simple explanations on every screen, in English and Zulu with a grade 4 reading level (as per WHO guidelines on literacy). Laboratory results will not be shown in isolation, but will be supplemented with

informative and relevant information explaining the result that has been shown[3] and the recommended action for the patient to take. Patients will also be able to view additional HIV-related information and a Frequently Asked Questions (FAQ) through the app. This information will be created with support from HIV clinicians and psychosocial teams and focus on information that is relevant for newly diagnosed HIV-positive individuals. Links to external sites (e.g.: National Department of Health HIV site, LoveLife, etc.), to get further HIV support/information will be provided (to be opened in the smartphone web browser) and access to them will be monitored by the app. Automated prompts will be built-in to the app, triggered automatically at five and a half months, six months and 12 months after the app has been installed. These triggers will inform the patient that it is (almost) time to attend a further laboratory test.

The app will measure the number of times and dates/times that it is opened, relative to the sending of the push notifications, so as to understand usage. In addition, we will be able to tell if the app is opened during a clinic visit (as measured by a laboratory request), marking a possible showing of the result to a health care worker. Health care workers in the study sites will be briefed about and explained how the app works. Patients will be encouraged to use the call back facility if they have linked to care but are still receiving reminder notifications to do so; this should allow us to evaluate the accuracy of the single patient identifier use. Note that patients who have been linked to care at the study sites will automatically stop receiving the reminder notifications until the next time they are required to attend the clinic. An overview of app specifications can be seen below (Appendix III).

Prior to study recruitment, the study team will conduct at least two focus group discussions (FGD's) with potential study participants. These FGD's will test the ease of installation and use of the app, language level of the content, understanding of the laboratory test results, and satisfaction of the participants. Feedback from the FGD participants will be shared with the app developers who will make improvements to the app.

Patient follow-up

Patients will be followed up for a minimum of one year and maximum of 18 months to monitoring linkage to care and retention in care. We anticipate recruitment taking 3 months resulting in data spanning 15-18 months, over the 2 year lifetime of the project (if funding is secured, as per issues cited in the "Risks" section, below). The outcome of the primary objective (linkage to care) will be analysed 8 months after recruitment of the last participant to allow for patients link to care slightly delayed.

[3] For example, if a CD4 count of 250 is returned, the number will be shown in red with an informative note explaining that that CD4 value is abnormally low and request that the patient attend to the clinic for further care as soon as possible. Alternatively, if the a CD4 count result of 700 is returned, the number will be shown in amber (a warning colour) with an informative note explaining that the CD4 count value is within the normal range and they should return to the clinic for wellness counselling and then have another CD4 count test in 6 months. For any result (CD4 or viral load) the patient will be able to get more information about HIV/AIDS, CD4 counts and viral loads within the app, see a list of frequently asked questions (FAQ), given clickable links to get external (web) information or provided contact numbers for the study team (for study or app-related questions) or the National HIV/AIDS helpline (for HIV-related questions).

Baseline recruitment will include questions on basic demographics. Throughout the study the team will monitor the number of times the app is accessed to view laboratory results and/or support information by the user; and loss-to- follow-up. Healthcare monitoring, measured by appropriate laboratory adherence to treatment guidelines, will be monitored through the NHLS database; in particular, we will monitor whether providing information to the patient to prompt the health care worker improves compliance with guidelines. All patients who exit from the trial will be given a survey that includes questions to assess CD4 count and HIV knowledge, health status, health care access, and patient satisfaction with the app, as well as with the health care services. This will allow us to compare how much the app has contributed to linkage to and retention in care, as well as to patient understanding of their health management.

After 8 months of participating in the study the research team will monitor participant attendance to a follow-up laboratory test through the NHLS test database. The patient will not be contacted at this point. Data will be analysed comparing the standard of care arm with the intervention arm.

With additional funding the study will include a patient follow-up 12 months after recruitment. Patients will be contacted by phone and asked to complete the WHO Quality Of Life BREF HIV tool (WHOQOL-BREF HIV[4]), those on ARVs will be given the ACTG ARV adherence tool while all participants will be asked to provide their feedback through an end-of-study questionnaire. The end of study questionnaire includes questions regarding their experiences during the study, their health status, their experience of HIV care, actual and opportunity costs, as well as a follow-up HIV/CD4 count knowledge questionnaire (tools can be found in appendix II). All responses will be recorded into REDCap on a mobile device by research staff.

Cost-Effectiveness analysis

A cost-effectiveness analysis will be conducted and compare the intervention arm with the standard of care arm from the societal perspective. Financial and economic costs will be assessed, which include ART costs, incremental health systems costs, and patient productivity loss due to morbidity and mortality. A potential for cost savings due to a reduction in low CD4 count results, Adverse Event (AE) and Opportunistic Infection (OI) will also be incorporated into the cost-effectiveness analysis.

Populations under consideration:

- General population
- General population categorised by 5 year age groups
- Specific populations: 18 to 25, over 25, men

Epidemiology outcomes:

- HIV mortality by 5 year age groups
- HIV incidence by 5 year age groups

[4] The WHOQOL-BREF HIV is a cross-cultural quality of life assessment tool based on the WHO-QOL100 and the WHO-QOL-BREF. The WHO-QOL-BREF HIV measures quality of life for those with HIV over 31 questions.

- HIV prevalence by 5 year age groups
- Rate of progression to death through four equal durations
- HIV stages defined by mean CD4 count

Economic outcomes (to be obtained through the patient chart review include):

- ARV drug costs
- Treatment literacy level
- Clinic consultations (for ART delivery and OI and AE treatment)
- Laboratory tests (including CD4, viral load and routine monitoring tests)
- X-rays
- Diagnostic procedures
- Personnel training costs
- Number of consultations with i) doctors; ii) nurses consultations; iii) other health care personnel
- Number of home visits
- Number of counsellor consultations
- Total annual per patient cost of providing a comprehensive model of ART linkage to care using the smartphone app (receiving laboratory results and linkage-to-care) plus cost over 10 years

Cost-effectiveness analysis involves the comparison of two or more competing methods in terms of both their costs and consequences. The outcome measure of the cost-effectiveness work will be the cost of ART initiation with a particular intervention in South African Rand (ZAR) per disability adjusted life year (DALY) averted. The lower the cost per DALY averted, the more cost-effective the intervention. It will be based on a 5% discount rate.

