A mixed method study of the factors influencing the validity of medical and medication histories obtained from potential healthy adult clinical trial participants.

By

Dr Hanan Ltayef

Thesis presented in fulfilment of the requirements for the degree Master of Philosophy in the Division of Clinical Pharmacology, Faculty of Health Sciences,

University of Cape Town

18 APRIL 2019

Supervisor: **Dr Elizabeth Allen, elizabeth.allen@uct.ac.za**

Co-supervisors: **Annemie Stewart, annemie.stewart@uct.ac.za**

DECLARATION

Im, Hanan Ltayef, hereby declare that the work on which this dissertation/thesis is based is my original work {except where acknowledgements indicate otherwise}and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 18/04/2019

Acknowledgements

After a rigorous period of working, I am writing this letter of thanks upon completion of my dissertation. It was a period of powerful education at a scientific and personal level. I would like to thank the people who have maintained help and support during this period

-Dr. Elizabeth Allen, I want to thank you for your excellent cooperation and for all of the opportunities, inspiration, and guidance throughout the process of compiling this work, and having your door open to encourage and give advice.

- My parents and parents-in-law for their unwavering support and constant prayers.

-My dear husband for his wise counsel. He was always there to cheer me up and stood by me through the good and bad times.

-Prof. Lubbe Wiesner, Ms. Annemie Stewart always supported and encouraged me with their best wishes.

- Special thanks to Mr. Harrie Bickle and Dr. Elizabeth Allen for their help in editing and correcting language.

Thank you very much, everyone.

Dr. Hanan Ltayef

Abbreviations

AE	Adverse event
ART	Antiretroviral therapy
AVAREF	African Vaccine Regulatory Forum
BMI	Body mass index
CCOAT	Collaborating Centre for Optimising Antimalarial Therapy
CD	Crohn's disease
CRO	Contract research organization
EMA	European Medicines Agency
F	Female
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good laboratory practice
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
IBD	Inflammatory bowel disease
LMIC	Low and middle-income countries
M	Male
MoH	Ministry of Health
NDA	New Drug Application
NHREC	National Health Research Ethics Council
NIH	National Institutes of Health
NIHR	National Institute for Health Research
PHDC	Provincial Health Data Centre
PPI	Patient and public involvement
SACRA	South African Clinical Research Association
SAHPRA	South African Health Products Regulatory Authority
SAMRC	the South African Medical Research Council
SANCTR	South African National Clinical Trial Register
SOP	Standard operating procedure
TB	Tuberculosis
UCT	University of Cape Town
UK	United Kingdom
US	United States
WC	Western Cape

Tables and Figures

Table of Contents

ABSTRACT

Background: The medical histories of patients are data picked up by a doctor by making inquiries of the patient and of other individuals who know the individual and can give a reasonable response. In clinical trials, obtaining an accurate medical and treatment history is also an important factor in establishing whether or not a person is an eligible participant, and thereafter supports the assessment of any change in health during the trial, for example, the assessment of adverse events (AEs).

Study objectives:
To understand discrepancies between the medical histories from online self-reports, electronic medical records, and in-depth interviews of those applying to be part of an adult volunteer database for clinical trials; explore ways of engaging with potential volunteers, such that self-reported medical histories are as comprehensive as possible; explore the feasibility of accessing electronic records for those responding to advertisements.

Methodology: This study was designed as mixed methods, with sequential explanatory design collecting quantitative and qualitative data and nested in an existing adult volunteer database. people from the Cape Town community were invited to join the database, in response to an advertisement and through a link to the database website; particularly those who were potentially eligible for a typical healthy volunteer trial, and who reported different information to that obtained from the electronic records.

Results: 38 people responded to the online questionnaire, the majority being female. According to the online self-report questionnaire, ten people (10/38; 26.3%) had chronic medical conditions; mostly HIV (7/10; 70%). We accessed the Western Cape electronic medical records for only 8/38 (21%). Comparing the online questionnaire with the medical records, it was found that 25% of respondents had no difference in information. 10/38 people (26.3%) agreed to participate and were available for an in-depth interview.

The main findings were: 1) a very low response rate to the advertisement, 2) people in this community are willing to consider taking part in clinical research, but have different understandings of what that means, 3) there were discrepancies between online self-reported health and medication data and what was found in a pilot database of electronic public health records and during a face-to-face interview, 4) the reason for these differences, as perceived by participants, included forgetting some information, feeling it was not relevant or important to report because of the attributes of the online questionnaire and 5) these participants had no concerns about us accessing their electronic medical records.

Conclusion: Our study provides some evidence for optimal places to advertise for an adult volunteer database, and the appropriate wording and format of both the advertisements and the online questionnaire. More efforts are needed to educate the general public on understand the meaning of clinical trials. Electronic medical records may be accessed to help understand potential participants' eligibility for trials, but the feasibility of accessing such data timeously may need further negotiation.

CHAPTER 1: BACKGROUND

Doctors collect medical histories of patients by interviewing the patient or individuals who know the patient. This information, combined with the results of physical examinations, tests and historical data in their medical records, may allow the doctor to make a diagnosis and propose a treatment plan(1,2) . With regard to clinical trials, obtaining an accurate medical and treatment history is also critical as it is the first step towards establishing whether or not a person is eligible for the trial. This baseline assessment is also essential for monitoring any change in health during a trial, such as the assessment of efficacy and safety, the latter through the collection of adverse events (AE) reports.

Clinical trials may assess patients with an existing condition or healthy participants with no pre-existing conditions; both may provide valuable data, for example, on efficacy, safety, pharmacokinetics, and drug interactions. Potential participants' prior medical and treatment histories are usually obtained from a combination of self-reports at the time of recruitment or screening and access to existing medical records, which are then assessed together with results from any trial-specific assessments(3) .

Self-reporting is vulnerable to participants not accurately reporting their medical or medication history. This may occur for a variety of reasons, such as language barriers, the participant forgetting about a particular event or medication, their perceptions that some information is not relevant or important to report, or even because they are concerned, for various reasons, about disclosing certain information(3) . Meanwhile, obtaining complete medical records from all points of care accessed by a potential participant, which could be multiple healthcare providers and clinics, can be challenging for the clinical trial researcher. Healthy volunteer studies are especially vulnerable to poor record access and inaccurate self-reporting as they are often conducted in units that are separate from the patient's routine medical care facilities. This is compounded when people obtain medical care from multiple healthcare providers, both public and private, or self-medicate(3,4).

In addition to undermining the validity of a trial's results, inaccurate medical histories may contribute to participant being harmed if ineligible, applicants are enrolled, and there may be financial or ethical implications if the trial's objectives are not achieved because the data is invalid(3,4) .

To enable healthy volunteer studies, it is common practice for researchers to build a database of potential participants interested in taking part in future studies, such as the UCT Collaborating Centre for Optimising Antimalarial Therapy (CCOAT) database, produced in collaboration with the UCT Clinical Research Centre (~~see~~ Appendix 1). This database is populated with demographic details and medical histories of members of the public who responded to advertisements and answered questions about their health and use of medicines, either telephonically or through an internet website. When a clinical trial in the planning phase, the database may then be queried and potentially suitable participants contacted to invite them to hear about the trial and undergo more intensive screening, based on the trial's eligibility criteria.

Information technology is a rapidly expanding branch of science. In medicine, the increased availability of electronic medical records should enhance the researcher's ability to build such a database of potential volunteers. Data obtained from available records and self-reports provide a comprehensive overview of a participant's suitability for a trial. However, the feasibility of accessing such records for these purposes is unclear.

This study, therefore, aims to understand whether and, if so, why self-reports from potential clinical trial participants are different to the data obtained from medical records using a pilot program that links information from multiple sources within the public healthcare sector in Cape Town, Western Cape. It also explores the feasibility of obtaining such electronic records, and the process of recruiting potentially healthy clinical trial volunteers. Together, these insights are expected to help refine the CCOAT volunteer database methods and contribute to cost-effective recruitment strategies for future clinical trials involving healthy volunteers.

CHAPTER 2: LITERATURE REVIEW

2.1 The development of medicines

Clinical trials are a fundamental aspect of the drug development process. The information collected from such trials may provide evidence that the product is effective and safe, which will support product registration and marketing(5) . This section will illustrate the steps that most drugs take from concept to the medicine cabinet.

2.1.1 Drug discovery and pre-clinical research

Researchers generally discover new drugs through insight into a disease process, which allows them to design a product to prevent or treat the effects of this disease. Discovery also includes observations regarding current treatments that have unanticipated effects. Promising molecular compounds need to be tested to identify those with useful effects and, initially, thousands of compounds may be potential candidates for development. Thus, the drug developer will first confirm which of these are associated with the disease in question and, after screening, will select hose that have demonstrable results(6,7) .

Preclinical research takes many years to conclude results and, despite not being very large studies, they can provide important information on possible human dosing and toxicity levels. *In vitro* testing examines the drug molecule within the laboratory, outside of a living organism, while *in vivo* testing observes its effects on animal models. By studying rodents or specific cells in a laboratory before testing a drug in humans, investigators aim to establish whether or not a candidate drug has the potential to cause serious side effects, such as cardiac, neurological, teratogenic or genetic toxicity. Animal studies, however, cannot fully elucidate how treatments would work in humans (7).

Regulatory bodies, such as the United States Food and Drug Administration (US FDA), require pre-clinical researchers to use good laboratory practices (GLP), which establish the basic requirements for trials. These define accepted approaches to conduct such studies, appoint personnel, provide facilities, equipment, written protocols, operating procedures, study reports, and a system of quality assurance oversight to ensure the safety of products (6).

As these tests are conducted, investigators will reduce the many drug molecules first identified to a small number of potential candidates safe enough to proceed to human clinical trials.

2.1.2 Human clinical trials

Once a promising compound is identified for clinical development, researchers conduct clinical trials, to collect information on its pharmacokinetics, pharmacodynamics, dosage, route of administration, the potential for adverse effects, and drug-drug interactions. Over time, they will examine the effects on different groups of people of varying ages, genders, race and ethnicity, and compare these effects with drugs for the same indication that are already on the market, if these are available.

Ultimately, researchers aim to establish whether or not the benefits of the new treatment outweigh the potential side effects(7) .

As researchers design this clinical development plan, they will consider what they wish to accomplish for each of the phases, in order to answer specific research questions, leading to submission to a regulatory authority for the registration of the drug. Thus, each phase builds on the results from the preceding phase, helping to create a comprehensive understanding of the drug's effects(5,8,9) :

- Phase I trials: These are conducted in a small number of (usually healthy) volunteers with a focus on safety monitoring. The objective is to determine whether the drug is safe for human use, and to begin the process of understanding how the drug works in the human body .

- Phase II trials: These are conducted in a larger sample of patients with the disease under investigation. The objective is to establish therapeutic efficacy and to further evaluate its safety. A significant objective of this phase is to determine the dosage for Phase III trials. If there is evidence of a disease-management effect and any associated risks are acceptable, the treatment may move to the next stage .

- Phase III trials: These trials aim to confirm the efficacy of the drug and whether it is better than the current standard treatment(s). These trials are conducted in a larger population of patients who will have other medical conditions and might be taking additional medicines. This phase is also used to collect further information about the drug's safety in the target population. These trials usually involve two groups: one group of patients will receive he standard drug, and the other group will be given the newer drug. They are typically blinded trials, in that the patients and the investigators are not aware of which treatment the patient is receiving. Due to the large size of the group of patients exposed to the therapy, this study provides a better understanding of any potential side effects of the new treatment .

- Phase IV trials: After a drug or treatment has been approved by the appropriate government regulatory agencies, it is necessary to study its safety and effectiveness, how it works in reality in a larger number of people. Thousands of people usually participate in Phase IV trials .

All trials will follow a specific plan, called the protocol, which is developed by the researcher or manufacturer. Beforehand, a team reviews what is already known about the drug from previous experiments in order to develop the trial's research questions. This facilitates the creation of a comprehensive plan for the trial, which includes the objectives, design and methods, and the statistical analysis. The protocol will also include the type and number of participants, known as the sample size, their eligibility criteria, demographic data, the duration over which the therapy will be administered and endpoints that will be measured to achieve the objectives(10,11) .

In addition to the different trial phases discussed above, clinical trials may either be interventional or observational. Interventional clinical trials involve giving a participant a treatment in accordance with a research plan. Observational clinical trials involve giving a participant a treatment in accordance with clinical practice. The appropriate

type of clinical research depends upon what is being studied and during which stage of development or beyond(12,13) . The following expands on these different types of studies:

Treatment studies refer to an intervention, such as medication.

Prevention studies explore more effective ways of preventing disorders from developing or recurring. Different kinds of prevention research may study medicines, vitamins, vaccines, minerals, or lifestyle changes. This may include the examination of exposure to substances and environmental factors that may raise or lower the risk of developing a disease or even reduce the risk of an accident.

Diagnostic studies refer to the practice of searching for better ways of identifying a disorder or condition. Typically, they investigate the most effective methods of diagnosing disease. They may also be conducted to ascertain the safest, least invasive, and most cost-effective ways of determining if the disease is present.

Screening studies determine the best means of detecting certain disorders or health conditions. They evaluate methods of detecting disease in the earlier, and possibly curable, stages of the disease to improve survival, for example, evaluating the effect of screening mammograms on breast cancer survival.

The goal of **genetic studies** is to make efficient predictions about disorders by defining and understanding how genes and disease may be related to each other. By examining the genetic code of participants and their disease status, a study may expose routes in which a person's genes make an individual more likely to develop a disorder.

Epidemiological studies identify the manner, causes, and control of disorders in groups of people. These are useful for situating background rates of a condition, which can then be compared to what is found in clinical drug trials, for instance.

Quality of life or **supportive care studies** look for ways to improve comfort and the quality of life for individuals with a chronic illness. Such studies estimate the potential of a medication, procedure, or non-medical intervention such as a support group, to lessen the symptoms of or those related to the treatment of a disease, for example, examining the effect of palliative care on the quality of life for people with cancer. Such studies may be effective in demonstrating that care improves quality of life and longevity .

2.1.3 Regulatory review

If a drug developer has evidence from preclinical research and clinical trials that proves the drug is safe and effective enough for its proposed use, they will apply to register the drug with various regulatory authorities. In the US, this will be the submission of a New Drug Application (NDA), from the start of clinical trials, to the FDA, culminating in the submission of a dossier of supporting evidence. Once the FDA

receives the submission, the review committee determines if it will accept the approval of the drug for registration. If accepted, the review team has six to ten months to decide on whether or not to approve the drug(14) . In South Africa, the equivalent body is the South African Health Products Regulatory Authority (SAHPRA), which is responsible for the regulation of health products proposed for human and animal use, the licensing of manufacturers, dealers and suppliers of medications, medical devices, radiation-emitting devices and radioactive nuclides, and the conduct of clinical trials. Applicants must submit reports proving the quality, safety, and efficacy of such medications planned to be sold in South Africa. The South African regulatory review process is presented in Figure 1.

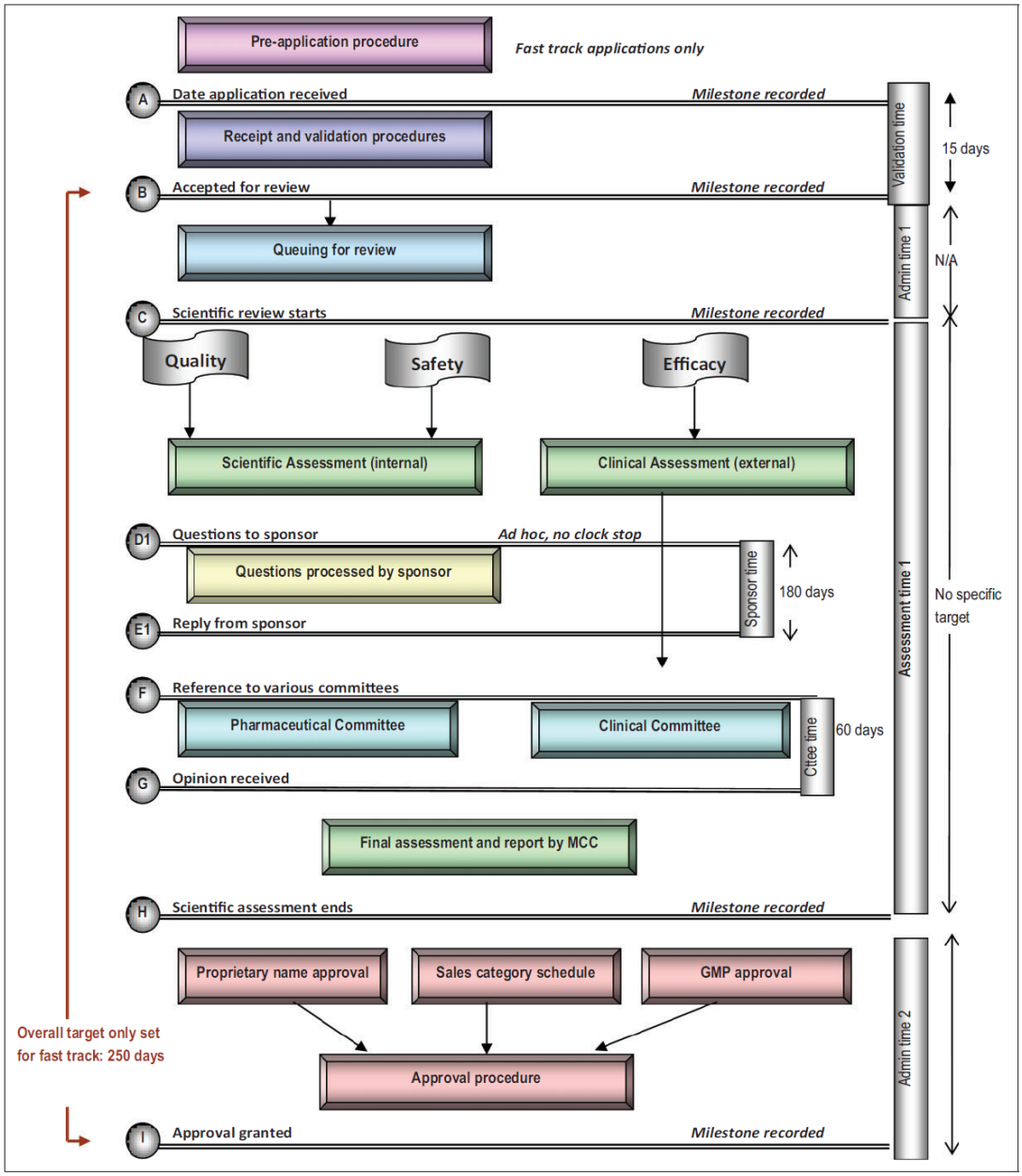

Figure 1: Regulatory review process map for South Africa. Adopted from the Regulatory Review Process in South Africa: Challenges and Opportunities for a New Improved System(15) .

2.2 Clinical trial participation: the role of healthy volunteers and patients

2.2.1 Background

As indicated above, clinical trials are used to develop new medicines for the treatment or prevention of illness. They expand our understanding of basic scientific research and encourage an evidence-based approach to disease management(16) .