For each target and cost scenario, this analysis will be able to provide the estimated impact in terms of OI and AE averted, impact in HIV stage defined by CD4 count and treatment costs and deaths averted due to ART linkage to care of those using the smartphone app.

Participant opt-out

All participants will be provided with contact information for the study team and will be informed that they can drop out of the study at any time with no consequences (as per Good Clinical Practice guidelines). Should a participant request to withdraw from the study the team will identify their informed consent sheet and mark it accordingly, remove the patient's data from REDCap and notify the NHLS if they are part of the intervention arm to ensure they will not receive additional notifications of laboratory results. The participant will be asked if they would like to keep their username and password active to access the app in the future; their account will be deleted or kept accordingly.

Safety considerations

Accidental disclosure (through phone loss/theft/borrowing or any other method) will be limited by the study team as much as possible. This will be done actively by having a username, password AND PIN code for app use. Additionally, the recruitment team will inform participants of the sensitive information on the app and request that they don't share it with

anyone. Lastly, the app icon and name will not relate to health or HIV in any way; only after the username and password is entered will health-related terminology be used.

Should a participant have any issues regarding their diagnosis or the study they will be able to access help. At recruitment they will be told that for HIV-related queries they can call the HIV/AIDS helpline numbers that are shown in the app. For study-related queries, they can call the study team on the phone numbers that are listed in the study documentation.

Data management & statistical analysis

Data management

Patient recruitment, demographic, baseline and follow-up survey data will be collected by a trained and GCP certified researcher using a mobile device (tablet) connected to the REDCap database. REDCap is a secure web-based application designed for virtually collecting clinical research data and is used by over 150,000 projects around the world (more information at: http://project-redcap.org/). The REDCap Android app, which will be installed on the tablets, allows for off-line data collection if there is no internet connection available.

Laboratory results will be added to the NHLS laboratory database as they are received and pushed to the participant through an application layer that is part of the smartphone app. The REDCap database will be connected to the NHLS laboratory database using an API (application programming interface). All HIV-related NHLS laboratory results will be recorded as part of the study to monitor the total number and frequency of laboratory tests on study participants. All data transmission between electronic databases/servers will be secured and encrypted.

Paper records (completed informed consent) will be in the control of study staff for the day they are collected. At the end of each day they will be returned to a centralised location (e.g.: RHI offices) where they will be scanned and archived in a data storage room. Once archived the paper records will only be accessed under special circumstances (e.g.: a patient withdraws or a confirmation of a patient's acceptance to be in the study is required).

Data analysis will be conducted by research staff with all identifying participant data de-identified.

Analysis plan

The primary outcome, linkage to care around 6 months after initial diagnosis, will be available after the final patient recruited has reached the 8 month mark, allowing immediate assessment of the feasibility and immediate impact of the app on initial linkage to care. Thereafter, retention in care, defined as continuation of HIV care (regular clinic visits with laboratory tests and/or medicine pickup) after the linkage to care visit will be assessed 12 months after linkage to care had been made.

Analysis will be done by the study team using STATA. Intention-to-treat will be the primary approach of the analysis and all missing data points will be considered to be loss-to-follow-up. Analysis of the primary outcome will be based on a chi-squared test comparing the proportion of individuals between the study arms and within study sites. A

logistic regression model, with linkage to care as the dependent variable, will be a secondary analysis of the primary outcome.

For secondary outcomes, chi-squared tests will be used for binary variables, Mann-Whitney-U tests for non-normally distributed variables, and t-tests for continuous variables. Relative risk calculations (at 95% confidence) will be used to compute binary variables. Survival analysis will be conducted to determine linkage outcomes at 6 months. A sensitivity analysis will be conducted using regression analysis to identify and adjust for potential confounders.

For the cost-effectiveness analysis, we will have data on direct costs and understand the resource requirements for the development of the app. We will corroborate our existing estimates of the smartphone data costs of the patient. The study team will collect data on clients' opportunity cost as part of the end of the study participant interview as linkage to care (as opposed to non-linkage to care) actually takes more time. We will use primary data collect through this study to calculate unit costs associated to providing HIV services.

From the opportunity cost data collected from patients we will analyse clients' time spent travelling to and being at health facilities to assess service uptake to measure actual patient opportunity cost. The team will separate costs of implementing the SmartLtC intervention and standard of care into categories (e.g. ART, other medicine, laboratory & other tests, health personnel time, overhead and capital costs, patient transport, and lost patient time) which will come from the WHO CHOICE database. Additionally, we will calculate DALY's saved based on disability and deaths averted due to the intervention with weights based on the 2010 Global Burden of Disease Study.

Regulatory compliance

The following methods will be employed to ensure high quality assurance throughout the study period:

- All study staff are GCP trained and certified throughout the study period.
- The study will not start before it receives ethics permission from the University of Witwatersrand Human Research Ethics Committee (Medical) and approval from the district research committee.
- All data collected for the study will be treated sensitively and stored in a secure location (for paper documents) or a secured, password and encrypted database (for electronic records)

Ethics

As a research institute, all RHI research projects go through both internal and external research review. The external review is done through the University of Witwatersrand's ethics board, the Human Subjects Research Committee (HSRC). The SmartLtC study will not start recruiting patients before the committee has reviewed the study and has provided ethics clearance.

Informed consent forms

Informed consent form can be found at the end of this document in Appendix I.

Expected outcomes

This study is expected to have the following outcomes by the end of the project:

- An analysis of the effect of the app in linkage to care for the study population and in different demographic and socioeconomic subgroups
- An understanding of the acceptability of the laboratory result app
- Incremental cost-effectiveness ratio for SmartLtC compared to SOC from the societal perspective and the DOH perspective
- One or more conference presentations on the study and outcomes
- One or more published academic journal articles describing the study and outcomes
- A study report providing recommendations to policy makers, other study teams, and health practitioners.

Dissemination of results and publication policy

Study results will be presented at national and international HIV/AIDS management and clinician conferences and meetings. Study manuscripts will be submitted to the appropriate journals. Results outcomes will be shared at internal and external research days as well as academic meetings. All these dissemination activities will be planned and carried out in close collaboration with the World Bank team.

Duration

Planning is currently ongoing. Recruitment is expected to start: June 1 2015 with 8 months of follow up minimum. Should additional funding be found, a further 12 months of follow-up will be conducted (ending December 2016).

A brief overview is as follows:

Activity	**Year 1**												**Year 2** (to be fully funded)											
	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Project launch																								
Ethics application																								
Hiring																								
Training																								
Educational development																								
Smartphone app development																								
Patient recruitment																								
Data analysis (6 month outcomes at 8 months)																								
Participant follow-up																								
Data analysis (12 month outcomes at 14th month)																								
Report/article writing																								

Problems anticipated

Potential risks

The largest potential risk revolves around permission from tiers of government for the project to continue. We hope to perform this in different provinces, but are constrained by the limited funding times, so we will need to assess the quickest way forward after we have submitted for permission.

We have noted that funding is not currently committed for year two, and will mobilise internal and other funding should World Bank not be able to commit resources to completing the last phase. A 12 month extension is essential as the primary outcome extends into the second year. The second year will allow the team to look at the effects of the app on ongoing pre-ART monitoring and on patient information concerning VL testing, VL as an adherence tool, and actual viral suppression.

Since the study is voluntary, there is a chance of bias in patient selection. It is possible that more involved patients will want to participate and thus more likely to be linked to care and retained in care (the healthy participant effect). The randomisation process should mitigate some of these issues ensuring the same number of 'involved patients' are in each arm. As with all voluntary studies, there is a chance that the results might not be completely representative of the general population. This is acknowledged here and will also be acknowledged in any study outcomes that are published.

As the app is not hidden from the facility nurses, there is a chance that they might change the care they provide due to fear of being reported by the participant or the app. To minimise the chance of this, the study team will meet with the HIV nursing team prior to recruitment to explain exactly how the app works including what it can and cannot do.

Finally, there is the challenge of making this app broadly available. If the primary outcome is achieved, that is improved linkage to care, we will engage the government to support the national rollout of this application, potentially at the point of first CD4 test.

Limitations

The study team acknowledges that self-testing and door-to-door testing clients will not be included in this trial. This is relevant as South Africa will soon have a large push on home-based HIV testing. However, further studies could include these client populations.

Project management

The project management team is as follows:

Name & organisation	Area of expertise relevant to study	Designation for study	Assigned tasks	% time
Jesse Coleman, RHI	mHealth project management & health care research	Principal Investigator/project manager	Project management	50%
Vincent Lau Chan, RHI	mHealth project coordination	Project coordinator	Project coordination	50%
Mothepane Phatsoane, RHI	mHealth project coordination	Research assistant	Research assistance	50%
Maano Nengwani, RHI	Data management	Data manager	Data management	25%
Lynsey Isherwood, NHLS	National Health Laboratory Service	App development & project support	App development management	20%

Willem Daniel Francois Venter, RHI	HIV technical expert	Support to project	Review of research design and conduct, as well as technical support on HIV educational materials	10%
Sergio Carmona, NHLS	National Health Laboratory Service	Support to project	Review of research design and conduct	10%

Budget

The total budget for the first year of the study is $200,992 (approximately R2.3 million as of 8 February, 2015). 62% ($125,108) of this will be used for staff remuneration while the remainder ($75,814) will be used for non-human resource study expenses including contracting for app development.

Timeline

Detailed timeline of first year:

- January report submitted: 5 February 2015
- Study protocol complete: 11 February 2015
- Site selection: 13 February 2015
- Project start-up workshop: 19 & 20 February 2015
- World Bank protocol review: 24 February 2015
- Wits ethics submission: 6 March 2015
- February report: 9 March 2015
- Expected ethics approval: late March/early April 2015
- Data management system (RedCAP) setup: Feb-Mar 2015
- REDCap ready: March 30 2015
- Submission to and approval from district research team: April 2015
- March report: 3 April 2015
- App development: Feb-April 2015 (App developer sub-contract to be signed in early March - Specifications can be found in Appendix III)
- App testing: April 2015
- Minimum viable product (app): 1 May 2015
- April report: 8 May 2015
- Study recruitment start: 1 June 2015
- May report: 5 June 2015
- June report: 6 July 2015
- July report: 6 August 2015
- Study recruitment end: 31 August 2015
- August report: 7 September 2015 (8^{th} monthly report summarising 8 months of implementation and a contract deliverable)
- Follow-up: June-December 2015
- Data analysis: Nov-Dec 2015
- Draft study report: 11 December 2015
- Expiration of contract: 31 December 2015
- Final report & STATA database: 29 Jan 2016
- Academic manuscript: 1 April 2016

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Appendix I: Informed Consent

Information Leaflet and Informed Consent

Smartphone Linkage to Care (SmartLtC)

SPONSOR: The World Bank

INVESTIGATOR: Jesse Coleman

CO-INVESTIGATORS: Vincent Lau Chan, Prof. Francois Venter

INSTITUTION: Wits Reproductive Health and HIV Institute (RHI)

DAYTIME AND AFTER HOURS TELEPHONE NUMBER(S): 011 358 5400/072 676 9854

1. INTRODUCTION:

Hello, my name is _____. I am a fieldworker with the Wits Reproductive Health and HIV Institute; an organisation associated with the University of the Witwatersrand I am assisting with some research. We would like to invite you to consider being a part of a research study which aims to test a new way to support HCT clients. I would like to take a few minutes to explain to you how this programme works. Before agreeing to participate, it is important that you read and understand the following explanation of the purpose of the programme, the procedures, benefits, and risks, and your right to withdraw from the programme at any time. This information leaflet is to help you to decide if you would like to give your permission to participate. You should fully understand what is involved before you decide to take part in this programme. If you have any questions, do not hesitate to ask me. You should not agree to take part unless you are satisfied with the information relating to all the procedures involved. If you decide to take part in this study, you will be asked to sign this document to confirm that you understand what is involved. You also be required to give us your cellphone number so that we can contact you at a later stage. You will be given a copy of the information sheet to keep.