Clinical trials may investigate new drugs, a combination of drugs, or a new approach to existing treatments. The outcomes of clinical trials can influence and improve patient care by providing information on the benefits and risks of new therapeutic, preventative, or diagnostic products. Clinical trials also contribute useful information about the benefits and safety of existing therapies, allowing doctors and patients to make informed choices about alternative approaches(17) .

Clinical trials may be sponsored by pharmaceutical companies, medical technology companies, biotechnology companies, universities and other funding bodies, such as a government agency, for example, the National Institutes of Health(NIH), or the South African Medical Research Council(SAMRC)(17–19).

During the conduct of a clinical trial, a sponsor is principally in charge of all the working aspects thereof. Their responsibilities include selecting capable investigators, providing them with the evidence needed to investigate accurately, and verifying appropriate monitoring of the trial, ensuring that the investigation is conducted in accordance with the general plan and protocols(20,21).

The sponsor is also accountable for sufficient oversight of the manner in which the study is conducted, along with the explanation for and choice of monitoring systems. Any trial-related obligations moved to a contract research organization (CRO) must be in writing. As established in South African GCP, the sponsor will undertake quality assurance measures to ensure that all activities are in line with the monitoring plan. If a study is postponed or terminated early, a sponsor is obligated to inform the investigators, institutions, and SAHPRA, as well as update the South African National Clinical Trial Register (SANCTR). The sponsor then needs to preserve important documentation for at least 15 years, or for a minimum of two years subsequent to the final approval of a marketing application(22).

A clinical trial is conducted by an investigator who is registered as a doctor or dentist and, depending on the population or protocol, performed in a clinic or hospital setting, or specialised research unit outside of a formal medical environment. Some clinical trials are “outpatient trials”, meaning that participants do not stay overnight. Others are “inpatient trials”, which means that participants will need to stay in the hospital or research centre for at least one night (5). Some trials (including Phase I trials) require healthy participants who have no previous medical conditions, while other studies apply inclusion criteria regarding the presence of certain diseases. Apart from Phase II and later trials, the latter would also be pertinent in Phase I for drugs that would be too dangerous for healthy volunteers, such as chemotherapy agents for cancer treatment(5,23) .

The investigator will work alongside a team of healthcare professionals, such as doctors, nurses, and pharmacists to conduct the various tasks involved . Investigators and sponsors alike must follow ethical and legal guidelines to protect participants' safety. Ethics are especially pertinent as the philosophy behind a trial is to understand, not treat, and there will be remaining questions about the investigational drug needing to be answered. Trials should be designed, conducted and monitored in adherence to the same standards, whether they occur in South Africa, the United States or elsewhere. By applying a scientific approach, important medicines are made accessible to people around the world through evidence-based healthcare(24,25) .

The duration of trials varies widely and depends on what is being researched. During the informed consent process, participants will be provided with estimates regarding the duration of their participation. Some trials last days, while others continue for years. Before embarking on a trial, participants must know how long it is expected to last(5) .

Participants may then be separated into different treatment groups. In a controlled trial, the trial group will be given the investigational treatment while the control group will receive

an existing or standard treatment or placebo. The placebo is an inactive pill, liquid or powder that looks identical to the experimental treatment, but has no effect on the body. Participants are randomly assigned to either the control or non-control groups at the start of the trial. At the end of the trial, participants must be made aware of which group they belonged to. The results should be communicated to all participants so that they will be able to make future decisions about their well-being(5,6) .

2.2.2 Motivations for participating in a clinical trial

For many patients, clinical trials are an important step in accessing newly discovered therapies before they become widely available, and the choice to participate in one is personal and depends on each person's unique situation. If a treatment proves successful, such participants may be among the first to benefit. In addition, they are closely monitored by healthcare providers during a trial and may emerge with a better understanding of their condition (5,26).

As mentioned earlier other clinical trials rely on the recruitment of healthy volunteers, where there is no personal benefit to participation. People volunteer for such trials for a variety of reasons, including financial ones. This is especially true of people in lower-income brackets, who might participate without being fully aware of the benefits and risks of the study. CROs in India have been known to use "middlemen" to recruit poor volunteers, who had no knowledge of what the studies were about and had not informed their families, mostly participating in the trials due to unsatisfactory income and unstable jobs(27). In developed countries, volunteers are often university students with a high level of education and reasonable living standards(28,29).

A study conducted in the US, Canada, and the Netherlands by Colfax et al. showed that most individuals provided altruistic motives for trial participation, having joined to assist with discovering an HIV vaccine and to support their community. Some had other motives, such as acquiring protection from the vaccine, being influenced to avoid dangerous behavior, receiving care or compensation, and also financial repayment(30). Such potential motivators have to be considered when recruiting for HIV vaccine trials in particular communities, regardless of context(31).

A similar study in a Sub-Saharan location, namely Nairobi, Kenya, targeting volunteers for an HIV vaccine trial, showed that most participants had been inspired by potential personal and social benefits(32). The specific motivations for South Africans enrolling in medical trials are poorly understood as there are few studies available. However, research in South Africa has found that both adolescent and older volunteers in HIV vaccine trials were equally inspired by altruism, younger women were less likely to consider the trial remuneration and young men were more likely to perceive the trial as potentially providing protection against HIV(33). One Cape Town study also showed that obtaining medical care and contributing to scientific advancement seem to be two of the most frequent motivations for taking part in cardiovascular trials and that remuneration was less important. Understanding these findings will help improve recruitment strategies and enhance retention of subjects(34). There is a dearth of research relating to healthy volunteers in South Africa. However, a Portuguese study by Almeida et al. determined that participants with low education have been more likely to cite economic motivations for taking part in a trial(35), while a US study by Kass et al. discovered contrasting results: participants with greater education were more interested in monetary benefits than those with less education(36).

Regardless of the target population, the interpersonal relationship between study participants and the recruiter has long been identified as integral to the recruitment process, although this has not been well studied(37–39). Some strategies integral to participant recruitment have been identified, such as regular follow-ups with prospective participants to inform them of the research study and building trust-based relationships between prospective participants and the researcher(3). Recruiter characteristics, such as enthusiasm and competency, positively influence the recruitment process(40). Patel and colleagues further assert that qualities, such as conscientiousness, care, compassion, integrity, respect, tolerance, tact, and approachability, serve the researcher well in the recruitment process(41).

One approach to recruiting participants is to assign a designated referral person who embodies the characteristics known to facilitate participant recruitment, this individual should conduct initial participant screening, identify eligible applicants, and inform them about the research study. A clear advantage of this approach is that a designated individual would be assigned specifically to participant recruitment. Barriers to this approach are the associated cost and the availability of specialized researchers dedicated to recruitment(42).

In a review of studies on recruitment, Treweek and his team aimed to quantify the effects of strategies for improving the recruitment of participants to randomised trials. They identified 68 eligible trials with more than 74,000 participants and all of the studies were in healthcare. They found 72 comparisons, but only three were supported by high-certainty evidence, and they also commented that only two were clearly effective.

1. Telling people what they are receiving in the trial rather than not telling them improves recruitment.

2. Telephoning people who do not respond to a postal invitation is also effective; although it is not certain if this works as successfully in all trials.

3. Using a tailored, user-testing approach to develop participant information leaflets makes little or no difference to recruitment(43).

2.2.3 Participants' protection, rights, and informed consent

Whether involving patients or healthy people, all clinical trials are designed to minimise the risks to participants, although some risk is unavoidable when the research involves new treatments, as there are still unknown potential effects. Mandatory ethical and regulatory reviews prior to the trial help to ensure that the aims, risks or benefits of a particular trial are thoroughly considered and that the chosen options are scientifically sound and ethically justified.

Part of the ethical commitment of a trial is voluntary choice, while compliance with Good Clinical Practice (GCP) should signal to the public that the safety and rights of participants are protected(44) . It aims to:

- protect the rights, safety, and welfare of participants
- guarantee that data collected is reliable
- have integrity and be of an appropriate quality
- provide guidelines and standards for the conduct of clinical research

The foundations of GCP were first laid out in 1947. The salient focus was that during any trial, researchers must guarantee voluntary participation, informed consent, and minimization of risk. Participants who choose to be part of the sample population are required to sign an informed consent form, before being enrolled in any study procedure. This is part of a process which ensures that a prospective participant in a clinical trial understands what known risks might be associated with the study and whether there are potential and unknown risks that may be associated with the chemical formulation or procedure under investigation (24,44).

The participant should be given sufficient time to consider participation in the clinical trial and their questions addressed satisfactorily before agreeing to participate in the clinical trial. Signing the informed consent form and providing consent is not a

contract. Participants may choose to withdraw at any time from a clinical trial without any penalty, even if the clinical trial has not been completed (45,46). Although provision is available for potential participants who are illiterate, the structure of informed consent is a written form, providing detailed information explained in accordance with GCP(42,44) .

Table 1 - Summarised European Medicines Agency (EMA) guidelines for information to be provided to participants in clinical trials.

Information provided to the potential participant:	**Participants must be informed:**
• Research involving the trial of drugs with possible random assignments • Aim and procedures to follow in the trial (invasive and experimental aspects) • Reasonable risk and the relative expected benefit • Compensation or therapy in case of trial-related injuries • The anticipated expenses and remuneration • Responsibilities of the participant	• Voluntary participation • The research team are granted direct access to the participant's original medical records and these will be confidential and not publicly available • Participant's identity remains confidential when results of the trial are published • Contact details of the research team to gain more information or in case of trial-related injuries • Expected circumstances: participation in the trial may be terminated • Length of their participation in the trial

For their part, participants agree to undergo the study procedures outlined in the informed consent form and follow the advice provided by the study team. It is important to ensure that the information is written clearly and concisely, and in the participants' first languages(5,47).