2. PURPOSE OF THE STUDY:

· The purpose of this study is to test a new way of improving HIV care in public health care facilities.

· Some participants of the study will receive extra health information relating to their HIV status.

· If you agree to participate, please indicate your willingness to the research staff.

3. LOCATION OF THE PROGRAMME AND DESCRIPTION OF PARTICIPANTS:

·The research will be conducted with users of Hillbrow CHC and Helen Joseph Hospital.

·All participants will be older than age 18 and be receiving health services from the locations listed above.

·Potential participants must own an Android smartphone (e.g.: Samsung, Sony, LG)

4. PROCEDURES:

· If you agree to participate in this programme, we will put your name and other information in a secret database. No-one except me and the project team will have access to this information.

· You will continue to receive care as usual from the health care site, including blood draws, laboratory results, medicines, and counselling.

· You will not be given any experimental medicines as part of this programme and there will be no other procedures performed which is not part of your routine care.

· You will have access to the same treatment regardless (even if you do not agree to participate)

· You may at any point during the study decide to withdraw. Your feedback is welcome. If you consent to participate, and decide to withdraw at a later stage, an opt-out option will be provided.

· During the course of the study, you might be asked to give feedback about your experiences with the study. Participation is optional and you will receive the same treatment and care if you decline to participate

· You have a 50% chance of falling into the group that will not be using the cell phone App

· Irrespective of the group you are in, you will be provided R50 airtime

5. WILL ANY OF THESE STUDY PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

· We will not cause you any additional pain or discomfort beyond the routine care which you will receive.

6. BENEFITS & RISKS

Benefits

By enrolling in this programme, you may receive access to additional health and wellness information about status. The chances of you receiving access to this information is random, similar to flipping a coin. If you do not receive this information, you will still receive normal informational and care.

Risks

Due to the nature of this study, there is a possibility of accidental disclosure of your HIV status. The study team staff will explain to you how to minimise accidental disclosure.

7. RIGHTS AS A PARTICIPANT IN THIS PROGRAMME:

§ Your decision to participate in this study is completely free and you can decline to be part of the programme at any time, without stating any reason.

§ Your decision participate in this study will not affect the care you receive in the clinic or your relationship to the hospital/clinic in any way.

8. FINANCIAL ARRANGEMENTS:

· There are no costs to participate in the study.

9. REIMBURSEMENT FOR STUDY PARTICIPATION:

· You will be provided with a R50 mobile phone credit voucher if you participate in this study to say Thank You for giving us some of your time today for this research.

10. ETHICAL APPROVAL:

· This quality improvement protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been granted by that committee.

· The programme has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2008), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

· **The 24-hour telephone number** through which you can reach me or another authorised person – 011 358 5400/ 072 676 9854

If you change your number during the course of the study please send a please-call-me to the following number 072 676 9854. We will then contact you to get your new phone number.

· If you want any information regarding your **rights as a research participant, or complaints regarding this programme**, you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.

11. CONFIDENTIALITY:

· All information obtained during the course of this programme implementation, including hospital records, personal data and routine programme or clinical data will be kept strictly confidential. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this programme.

· The information might be inspected by the University of the Witwatersrand, Human Research Ethics Committee (HREC), and the South African Medicines Control Council (MCC). Therefore, you hereby authorise me to release your medical records to the South African Medicines Control Council and the University of the Witwatersrand, Human Research Ethics Committee (HREC).

· These records will be utilised by them only in connection with carrying out their obligations relating to this programme implementation.

· Any information uncovered regarding your test results or state of health as a result of your participation in this programme will be held in strict confidence. This information will not be disclosed to any third party in addition to the ones mentioned above without your written permission. The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the Department of Health exists.

WRITTEN PARTICIPANT INFORMED CONSENT:

I hereby confirm that I have been informed by the **interviewer (fieldworker's name)** _____, about the nature, conduct, benefits and risks of the mobile health programme which gives me personalised health information.

I have also received, read and understood the above written information **(Participant Information Leaflet and Informed Consent)** regarding the programme intervention.

- I am aware that the information obtained from this programme, including personal details regarding my sex, age, initials and diagnosis will be anonymously processed into a report.
- In view of the requirements of research, I agree that the data collected during this programme can be processed in a computerised system by the Wits Institute of University of Witwatersrand.
- I may, at any stage, without prejudice, withdraw my consent and participation in the programme.
- I have had sufficient opportunity to ask questions and (of my own free will) declare permission to participate in this programme.

PARTICIPANT:

Name Surname

_____ _____

Signature Date and Time

_____

I**, (Interviewer)** _____, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above programme.

Interviewer (Fieldworker):

Printed:

Name & Surname Signature Date and Time

VERBAL PARTICIPANT INFORMED CONSENT:

(Applicable only when participants cannot read or write)

· I, the undersigned, (**interviewer**) .....have read and have explained fully to the participant, named ..... the participant information leaflet.

· The account I have given has explained both the possible risks and benefits of participating in this programme.

· The participant indicated that he/she understands that they will be free to withdraw from the programme at any time for any reason and without jeopardising his/her subsequent treatment.

I hereby certify that, the participant has agreed to participate in this programme.

PARTICIPANT:

Printed Name _____ Printed Surname _____

Mark or Thumbprint (if applicable) _____ Date and Time _____

Witness Name _____ Date and Time

Witness Signature _____

Interviewer (Fieldworker):

Printed Name **Signature** **Date and Time**

Appendix II: Participant survey tools

	Population survey (To be given to all newly diagnosed HIV-positive patients that have had CD4 count bloods drawn)
1	Recruitment Date:
2	Recruitment site:
3	Gender:
4	Date of birth:
5	Marital status:
6	Suburb currently living in:
7	Country of birth:
8	Highest education received:
9	What is your current employment status?
10	Usual monthly household income: (Note: still being reviewed based on discussions around Proxy Means Test method)
11	Preferred language for reading:
12	Do you share your phone with someone?: Y/N
13	Do you own a smartphone? Y/N
14	Do you use data on your smartphone (eg: WhatsApp, WeChat, Mxit, web page, email)?

	Recruitment survey (To be given to all eligible and willing participants)
1	First name:
2	Last name:
3	Phone number:
4	SA ID, Passport or refugee number:
5	Lab Specimen ID number:

6	WHO staging on patient chart: 1, 2, 3 or 4

	Reason for ineligibility survey (To be given to ineligible patients)
1	Age - Under 18
2	Phone - Not Android/Not working/Not active
2a	Type of phone:
3	No photo proof of identity
4	Cannot read English or Zulu
5	Not willing/unable to sign informed consent
6	Pregnant
7	Refused to participate

	HIV/CD4 Count/VL knowledge All answers are true/false (Correct answer in parentheses) (To be given at baseline and end of study for all participants)
1	A healthy-looking person can have HIV. (True)
2	Coughing and sneezing DO NOT spread HIV. (True)
3	A person can get HIV by sharing a glass of water with someone who has HIV. (False)
4	A woman can get HIV if she has anal sex with an HIV positive man. (True)
5	Showering, or washing one's genitals/private parts, after sex keeps a person from getting HIV. (False)
6	A pregnant woman infected with HIV and taking medicines will always have a baby born with HIV. (False)
7	People who have been infected with HIV quickly show serious signs of being infected. (False)
8	A woman cannot get HIV if she has sex during her period. (False)
9	There is a female condom that can help decrease a woman's chance of getting HIV. (True)

10	A person will NOT get HIV if she or he is taking antibiotics. (False)
11	A person can get HIV from oral sex. (True)
12	HIV can be transmitted through vaginal sex without condoms. (True)
13	HIV cannot be transmitted through use of public toilets. (True)
14	HIV cannot be transmitted through sweat. (True)
15	Use of birth control pills cannot prevent people from getting the HIV/AIDS virus. (True)
16	There is no vaccine available that can keep people from getting AIDS. (True)
17	Antiretroviral drugs keep people living with HIV/AIDS. from getting sick or dying. (True)
18	HIV can be transmitted by eating and drinking from the same plate or glass of an HIV-positive person. (False)
19	HIV can be transmitted through a mosquito bite. (False)
20	HIV can be prevented by properly using condoms during sexual intercourse. (True)
21	Antiretroviral drugs can cure HIV/AIDS. (False)
22	Antiretroviral drugs can prolong the life of people infected with HIV/AIDS. (True)
23	Men and women normally have the same CD4 count. (False)
24	Physical activity can impact CD4 count. (True)
25	A lower CD4 count is better. (False)
26	HIV decreases CD4 count in people who don't take ARVs. (True)
27	A person's CD4 count helps determine if they should be on ARVs. (True)
28	An HIV-negative person always has the same CD4 count. (False)
29	People with HIV who are not on ARVs should check their CD4 count every 6 months. (True)
30	People with HIV are more likely to get other diseases like TB. (True)
31	A viral load test determines how much HIV is in the blood. (True)
32	CD4 counts and viral load tests don't help HIV infected people at all. (False)
33	A higher viral load is better. (False)
34	Someone who takes their ARV medicine regularly will likely end up with an 'undetectable' viral load. (True)

	WHOQOL-BREF HIV (To be given at end of study for all participants)
1	What is your marital status?
2	How is your health (Very poor/Poor/Neither Poor nor Good/Good/Very Good)
3	Do you consider yourself currently ill? Yes/No
4	If there is something wrong with you, what do you think it is?
5	In what year did you first test positive for HIV?
6	In what year do you think you were infected?
	All questions below are Likert-scale (1-5) based on the original WHOQOL-BREF HIV tool
7	How would you rate your quality of life?
8	How satisfied are you with your health?
9	To what extent do you feel that physical pain prevents you from doing what you need to do?
10	How much are you bothered by any physical problems related to your HIV infection?
11	How much do you need any medical treatment to function in your daily life?
12	How much do you enjoy life?
13	To what extent do you feel your life to be meaningful?
14	To what extent are you bothered by people blaming you for your HIV status?
15	How much do you fear the future?
16	How much do you worry about death?
17	How well are you able to concentrate?
18	How safe do you feel in your daily life?
19	How healthy is your physical environment?
20	Do you have enough energy for everyday life?
21	Are you able to accept your bodily appearance?
22	Do you have enough money to meet your needs?
23	To what extent do you feel accepted by the people you know?

24	How available to you is the information that you need in your day-to-day life?
25	To what extent do you have the opportunity for leisure activities?
26	How well are you able to get around?
27	How satisfied are you with your sleep?
28	How satisfied are you with your ability to perform your daily living activities?
29	How satisfied are you with yourself?
30	How satisfied are you with your personal relationships?
31	How satisfied are you with your sex life?
32	How satisfied are you with the support you get from your friends?
33	How satisfied are you with the conditions of your living place?
34	How satisfied are you with your access to health services?
35	How satisfied are you with your transport?
36	How often do you have negative feelings such as sadness, despair, anxiety, depression?