2.2.4 Eligibility criteria

As mentioned previously, each clinical trial has a proposal or idea for the study, the conduct of which is described in detail in the protocol. Eligibility criteria define the patient population being studied, isolating the potential effects of an investigational drug. Enrolling participants with similar characteristics increase the possibility that the results will be an effect of the study variable and not an artefact of other factors. In this way, researchers may collect accurate and powerful results. Protocols, therefore, ensure that participants in a trial meet the same criteria, such as age, sex, and race, type of disease, current general health, and previous therapies. These criteria are also developed so that people are not exposed to undue risk.

Eligibility criteria are separated into inclusion and exclusion factors: inclusion criteria allow a person to participate in a clinical trial and exclusion criteria prohibit a person from participating. These may specify certain factors, such as laboratory test

values, age, or other comorbid conditions that make a patient eligible or ineligible for enrolment.

2.3 The practicalities and challenges of recruiting participants for clinical trials

Before formal enrolment in a clinical trial, people who are interested in taking part will go through a screening process. Applicants who meet initial requirements are generally invited to a screening appointment where they will be provided with detailed information about the trial and, if they agree to participate, the informed consent form will be signed by both them and the person administering the information(48) .

2.3.1 Advertising to recruit for clinical trials

The methods used to promote specific clinical trials are usually controlled by legislation. In South Africa, an ethics committee must review the content of advertisements used to recruit participants for a study before they are used (49). The trial team may then look for potential participants via access points, such as patient organisations, hospitals, and pharmacies. Participants can also find out about clinical trials from online clinical trial registries, such as clinicaltrials.gov, the South African National Clinical Trials Registry (SANCTR), the Pan African Clinical Trials Registry (PACTR) or Center Watch (46). More recently, print-based advertising methods, such as posters in doctors' offices, have been replaced by digital tools, including clinical trial recruitment websites and social media sites, for example, Facebook and Twitter(46,50) .

While the methods used to enrol participants through advertisements can differ, all advertisements should display the contact information of the group conducting the clinical trial, details of the disease being studied, if relevant, and the aim of the trial. Ideally, eligibility criteria should also be provided, as well as a summary of reasons to be part of the trial, and the duration thereof. In contrast, advertisements must not promise any outcome, such as a cure for the disease, state that the drug being tested is safe or effective, or be coercive. This is especially important if a trial is recruiting vulnerable people, such as those with learning difficulties (50).

Study sites in developing countries, in particular, need to develop an effective enrolment strategy, considering the necessities of the protocol and potential participant population. Options include hanging posters in clinic waiting rooms, offering brochures, writing letters to referring clinicians, placing advertisements in newspapers and, more recently, using the internet to attract interest. Each of these procedures has a possible role to play in the overall enrolment plan, although some might be more effective than others in a particular context. For instance, print advertising has proven to be a costly, but extremely effective, enrolment system compared to other means of enrolment. However, its success depends on the therapeutic area and the population of patients (51).

2.3.2 Overcoming challenges and strategies in the recruitment of participants

Medical advances depend on patient participation in clinical trials. Unfortunately, meeting enrolment goals remains a challenge despite the money and effort invested(52) . Enrolment of participants in a study can be complex, frequently leading to the study being completed late, or even abandoned. This includes the fact that when there are too few volunteers, a conclusion may not be drawn, resulting in even promising treatments seeming to underachieve. The South African Clinical Research Association (SACRA) states that in 2008 approximately R2.2 billion was generated through clinical trials via international companies(53) . This business is affected by local regulatory approval times and the availability of appropriate research sites. However, international sponsors are interested in South Africa for research for various reasons, including the fact that the population is genetically and socio-economically varied(49) . Furthermore, South Africa has a strong regulatory framework and good telecommunications, with mandatory GCP training updated three times a year and is predominantly English-speaking. Recently, in South Africa, several GCP courses have been presented and other clinical trial-related courses are slowly developing, for example, Introduction to Clinical Research and Project Management for Clinical Trials (53).

Due to lack of capacity, building and transformation, the number of principal investigators (PIs) has declined by 11 % globally, with one suggestion being to encourage more young experts and professionals in various sectors to move from co-investigator to PI(15) . Co-operation between stakeholders is essential, such as between SAHPRA and the National Health Research Ethics Council (NHREC). South Africa, as a participant of the African Vaccine Regulatory Forum (AVAREF), in the meantime in 2006 which is pointed to improve the regulatory oversight of interventional CT have been behaviour in Africa. Bi-annual meetings with stakeholders started expanding to Ethics Committees and Academia. In addition, working on electronic systems to develop the timelines. Requirements for new innovative medications to struggle with the public health problem as well as diseases. and Source funding and creation of further study sites and facilities(22).

Recruitment begins with the documentation and enrolment of participants. It includes providing adequate information to the potential volunteers to capture their attention for the planned research(54) . There are two main aims of enrolment. The first is to enrol a sample that sufficiently represents the target population(55) . The second is to enrol enough volunteers to achieve the sample size and power necessities of the research (56).

Public perception is another factor that impacts recruitment. There is often a lack of awareness and many do not think they qualify to participate in the clinical trial. Fear and inconvenience are also contributing factors. There are a minority of patients who actively pursue participation in clinical trials. They are motivated to advance medical knowledge and assist in improving ways to avoid, detect, identify, control, and treat diseases (44,54).

Recruitment is enhanced when it comes as a recommendation from someone the patient trusts. When searching for trials, 60% of individuals go to their clinicians. The inspiration from physicians, pharmacists, family, friends, and others could affect the decision to take part. Compensation is not always a motivator, as not all clinical trials pay, but 78% of individuals reported that compensation had a significant influence on the decision to take part in studies. Some individuals participate in research to earn money, while payment is merely an advantage for others . Following a positive experience in a trial, 95% reported they would consider joining another one. This may explain the numerous applicants who take part in further studies after having gained more knowledge about research studies(40).

Recruiting participants, both healthy and not, is an important and challenging task. It is also costly and can take more time than any other part of a study. Pharmaceutical sponsor companies lose up to $1.3 million per day in the US when a study postpones a drug's development and registration. Up to 80% of clinical studies are not completed on time, and most studies are delayed by an average of six weeks. There is strong competition between pharmaceutical companies to produce the essential data as quickly as possible, and globalization of trials is motivated mainly by considerable cost savings, a large number of participants who could be quickly engaged in short timelines also to over control regulatory barriers in these developing countries which suggestion potentially lucrative markets.

Furthermore, the mainstream of individuals has been engaged following recruiter-completed questionnaires, highlighting the challenges encountered through exclusive recruitment approaches, training, and practical concerns for future studies, documentation from medical records and registers, or from ward and clinic-based plans, which enabled the accrual of a goal pattern of distinctly eligible participants. In addition, they reflect on the possibility of using cell phone and website tools. Numerous LMIC study strategies can be improved upon, and such deployment ought to lead to higher recruitment and retention success and quicker trial periods(57) .

The effects of gatekeeping, which is when people or organisations assist in finding potential participants for clinical trials, have been insufficiently acknowledged in research although they may inspire interest and refer only those individuals who are highly likely to participate. This may result in "expert patients" with an above-average understanding of the disease being recruited for, instead of those with a more average clinical problem, or even more vulnerable participants, which could be a limitation needing to be acknowledged(58) . Moreover, there is a danger that a population becomes overburdened by research requirements, leading to reluctance to join future studies, thus negatively impacting future enrolment success(59) .

Many factors that affect response rates for recruitment to clinical trials have been reported in literature: old age, male sex, non-white race, urban residence, low education status, unemployment or low occupational status, low family income, smoking, recent

illness or poor present health(56,60) . Understanding how this aligns with the recruitment plan and the desired sample is useful.

Gender differences have also been demonstrated by the underrepresentation of male caregivers, such as male partners Purposive sampling could be a solution if this is recognized as essential to the integrity of the study(61,62). Finally, consideration of the terminology used to describe a study can also affect participant enrolment(37) .

2.3.3 Overcoming challenges through volunteer databases

Efficiencies in recruitment for clinical trials may be achieved through web-based recruitment for specific trials and in setting up databases of potential participants, for future trials, whether for patients with a certain condition or healthy volunteers.

Internet-based questionnaires can be an essential tool for collecting important self-declared medical data to aid in the selection of participants for screening for a particular trial or for building up such databases. While not specific to trials, Kelstrup et al. suggest that the advantages associated with this approach to observational research include the minimum amount of infrastructure needed, lower cost when compared to individual recruitment and extraction of medical records, and the overall capability of involving many participants(63) . This web-based technique facilitates the rapid completion of enquiries, extracting a detailed medical history from the patient(63) . E-recruitment is an informal term for any electronic-based recruiting and recruitment administration, such as recruitment marketing, which is a way to acquire research volunteers. In the United Kingdom (UK), there are several websites seeking healthy volunteers for clinical trials, such as UK Clinical Trials Gateway by the National Institute for Health Research (NIHR) or Clinical Trials Cambridge by GlaxoSmithKline GSK. People will search for relevant trials by choosing icons on web pages and filling in application forms, after which the research team will contact them. In South Africa, an example of this approach is the UCT Collaborating Centre for Optimising Antimalarial Therapy (CCOAT) database, in collaboration with the UCT Clinical Research Centre.

2.4 Validity and accuracy of medical and medication histories in clinical trials

For clinical trials, gathering an accurate treatment and medical history is essential to help establish if an individual is eligible for a given trial, and following that, to assess any change in health during the time of trial(2) .