	Satisfaction survey Likert Scale (1 Strongly disagree - 5 Strongly agree) (To be given at end of study. Note: Questions in bold will only be asked to intervention patients)
1	Overall I am very happy with the study
2	**Overall I am very happy with the app**
3	**The app helped me learn about my condition**
4	**The app was easy to use**
5	**The language in the app was easy to understand**
6	**I felt like I could trust the information in the app**
7	I learnt a great deal about HIV in the past 12 months
8	I learnt a great deal about CD4 count in the past 12 months
9	I learnt a great deal about viral load in the past 12 months
10	**I would recommend the app to other patients**

11	**The app made life easier for me**
12	The clinic staff was always friendly when received HIV care
13	I feel I know a great deal about HIV
14	I feel I have the tools to keep myself healthy
15	I feel I could help a friend who was HIV-positive
16	**I visited the frequently asked questions (FAQ"s) in the app**
17	**The frequently asked questions (FAQ"s) were helpful**
18	**The frequently asked questions (FAQ"s) were relevant**
19	**I read the "More Information" section of the app**
20	**The "More Information" section of the app was helpful**
21	**The "More Information" section of the app was relevant**
22	**The explanation of CD4 count was useful**
23	**I went to the links to additional sites to get more information**
24	**The reminder to go for an additional test at 6 months was helpful**
25	**The reminder to go for the additional tests was useful**
26	**I would recommend the app to other people**
27	**The app would have been more useful if it covered other health issues.**

	Costs incurred tool (To be given at end of study for all participants)
1	How much do you usually pay per month to support the routine use of your mobile phone (including air time, maintenance, and other costs)?
2	How much money do you usually spend on transportation to attend the HIV clinic?
3	Do you usually take time off from work to attend the HIV clinic?
3a	If yes, how much money or income did you lose because of this absence from work?
4	What is the amount of time (in minutes) you usually spend on your HIV clinic visits from the time you depart (your home, work or elsewhere) to go to the health facility until the time you returned?
4a	Travel time (round trip): _____ Waiting time: _____

	Consultation time: _____ Pharmacy time (obtaining medicines): _____ Total time: _____
5	Did you have to pay someone to take care of any other children while you attended the HIV clinic?
5a	If yes, how much did you spend?
6	How many times have you been to the clinic to receive HIV care since your HIV diagnosis?
7	Did you ever attend the clinic for care and were not seen?
7a	Why were you not seen? - Attended wrong time/day - Clinic too busy - Other: _____

	ACTG Adherence Tool - Standardised HIV treatment adherence tool (To be given at end of study to study participants on ARV medicine)
1	What HIV medicines are you currently taking?
2	How many pills of each do you take each time?
3	How many times a day do you take each of your pills?
4	How many doses of each of your pills did you miss yesterday?
5	How many doses of each of your pills did you miss the day before yesterday?
6	How many doses of each of your pills did you miss three days ago?
7	How many doses of each of your pills did you miss four days ago?
8	During the past 4 days, on how many days have you missed taking all your doses?
9	Most anti-HIV medications need to be taken on a schedule, such as '2 times a day' or '3 times a day' or 'every 8 hours.' How closely did you follow your specific schedule over the last four days?
10	Do any of your anti-HIV medications have special instructions, such as 'take with food' or 'on an empty stomach' or 'with plenty of fluids?'
10a	If Yes, how often did you follow those special instructions over the last four days?
11	Some people find that they forget to take their pills on the weekend days. Did you miss any of your anti-HIV medications last weekend-- last Saturday or Sunday?
12	When was the last time you missed any of your medications?

13	People may miss taking their medications for various reasons. Here is a list of possible reasons why you may miss taking your medications. How often have you missed taking your medications because you: Were away from home? Were busy with other things? Simply forgot? Had too many pills to take? Wanted to avoid side effects? Did not want others to notice you taking medication? Had a change in daily routine? Felt like the drug was toxic/harmful? Fell asleep/slept through dose time? Felt sick or ill? Felt depressed/overwhelmed? Had problems taking pills at specified times (with meals, on empty stomach, etc.) Ran out of pills? Felt good?
14	The following questions ask about symptoms you might have had during the past four weeks. Please select, from 1 (I do not have this symptom) to 5 (I have this symptom and it bothers me greatly) the answer which describes how much you have been bothered by each symptom: Fatigue or loss of energy? Fevers, chills or sweats? Feeling dizzy or lightheaded? Pain, numbness or tingling in the hands or feet? Trouble remembering? Nausea or vomiting? Diarrhoea or loose bowel movements? Felt sad, down or depressed? Felt nervous or anxious? Difficulty falling or staying asleep? Skin problems, such as rash, dryness or itching? Cough or trouble catching your breath? Headache? Loss of appetite or a change in the taste of food? Bloating, pain or gas in your stomach? Muscle aches or joint pain? Problems with having sex, such as loss of interest or lack of satisfaction? Changes in the way your body looks, such as fat deposits or weight gain? Problems with weight loss or wasting? Hair loss or changes in the way your hair looks?

Appendix III: App specifications

General use case description:

I. A newly diagnosed HIV-positive patient with Android smartphone will be enrolled to the SmartLtC study by study staff and randomised to receive the smartphone app or not. Upon being randomised to smartphone app arm, the study staff member will install the app on the phone through a USB cable connection, (or through a Library Box - http://librarybox.us/whatis.php). The app icon and name will not refer to health or medicine in any way to ensure privacy for the user.

II. Once app has been installed patient will create username and password, and select PIN code. The app can then be accessed immediately which will provide access to "More information" and "FAQ's" (Frequently Asked Questions)[5] sections, but will not include lab results. The study staff member will provide the patient with a brief training session on use of the app. Patients will be informed that they can read "More information" and "FAQ" sections at any time, but laboratory results will only be displayed after they have been received. All past results will be accessible to the patients and displayed along with any new results.