2.4.1 The factors that influence the accuracy of medical histories

One challenge that is associated with self-reported medical history is the poor quality of data that may be generated. Data quality is dependent on the overall ability of a patient to recall their medical history, and their willingness to take part in research (63). Conformity between web-based self-report questionnaires and data generated from medical records has been studied in several medical conditions, mainly outside of the clinical trial environment. Such studies typically focus on the self-reporting of specific health conditions, including those that are associated with cancer screening.

In addition to affecting research, Vincent et al. (2005) state that in the US, incomplete medication histories, obtained during patient admission to hospital, are responsible for nearly 27% of all prescription errors. Valid medication histories during admission to hospital are essential elements of safety in the treatment outcome. An inaccurate medical history might result in inappropriate or interrupted drug therapy during and following the stay in hospital(64) . The current computerized order entry that is used by physicians could fail to properly identify the errors in reporting medical history. For example, the computer system might not detect omissions, such as medications that are taken prior to admission, without having a strong link to the pharmacy database within that community (63).

Two main theoretical arguments have been applied when explaining the sources of validity problems associated with self-reported data on medical histories. These are known as the situational and cognitive perspectives(63) . Cognitive perspectives tend to focus strictly on the general mental processes that act to underline self-reported data and tend to attribute problems of validity to the type of inaccuracies that arise from recall, comprehension, and other cognitive operations. In contrast, the situational perspective tends to focus on problems of validity that are associated with the conditions during the interview, as well as perceptions of social desirability. It is important to note that the two perspectives are not mutually exclusive. For instance, basic cognitive arguments have been expounded on in trying to account for the known situational factors (65).

Brener, Billy & Grady further postulate that four main cognitive processes impact question answering: retrieval, comprehension, decision-making, and generation of a response. Respondents tend to first engage themselves in a comprehension process that determines how a given question is interpreted and encoded within the memory. The known retrieval cues are then generated on the mere fact of output from the whole process and then applied in searching for memory in the subsequent stages of retrieval. The overall sufficiency of the information retrieved is then evaluated in the-process of decision-making. If the information retrieved is assumed to be relevant to the question, then the respondent will give a response. If they deem the information inadequate, then they will make additional retrieval attempts or initiate heuristics. Scholars propose that errors tend to arise during all of these stages, which subsequently leads to the problem of the validity of medical history data. In addition, the specific cognitive operations applied when responding to a question can differ based on the period of time being referenced and the specific response needed. For instance, regarding the frequency of a given behaviour, validity varies greatly between questions(65) .

Further studies have also shown that the context of a question, together with the environment in which one is administering the question, also has an impact on how different cognitive processes tend to be executed. The process can eventually result in systematic biases when responding to the questions.

Brener, Billy & Grady use a situational perspective to explain the factors influencing the validity of medical and medication histories obtained from potential healthy adult

clinical trial participants. The situational perspective, in this case, focuses specifically on the validity problems that arise from the condition of the external environment rather than internal processing. Factors that are hypothesized to influence validity comprise of the availability of other people when participants are being asked questions about their medical history and their perception of the level of confidentiality or privacy that their responses are afforded(65). Social desirability, described as having a desire to give someone a favourable impression of oneself, is another construct that causes situational biases and hence, invalid self-reported medical histories(66) .

Questions influenced by social desirability bias might have response options that match desirable attributes or activities that are considered desirable to be part of. Literature reports that another construct associated with social desirability bias is the desire to seek attention. This attribute is most likely to lead to response biases among adolescent groups, for whom some behaviours such as drug use, alcohol abuse, and even sexual behaviours, are closely linked with status in several settings.

Brener, Billy & Grady suggest that a perceived lack of privacy, anonymity, or confidentiality in the situational context in which these questions are being asked can result in response biases due to fear of reproach. For instance, behaviours that are considered to be stigmatized, illegal, or laden with heavy moral implications are at greater risk of inaccurate reporting(65) .

Vincent et al. argue that, based on similar situational context pressures, the patient's self-reported medical history might be concordant with the information contained in medical records. They affirm that close to 90% of self-reported medical histories for hospitalization are concordant. Concordance has been reported to vary from as low as 80% for infections to nearly 100% for fractures or injuries, and other medical conditions. These arguments by Vincent et al. concur with other studies that have investigated concordance of self-reported medical history with the existing medical records(64) .

Kim et al. compared self-reports and medical records in relation to examinations of the eye and diabetes-related conditions, and found differences in the various levels of assessment of the health status of the participants. These figures confirmed that self-reported assessment is not associated with highly specific evaluations of the health status of a participant. It was also reported that sensitivity regarding outpatient visits and general hospitalization was very high among those people who self-reported their medical history to be poor than among those who reported their history as good. Specificity was reported to be higher among the participants who self-reported their health to be useful compared to those who reported their health to be poor (Kim et al., . Participants with sadness, depression or those who had not received the necessary medical services were found to be most likely to provide a false medical history compared to the opposite group(66) .

Kelstrup, Juillerat & Korzenik investigated how patients with inflammatory bowel disease (IBD) self-reported their previous diagnosis. The researchers, in this case,

compared the chart reviews, made available by the healthcare providers, and the self-reported diagnosis history of the patients. The information within the hospital database was more accurate, with a specificity of around 90% for the diseases investigated and sensitivity of 88%. The study noted that self-reporting was only 69% accurate among patients. These findings are very much consistent with the arguments put forward by Eze-Nliam et al. , who argued that 30% of their patients provided inaccurate medical histories regarding the diagnosis of IBD (63,67).

Patients' medical records have an essential role in clinical trials, particularly as they will hold key data to inform investigators of their eligibility for trial participation, including those volunteering for trials as healthy volunteers. Conversely, it is vital to ensure that a current record of the medical history of trial participants is available to any treating physician (i.e. outside of the trial team), during and after the trial, as all data relevant to the study will be filed in the medical records, thus they ~~come to~~ represent the source material of the clinical study. They are used to provide corroborating information to the sponsor, and they should be available for inspection by regulatory authorities (4,68,69) .

Access to electronic medical records may, therefore, improve trial quality, as shown in retrospective studies, although there is little literature on this topic(68–70) . More needs to be done to ensure that the self-reported medical histories of potential adult volunteers in clinical trials are as comprehensive as possible(67) .

2.5 Opportunities for accessing electronic records to aid clinical trial conduct

The Provincial Health Data Centre (PHDC) has developed a pilot database that links data from the following five resources:

- Electronic registers of human immunodeficiency virus (HIV) and tuberculosis (TB) treatment initiation and regimens. A three-tier approach permits the South African Ministry of Health (MoH) to strategically perform one of the tiers in every facility with antiretroviral therapy (ART) facilities. Every tier product the similar nationally essential monthly registration and three-monthly statements so that productions from the three tiers could be combined into one data at the level of the health system(71) (Figure 2).
- Hospital and primary healthcare patient registration and admission systems; outpatient and primary care clinic visits
- Hospital and primary care birth registers
- Various laboratory databases
- Dispensing data from a centralised dispensing system and warehouse pharmacy

While intended to help clinicians with patient management, this data-linkage system could be a beneficial resource for clinical trial investigators to access available medical records of the people who apply to take part in clinical trials and help ensure their eligibility and safety during a trial.

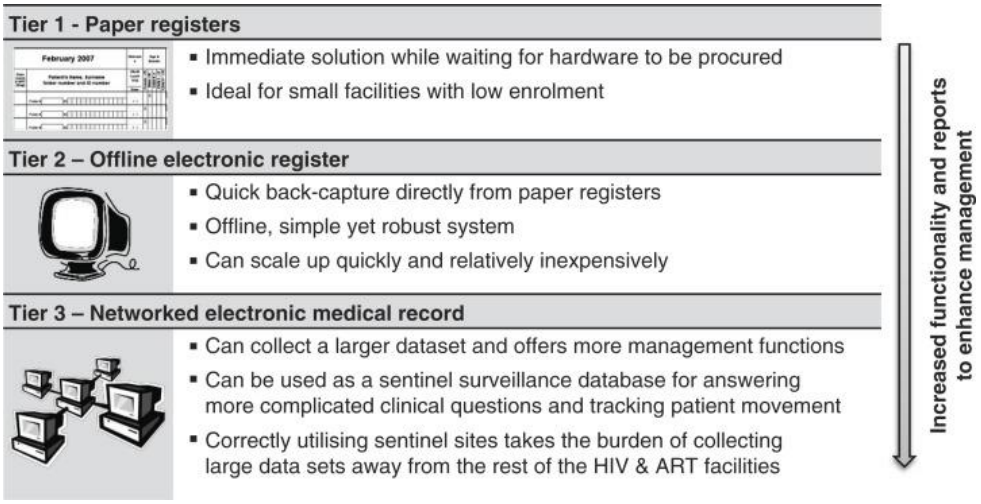

Figure 2: The three-tier monitoring and evaluation system for ART. Adapted from the National Department of Health in December 2010(71).

Chapter 3: Methodology and Data Analysis

3.1 Rationale of the study

This study aimed to investigate optimal methods for obtaining medical histories for future healthy volunteer trials by inviting members of the public to join a volunteer database via an online questionnaire portal and asking them for permission to access available electronic medical records.

3.2 Study methodology

3.2.1 Study objectives

- To understand discrepancies between medical histories obtained through online self-reports in response to a questionnaire, available electronic medical records in the public healthcare sector, and the information obtained during in-depth interviews with members of the public applying to join an adult volunteer database for clinical trials.

- To explore ways of engaging with potential adult volunteers in clinical trials, so that their self-reported medical histories are as comprehensive as possible.