III. When a CD4 count/Viral Load (VL) result is received by the NHLS database an App-based notification will show on the patient's screen informing them new information is available and to open the app. (Suggested text for the app-based notification "You have new information waiting. Please open the app".) Once the patient opens the app and enter their PIN code (which is verified by the server) their CD4/VL result is shown under "Lab results" in the app. The CD4 count/VL results will be written in red, yellow or green to highlight the relative immediacy of action needed by the patient.

IV. If the patient selects a CD4 count number (to be a suggested action on screen), a pop-up screen will provide a basic explanation of what that CD4 count means and what action they need to take. (Note: The numerical text will be coloured and the pop-up screen will also display a visual-analogue scale going from red to yellow to green, with a marker showing where the patient's CD4 count sits along the scale.) At the bottom of the pop-up will be a link to more detailed information about HIV and laboratory results. On every screen will be a link to a help page which displays the contact number for the National AIDS Helpline and the study coordinator.

V. HIV-positive patients require life-long care and treatment. For follow-up care, the app will notify the patient that it is almost time to attend a follow-up blood test (at both 5.5 months and 6 months after the first CD4 count result has been received). Patients will attend the clinic for a second blood test (the follow-up CD4 counts or VL) at the 6 month mark. The app will connect to the results server daily at this point until there is a new laboratory result in the database. When the app received the new lab result the app will create another notification for the patient to check their results through the app.

VI. Regular 6 month or 1 year (depending on patient's most recent CD4 count) blood tests must be done. The app will create reminder notifications, ping the

[5] Note: Wits RHI to supply medical content for the "More information" and "FAQ's".

server for results soon afterwards, and notify the patient when the results are received.

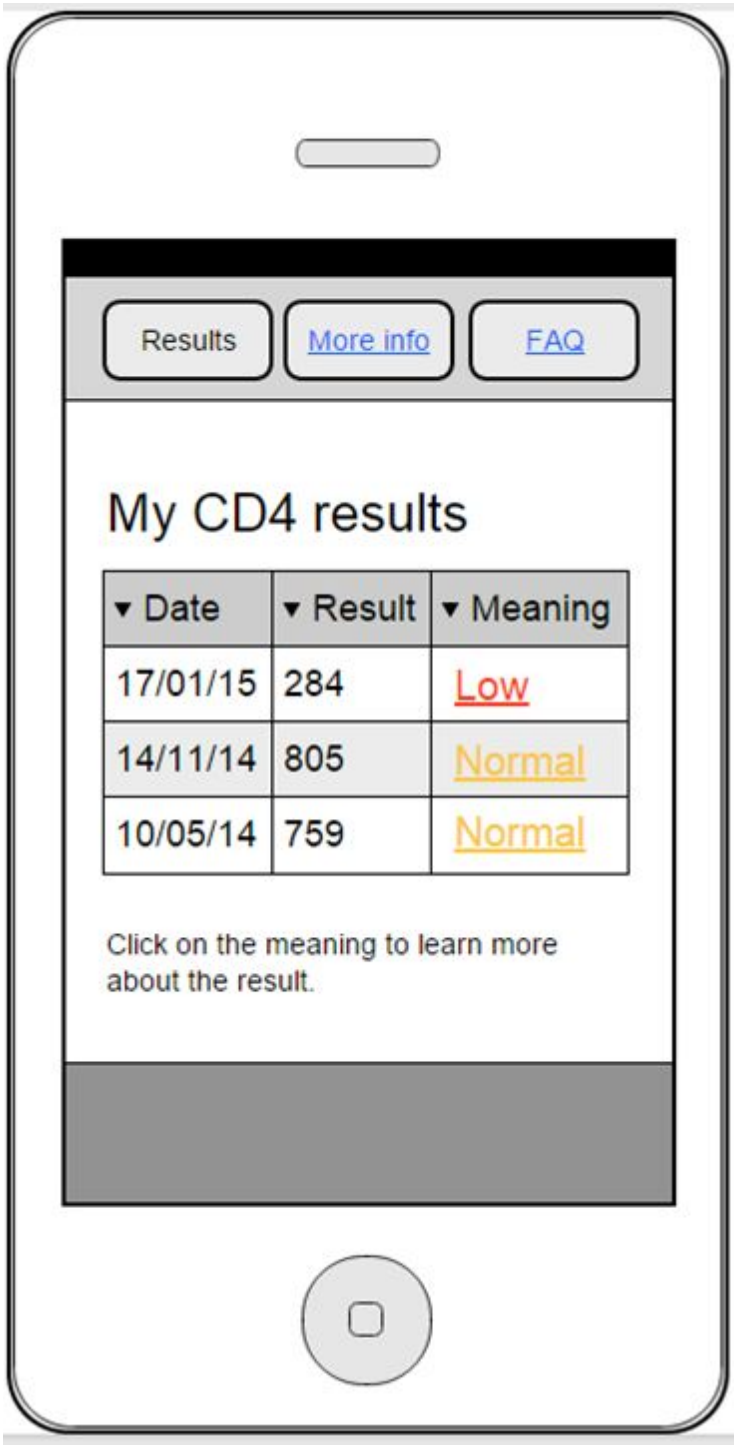
VII. App analytics on use is to be collected within the app. This will include patient use of the app such as length of time app is open, number of times app opened, which screens were seen, number of unsuccessful and successful lab result collections, number of incorrect username/password or PIN errors etc.

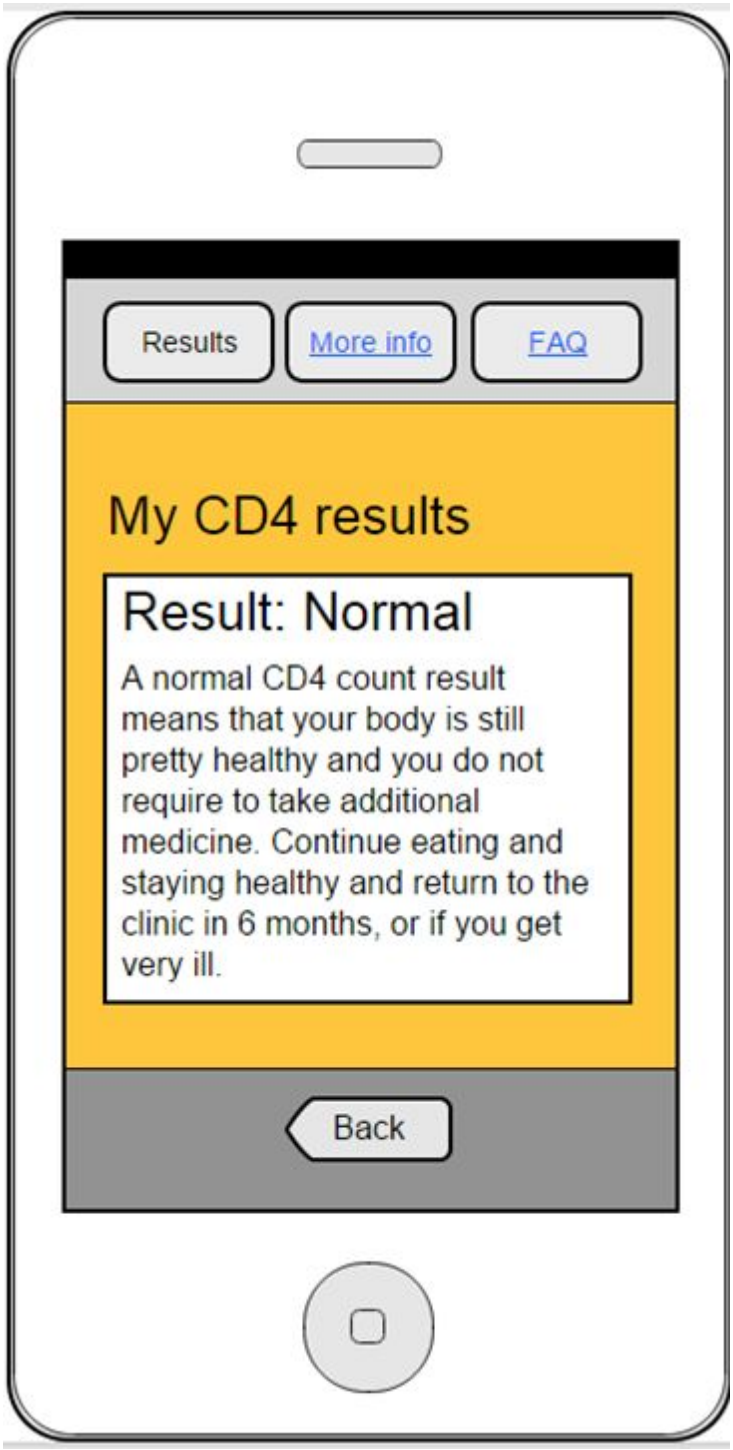
A tabular overview of app requirements is available below:

Platform	Android smartphone running Gingerbread or higher
Deployment	On-site USB/Wi-Fi (LibraryBox) install by research staff
Use of Smartphone App	- Patient registration will occur at clinic site with study staff member; Demographic information, photo ID and lab ID required. - Patient will receive an Android notification through their app on their phone when new CD4/VL result is in NHLS database - Patient can view CD4 results (new and historical) on app - NB: CD4 and VL results are colour-coded (red, yellow, green) based on - CD4 level: yellow >500, red < 501 - VL: green below 1001, red above 1000 - Patient can select individual results which will open up an information box explaining what that result means along with a visual-analogue scale showing green to yellow to red and where the patient's CD4 count or viral load sits on the scale - Patient offered FAQ and information sections to learn more about HIV (‘basics’. ‘signs and symptoms of co-infection, ‘sex and hiv’), laboratory results, online resources, and contact information (National AIDS helpline) - Contact numbers (study coordinator, SA AIDS helpline) and 3rd party HIV-related websites provided in app help - Patient to receive further Android notification at 5.5 months and 6 months after app installation to remind about upcoming visit to clinic for additional blood test.
Authorization & Authentication	**At first use:** - Patient to create username (e-mail address?) and password connected to SA ID/Passport number/Refugee number & Lab Requisition ID **Notes**: - Must create or connect to NHLS database for results! - Server-side user creation **At subsequent use:** - PIN required at every use of app (similar to Standard Bank android app) - Server-side PIN authentication - PIN and/or password change possible (how?)

App & data security	**Network** - All passwords and patient data encrypted **App** - All app data to be encrypted - PIN not stored locally
Main screens	- Login: UN/PW - PIN code - Lab results - More information - FAQ - Help me (available from any screen)
Notifications or Alerts (to patient)	**App-based notification when:** - Patient joins study: Welcome message - New patient laboratory result arrives to phone from lab database: Notification of new information - It is time for patient to return to clinic for blood test (reminders; early notification at 5.5 months, regular notification at 6 months): Reminder to attend clinic **Note:** - Notifications created by app based on time passed and results available
Patient enrolment details (to link to NHLS database)	- First name - Last name - SA ID, passport or refugee number - DOB (if no SA ID number) - Gender - Lab requisition ID of blood specimen
Important contact information	Help icon displayed at bottom of every screen (even login) to allow for easy access to support. Selecting icon will provide a list of support numbers (study coordinator, SA AIDS helpline) and 3rd party HIV-related websites
Analytics	All screens of the app should report to an analytics aggregator (Android Analytics?) to allow the study team to monitor app usage by user.

Appendix IV: App Mockup Screens


Results
More info
FAQ
My CD4 results
Date
Result
Meaning
17/01/15
284
Low
14/11/14
805
Normal
10/05/14
759
Normal
Click on the meaning to learn more about the result.


Results
More info
FAQ
My CD4 results
Result: Normal
A normal CD4 count result means that your body is still pretty healthy and you do not require to take additional medicine. Continue eating and staying healthy and return to the clinic in 6 months, or if you get very ill.
Back