- To explore the feasibility of accessing available electronic records for potential adult volunteers in clinical trials, responding to advertisements It was a mixed methods study with sequential explanatory design collecting quantitative and qualitative data.

3.2.2 Study design and participants

This study was designed using a mixed-methods approach, with sequential explanatory design collecting quantitative and qualitative data, and was nested in an existing adult volunteer database (Appendix 1). People from the Cape Town community were invited to join the database in response to advertisements that provided a link to the database website (Appendix 2). On the website, they completed a brief medical history according to a pre-defined questionnaire (Appendix 3) and could indicate consent for the study team to access their available electronic medical records or the reason for non-consent to access records if this was volunteered.

A subset of those potentially eligible for a typical healthy volunteer trial, who reported different information to that obtained through the electronic records, were invited to attend a face-to-face appointment, where consent was requested for a simple physical examination and in-depth interview (Topic guide, Appendix 4). If no such volunteers were identified, a random sample was chosen from those who responded to the advertisement, and they were invited to the face-to-face appointment.

Advertisements and the online questionnaire were restricted to English for financial reasons, and only those who were fluent enough in English to converse with the interviewers, as ascertained during phone calls when making appointments for the interview, were invited. Advertising posters From July 2018, advertising posters were placed at various locations within Groote Schuur Hospital in Cape Town, to recruit visitors rather than patients. Additionally, web banners were placed online in October 2018 and February 2019. Printed advertisements appeared in Vukani newspaper.

3.2.3 Data collection and management

Quantitative

Quantitative data included the number of participants responding to the advertisements, completing the online questionnaire, consenting or not consenting to access to electronic medical records and the interview, the number, and nature of medical history items obtained from the questionnaire, the database review and the interview. We also recorded basic demographic data, such as age, gender, home language, and employment status, and the results of the physical assessment, including temperature, heart rate, blood pressure, and body mass index (Appendix 3).

Qualitative

Using a topic guide (Appendix 4) in the recorded interview, participants were asked questions about where they had seen the advertisement, and their perceptions of it, their understanding of clinical research and trials, and their medical history, including any treatments used in the previous four weeks. Thereafter, the interviewer asked for the participants' assistance in improving methods of obtaining accurate medical and treatment histories regarding the online questionnaire, the electronic medical record (if available), and the physical examination and notes taken during the interview. This included exploring their understanding of the reasons for and process of obtaining their medical history information; the reasons for reporting or not reporting information obtained through the questionnaire, database review and interview; and the participant's advice on how clinical trial teams may collect comprehensive and accurate data during the process of building a volunteer database, with reference to advertisements and the website portal. We also explored how potential participants felt about us accessing their electronic medical records.

Recordings were transcribed according to a standard operating procedure (SOP) and transcripts were then imported into folders in NVivo® 12,a qualitative data management software program, which was restricted to the Master of Philosophy student and primary supervisor.

3.2.4 Sample size and analyses

There were no sample size calculation as enough potential participants who completed the online database questionnaire were invited for interviews until there was a saturation of themes being obtained in the qualitative analysis in excel spread sheet by frequencies. However, a maximum of 20 interviews were anticipated.

Quantitative data, including demographic variables, medical histories and medications used were described by number and proportion. Transcripts were analysed thematically, including descriptions given for differential reporting by question method; relevant text was examined line by line for repeating ideas, and the underlying meaning or concepts behind statements (72,73). These initial codes were entered into the NVivo® program and themes were identified as more transcripts were coded. The MPhil student conducted the initial coding, which was reviewed by the primary supervisor and an initial coding template was then agreed on. Thereafter, the MPhil

student proceeded with coding the remainder of the transcripts, which was again examined by the supervisor, and any changes to the coding were discussed. Once coding was complete, the data were explored for theoretical constructs(72,74) .

3.2.5 Data handling and record-keeping

At the outset of this study, we created secure electronic and paper-based filing systems to keep all study-specific information as per the CCOAT adult volunteer database protocol for the online information, supplemented by secure storage for the qualitative and physical examination data obtained in the interviews.

3.2.6 Ethical considerations

The study protocol was approved by the University of Cape Town Human Research Ethics Committee and is considered a low risk for participants (Appendix 6). Any personal data was protected, and no identifying features will be revealed in subsequent publications. Consent for the completion of preliminary demographic and health details in the online questionnaire was integral to the platform, while written information and consent documents were used before the face-to-face interview (Appendix 4 and 5). Potential participants were requested to allow access to their available electronic medical records and the information was not obtained if no such permission was provided.

Before the in-depth interview, the investigator read through the form with each participant and offered them the time and opportunity to enquire about the details of the study and to consider taking part. Participants were made aware that the interview would be recorded and that they were not required to discuss details if they were not comfortable doing so plans were in place for illiterate participants, such that an independent witness would have been used to validate that the verbal information was an accurate reflection of the written form.

If a participant was eligible for a face-to-face meeting, they were offered R75.00, as compensation for travel expenses and inconvenience, to attend the appointment as per the existing database protocol. All participants were also offered refreshments during the interviews.

Registered participants can request to be removed from the database at any time, for any reason (or no reason) upon their request.

Chapter 4: Results and Discussion

4.1 Results

Between July 2018 and October 2018, we received 11 responses, and between November 2018 and February 2019 there were a further 13. The last advertisement in February 2019 elicited 14 more responses. Therefore, in total, the three advertising campaigns over eight months resulted in 38 respondents.

Study participants

Table 2 provides a summary of the demographic characteristics of the 38 people who responded to the online questionnaire. The majority of respondents were female (28/38; 73.6%) with median age, at the time of the survey, of 31.4 years (19-42 years), and median height and weight of 160 cm and 77 kg respectively. 22/38 (57.8%) reported that they spoke or read English, 15/38 (39.4%) spoke Xhosa and 1/38 (2.6%) spoke Tswana. All participants gave consent for us to access their medical records from the PHDC except for 2/38 (5.2%), and a further 3/38 (7.89%) refused to give consent to remain in the database for consideration for future clinical trials.

Table 2: Demographic data of study participants

Total numbers	Gender Female %	Median Age Ys	Median Height Cm	Median Weight Kg	English speaker %	Previous clinical trials %
38	73.6	31.4	160	77	57.8	5.2

Medical and medication histories

Table 2 provides a summary of past medical, surgical and medication histories from three methods: online self-report questionnaire, online medical records, and an in-depth interview. According to the online self-report questionnaire, ten people (10/38; 26.3%) had chronic medical conditions, the majority being HIV (7/10; 70%). One of these had multiple comorbid conditions: previous pulmonary tuberculosis, systemic hypertension, chronic kidney disease, and arthritis. One (10 %) had Crohn's disease, one had sinusitis and one had polycystic ovary syndrome and endometriosis. No participants were reportedly suffering from diabetes, epilepsy, asthma, or heart problems. Twelve participants (31.5%) had had previous surgery, seven being caesarean sections, two had undergone an appendectomy, one a keloid removal, one a dental procedure and one a minor facial operation. Nine (23.6%) were on chronic medication, the majority of these (7%) being HIV antiretroviral therapy (ART). One was also reportedly taking an iron supplement and medication for a kidney problem. One was on azathioprine for Crohn's disease and another on combined oral contraceptive pills. There were 10/38 (26.3%) who reported being active smokers, with a median smoking index of three cigarettes per day. 11/38 (28.9%) were social alcohol drinkers and 2/38 (5.2%) were recreational drug users, one of which used marijuana and another used cannabis oil. All respondents had recently visited day clinics for different reasons, the majority for flu (14/38; 36.8%), a general check-up (8/38; 21%)

and a pregnancy follow-up (5/38; 13.1%). A minority had visited such a facility for the treatment of a rash, a dental problem, and constipation.

We accessed the Western Cape electronic medical records for only 8/38 (21%). This was largely due to a delay in obtaining permission from the data centre. The protocol was first submitted on 6 August 2018, to which they responded on 30 August 2018, asking for the study ethics approval form, which was then sent. Feedback on 18 October 2018 was in the form of a request for a protocol amendment to amend the wording on the online questionnaire to specify that the interviews would be exploring differences between the online questionnaire responses and electronic records. The revised protocol and re-approval from the ethics committee was submitted on 8 November 2018, after which we received approval on 25 January 2019. We obtained the first dataset of participants on 15 February 2019, and a second list on 5 March 2019. As of now, no further data has been received. Unfortunately, these unanticipated delays precluded us from accessing data for the first 24 questionnaire respondents.

Comparing findings from the online questionnaire and the medical records, it was found that 25% had no difference in information. The remaining 75% had discrepancies, as summarized in Table 2. 10/38 people (26.3%), the majority of whom were female (6/10; 60%), agreed to and were available for a face-to-face, in-depth interview. Unfortunately, we did not have access to their medical records (Table 3). The vital signs of those interviewed demonstrated a median blood pressure of 120/65 mmHg, a median pulse of 82.5 beats per minute and a median temperature of 36.95˚C. The median body mass index of those interviewed was 28 kg/m^2.

Respondent number	Gender	Online survey			Medical records		
		PMHx	PSHx	Medications	PMHx	PSHx	Medications
1.	Female	None	None	None	None	Dental Procedure	Clotrimazole, Flucloxacillin, Paracetamol
2.	Female	HPT, TB, HIV, Arthritis, Kidneys problem	C/S	Iron tablets, ARVs	Atopic Dermatitis	None	TB treatment, Pyridoxine, Promethazine, Hydrochlorothiazide, Aspirin, Valproic acid, Tramadol, Paracetamol, Laxative, Trimethoprim, Enalapril, Amlodipine
3.	Female	HIV	None	None	HIV, Chronic Constipation	None	Sennakot, Liquid paraffin, Ibuprofen, lidocaine, Amoxicillin
4.	Female	None	None	None	None	None	None
5.	Female	None	None	None	Dental problem	None	Metronidazole, Sodium citrate, Azithromycin
6.	Female	None	None	None	Dental problem	None	None
7.	Female	None	None	None	Family planning		
8.	Male	None	None	None	None	None	None

Table 3: Discrepancies between the online survey and medical records

Respondent number	Interview ID	Gender	Online survey			Interview		
			PMHx	PSHx	Medications	PMHx	PSHx	Medications
1.	ID6	Female	None	C/S	Cannabis Oil	None	None	Hair growth tablets, Sleeping pills, Vitamins
2.	ID2	Female	None	None	None	TB	Breast cystectomy	None
3.	ID10	Male	CD	None	AZA	Smoker Alcohol user	None	Vit B12 injection, Vit D, Calcium
4.	ID1	Male	None	Minor fascial surgery	Marijuana	Severe burn, Chronic sinusitis	None	Diclofenac
5.	ID9	Female	None	C/S	None	None	None	COC
6.	ID8	Female	HIV	None	ARVs	Shingles	None	COC, Marijuana
7.	ID4	Female	None	None	None	ND	ND	ND
8.	ID3	Male	None	None	None	ND	ND	ND
9.	ID5	Male	None	None	None	Alcohol user		Vit B complex, Paracetamol, Acetylsalicylic acid
10.	ID7	Female	HIV	None	ARVs	None	None	Antacid

Table 4: Discrepancies between the online survey and face-to-face interview

ART =antiretroviral therapy, HIV= human immune deficiency virus, C/S=caesarean section, PMHx= past medical history, PSHx=past surgical history, COC=combined oral contraceptive, CD=Crohn's disease, AZA=azathioprine, PCOS=polycystic ovary syndrome, TB=Tuberculosis, Vit =vitamin, None= no past medical, surgical and medication histories, ND=no discrepancies.

Qualitative data

The qualitative data explored participants' understanding of clinical trials and research studies, the reasons for and process of obtaining their medical history information, the participants' advice on how clinical trial teams may collect comprehensive and accurate data during the process of building a volunteer database, with reference to advertisements and the website portal, and the reasons for reporting or not reporting information obtained through the database review and interview. The main themes are described below.

Different understandings of clinical trials and research studies

The concept of a clinical trial had different meanings for the respondents, with two participants having a very accurate understanding, two appeared to have no understanding or an incorrect understanding, and also found it difficult to explain what they did understand, and the remaining eight were on a continuum of good to poor understanding. When asked why some members of the public had difficulty understanding the advertisement, one of the participants, with a good understanding, explained it as follows:

> *"Clinical research is not something that the general public consider, people in universities do*." *[ID 1]*

Although difficult to elucidate explicitly, the participants with a very poor understanding most likely believed they were applying for a job and were being recruited to be part of the research team, even if it was in a voluntary role.

> "INTERVIEWER: *So, in terms of clinical research studies, what do you think your role would be…*?
>
> INTERVIEWEE: *.... to take the service to the people who [can't] afford [to] go to the clinics or something like that*." Later: "*Maybe they are old people who don't know how to go to the clinics…*" *[ID 9]*

Of those with a very good understanding of the rationale, one participant gave a near-perfect description of the rationale and process, summing up her involvement as,

> "*You're looking for healthy people that's willing to volunteer and take part in research*" and *"[You will] check if I'm actually eligible, if I meet the criteria that you're looking for, of taking medication, you'll obviously monitor me, maybe do some tests and check what the outcome was.*" … "*Technically my role would be the rat." [ID 6]*

Despite the advertisement specifying that we were seeking healthy volunteers for a potential trial that would not treat their condition, some indicated that they did, in fact, believe the research would do so one of these was someone living with HIV on antiretroviral (ARV) medication, while another was living with Crohn's disease.

Healthy living with a chronic condition

In both of the above-mentioned cases, the participants considered themselves to be healthy. The participant with Crohn's disease, who had a good understanding of the process of clinical research, could not explain why he had applied when the advertisement explicitly stated that: "To qualify, you need to be/have: NO stomach or bowel problems".

"INTERVIEWER: So, we do say here "no stomach or bowel problems", do you remember seeing that part?

INTERVIEWEE: I can't remember.

INTERVIEWER: ...It says here "healthy volunteers". Do you consider yourself in this group?

INTERVIEWEE: I would like to say so." [ID10]

Helping others, through working in, or taking part in clinical research

Although some participants did not fully comprehend the concept of clinical trial participation after this was explained to them, of those who did understand, most were interested in taking part. They largely felt that participation would potentially help others, although some understood that it may help them, which, as previously discussed, represented a misunderstanding of the concept of being a healthy volunteer. They indicated that we needed healthy volunteers, but did not have many, hence the use of advertising to set up a database so that we could come back to them for future studies.

"What I saw was… You need volunteers to do the research. Probably didn't have a lot of volunteers. It's probably a difficult thing to advertise and get in front of people's faces. It's the first thing I found and obviously I saw I qualified for all the criteria: not pregnant." [ID 1]

Willingness to accept taking an experimental medication

Most would accept trying a new experimental medication, even if they may experience adverse effects, as they trusted that the doctor (i.e. the investigator) would not give them the incorrect medicine and make them sick. The participants who had pre-existing conditions were concerned that the new medication may lead to a worsening of their condition. Considering the unknown side effects, they also thought that every person would have different reactions, but were pleased to be trying the new drug and would ~~just~~ be ~~very~~ careful.

"INTERVIEWEE: If I take a new medicine, maybe it's going to get a side effects or something like that.
INTERVIEWER: And what do you think about that?
INTERVIEWEE: But I trust you don't let me – you [won't] give me the wrong medicine." [ID 9]

The practicalities of taking part in research may be a barrier

At the same time, it was found that some participants may base their decision to join a study to receive payment, but may then decline involvement because their family would not be supportive or they could not take time off from work, although this might be possible if the study doctor could provide a sick note for their employer.

"I don't have any problems with [taking part in a trial]. The only thing is that it mustn't clash with my work." [ID10]

Improvements to the content and placement of advert to maximize recruitment

A number of participants felt that the advertisement was placed in an appropriate location, although some suggested we advertise more widely. For instance, posters could be placed in clinic waiting rooms, particularly family planning clinics where people were likely to be healthy, in local shops or shopping centres, libraries, community centres, and sports facilities, particularly soccer stadiums. One person was suggested the MyCiTi bus network as an appropriate place for a poster. Another was pleased to see the advertisement on the clinic wall where she was accompanying a sick relative and had taken a photo of it to complete online.

"....some people who go to clinics, they are healthy but maybe they are going for some other things."[ID 5]

Suggested online locations included social media platforms, such as Facebook (which could raise awareness of clinical trials, including what taking part in a clinical trial involves) and Gumtree, in addition to the online newspapers that had been used, as people are becoming more proficient in their use of the internet. One person suggested the job site, https://www.indeed.co.za/, as it advertises both paid and unpaid opportunities.

While they generally approved of the advertisement itself, respondents suggested it would have been advantageous to have a larger poster, or possibly even a leaflet, in colour and with pictures. The link to the questionnaire could have been improved with a direct link to information about clinical trial participation. It was also felt that it is important to use a large font and simple language, as well as highlight the benefits and reasons for participating in research.

"INTERVIEWEE: You know it is already very basic. It is very – yes, but basic for you guys may not be basic for someone outside." [ID 10]

"INTERVIEWEE: To the whole picture of what it is that you'll be doing. Maybe for more info click on this link and then have an FAQ type."[ID 1]

Improvements to the online questionnaire

Although there was agreement that the questionnaire was generally clear, some participants did suggest recommendations for improving it, to prevent misunderstandings about the requirements of the trial.

This included changing some words, such as "*before*, rather than past", guiding respondents through examples for some questions (e.g. the mention of "*marijuana*" specifically), and giving a better indication of the time frame for certain required information.

Additionally, participants suggested that asking about a quantity of alcohol is difficult because "*one glass could be whisky"*, and they mused how best to ask this question. Regarding smoking, some suggested it would be preferable to ask, *"When last did you smoke?"*

"INTERVIEWEE: Maybe also if it's a 'do you drink alcohol?' and then maybe also 'when last have you had?' and then per week…….Like for me, I don't drink every week……Maybe the per week would maybe need to change. I am thinking if you ask when last you have drunk and then how much do you drink on an occasion. I'm just trying to figure out how much a person drinks when they drink."[ID 10]

Talking about health in the interview was a useful way to be comprehensive

Some participants reported that the conversations with the researcher in the in-depth interview enabled them to gather additional information about their health and use of medicines, including details they did not mention in the online questionnaire. The reason for this was that, by the end of the conversation, the researcher had a more comprehensive understanding of the participants' health than from the online form, which people sometimes failed to fill in completely.

"*INTERVIEWEE: I think the interview is probably the best way (to get comprehensive information on medical history)…….this kind of interview where you can directly ask questions like you would ask 'do you recall from an injury perspective?' So, if somebody filled out the form, I think most people would have the same sort of thing that I had, in terms of oh, I'm going to take part in a study. Do you have a condition? No. I fill out medical aid forms. I just had to fill out, because I'm moving medical aids now and similar sort of questions I also answer now, because it's not something that affects my risk pattern or anything like that. It's a once-off." [ID 1]*

"INTERVIEWER: Yes okay. So what sort of helps you remember some things about your health and treatments than others?

INTERVIEWEE: I think just – I was speaking to you now, it's sparking things. Yes. Maybe at the time, I [did] the questionnaire a bit in a hurry. Maybe I thought that like saying [I was only] on Azathioprine and not the other medication." [ID 10]

Reasons for reporting or not reporting information

When discussing discrepancies between what they said in the questionnaire and the face-to-face interview, participants often said they "*forgot to report things"*, or "*were in rush",* as mentioned above.

It did not seem relevant: participants did not mention anything unrelated to the research, and, therefore, it was not necessary to report, did not take it for specific diseases, or even consider it a medication, as that was for when one was ill.

"*INTERVIEWEE: I didn't think [the sleeping tablets] would count because I was thinking more like [medication] if you're ill, you know so I'm not taking it for any illness, I'm just taking it."[ID 6]*

Similarly, some information was perceived as not what was being asked for, or the medication was only used intermittently. If it was not current, frequent, or persistent use of medication, they did not feel the need to report it.

"INTERVIEWEE: No, the problem is that I think it's just the B-co. and the Panadol like it's not the medication that I [use most] of the time, that's the reason that I didn't mention on that……. So, if there was like a medication that I used often that I'm used to it, then I was supposed to mention it on that [form]."[ID 5]

One participant also considered that they would be required to have a blood test to check illicit drug use or smoking before starting a clinical study, thus there was no need to be dishonest.

"*I've seen them before in other questionnaires, so it's something I won't lie about. It's something you do if somebody does, say, a blood test on you, they'll see nicotine in your system. So, no issue with it really." [ID 1]*

Unanimous agreement for researchers obtaining electronic medical history information

When asked which clinic they attended if sick, most said they went to the community day hospital. A minority have medical aid, so may go to a private doctor, and all participants also go to a pharmacy or shop to buy over-the-counter medication for flu, colds or sinus, such as painkillers and vitamins for general health. Most participants reported, however, that they did not believe in traditional healers.

"I don't talk to them because I'm not…it's not that I don't trust them, but I prefer going to the clinic" [ID 4]

The only people who carry medical notes are those with chronic conditions, such as HIV and Crohn's disease. One did not carry such a record, saying*:*

"INTERVIEWER: Medical records, do you keep a record, either your own or something the hospital or clinic or a doctor gave you, of your medical…

INTERVIEWEE: No, I don't have one at the moment, my doctor has one I'm sure, he always writes everything down." [ID 6]

None of the participants expressed any concern about us accessing their electronic records through the public health system. Some felt this would be the best option for obtaining the most comprehensive information on their health, as they did not remember everything that had happened in all clinic or hospital visits. Some doctors also did not provide them with all of the information. So, by accessing these medical records, researchers would get all the necessary data.

"*No, I think you can have a look, but I mean I might not remember every visit, I don't…there might be things doctors don't always tell you exactly what they're writing, so I don't know, you can check." [ID 6]*

4.2. Discussion

Medical research is common in South Africa, so it is important to know what participants understand about taking part. In addition, it is essential to understand what influences potential participants' reporting of their medical history, as sub-optimal reporting may affect whether people are eligible for a trial and the trial results. Healthy volunteer studies, in particular, rely on good medical history data. To the best of our knowledge, this study is the first in South Africa to investigate the situation of a healthy adult volunteer database, the information that applicants report when completing an online

questionnaire during recruitment, as compared to available medical records and a subsequent interview.

The main findings of the study were: 1) We experienced a very low response rate to the advertisement for joining the healthy volunteer database, 2) people in this community are willing to consider taking part in clinical research, but have different understandings of what this means, 3) there were discrepancies between online self-reported health and medication data and what was found in a pilot database of electronic public health medical records, and a face-to-face interview, 4) the reasons for these differences, as perceived by the participants, included forgetting some information, feeling it was not relevant or important to report, or because of the attributes of the online questionnaire, and 5) these participants had no concerns about us accessing their electronic medical records.

Efficient, cost-effective participant recruitment is widely recognized as a key determinant of success for clinical trials. Initially, we believed there would be a high response rate to our advertisements based on previous experience advertising for healthy participants in a malaria clinical trial, with advertisements placed in similar locations in the same hospital, as well as in print and online newspapers. In that case, hundreds of people responded within a very short time (personal communication: KI Barnes). While more research is needed to explore this, as the focus of the advertisements in these two scenarios was slightly different and because we did not explore this explicitly in our interviews, we propose that a key success factor was the inclusion of a phone number on the Barnes trial advertisements for people to send a "please call me" text to. Our findings suggest, therefore, that online recruitment on its own is not feasible for our context and investigators need to budget or staff and to factor in a reasonable time to call interested parties to elicit medical histories when planning their trials.

A small number of participants attended the face-to-face interviews. The various reasons for this include the inability to contact them for interviews on the number or email address provided and often participants did not arrive for the appointment. Among this small sample, the willingness of the public to join clinical trials seems reasonably accepted, although this does not indicate acceptance within the community. Ohmann et al. found that only 25% of 225 visitors interviewed at a German university accepted taking part in clinical trials, with a likelihood of lower participation in surgical trials than in dental or pharmaceutical trials(75). Patients with cancer often participate to gain possible therapeutic benefits(76,77).

The recruitment of participants is generally facilitated with financial reimbursement. In fact, a key reported motivation for participation is the financial reward(78,79). Kass et al. investigated study participation in the US and reported that for healthy volunteers, money was a motivating factor for 55% and the deciding factor for 46% many other motivations are described by healthy volunteers, such as contributing to science, helping others or personal benefits(36,80). In our study, the most frequently mentioned motivation was participants being content to help people through their contribution, even if they did not fully understand the meaning of being involved. Participants with chronic diseases, in particular, were eager to try a new medicine for their own benefit, while others were willing to be part of the research team. Both observations raise concerns, as it indicates a therapeutic misconception. However, while the people with chronic conditions, who considered themselves healthy, and therefore eligible, may not have been our target population for the volunteer database, they may be eligible for other studies. Similarly, while ~~the~~ high BMIs may exclude people from healthy volunteer studies, they may be suitable for studies with wider eligibility criteria, particularly where optimal dosing by weight is being investigated.

Understandably, people would consider taking an unpaid job as a trial participant or as part of the research team. As unemployment is very high in this community and unpaid positions are common, there is the hope that this may lead to paid employment as skills increase. However, it is critical to ensure that potential trial participants understand what taking part in a trial means, so that they may make an informed choice. Advertising for a volunteer database or specific trial, and completing an online health questionnaire, is the first step in a longer process of obtaining informed consent. Our study elicited useful suggestions from the Cape Town community for improving understanding of clinical trials, including a simply-worded social media page, and clear posters with pictures. We anticipated a low level of understanding of clinical research based on our previous experience of conducting trials in South Africa, yet our small sample showed diverse awareness, which may reflect what is also found in other settings. Despite what may be presumed about the relative ease of conducting trials in the US, where one would expect awareness of research to be higher, according to an article from Nature, nearly 20 percent of publicly-funded clinical trials there are delayed because they cannot register enough participants due to the general public's lack of education on trials(81,82).

In our small study, there were variations between self-reports of health and medicine use through the online questionnaire, the electronic medical records and the face-to-face interviews, which are similar in comparison to other reports. While not referring to a specific clinical trial, Eze-Nliam et al. reported that more than half of the discrepancies in their study were due to lack of self-reports by the participants(67). In contrast, another study aimed to compare the accuracy of online versus paper assessment methods to ascertain cigarette smoking status using a structured face-to-face interview as the gold standard. They found no statistically significant differences (83) . We cannot ascertain which method is more accurate than another because of our low sample size. However, were similar factors that influence medical history reports to another study conducted in Cape Town and Tanzania(4). These should be considered when trialists design ways of eliciting medical histories during recruitment.

While electronic records will undoubtedly provide more information for clinical trial teams to accurately assess potential participants' eligibility for trials, there were significant delays in obtaining the data from the Western Cape pilot data linkage project for this study. Thus, the feasibility of accessing data needs further exploration to ascertain if the problem was due to our study design, and a lack of understanding of this example of a clinical trial methodology research study, or to do with the ethics or practicalities of accessing such data, in general, for clinical trial purposes. Clinical trial methodology research is a new, but expanding, field. It aims to question the way clinical trials are designed, conducted, managed, analysed and reported. It is very important to understand some of these processes from the perspective of the trial participants, or potential participants, as it is for understanding patients' experiences of healthcare in general. Hence, there has been a move towards patient and public involvement (PPI). The term "public" includes patients, applicants, caregivers and people who use health services and social care, and organizations representing people who use such services. Research that emphasises the public's needs and views is more likely to yield results that can be used to enhance health and social care. PPI in clinical research has greatly expanded and significant attention has recently been paid to understanding its impact on research. People take part in research for individual reasons, including a wish to improve their own or others' treatment, and it could also be to have a 'voice' (84).

It is significant, therefore, for both ethical and practical reasons, to involve the public in research. In addition to the benefits of contributing to the quality and relevance of research, broader democratic principles of citizenship also inform the underlying reason for involving members of the public in research. Ethically, PPI is encouraged on the basis that individuals who are affected by the state, or the community, in the case of a public health study, have the right to join in study decisions that may affect them. This includes the development of systems and processes to involve patients and the public in research; advising on the recruitment of patients as participants; engaging the public in the design and implementation of research; the dissemination and implementation of research findings once a study is completed(85).

Reports of PPI outcomes are both positive and negative. Positive effects of PPI have influenced different studies, from the design of the study and the selection of outcomes to the distribution and implementation of results. Potential negative effects of PPI on studies have also informed, including "potential scientific and ethical conflicts in the design of protocols"; potential reductions in recruitment; prejudices in enrolment; power struggles between investigators and patients; untimely dissemination of study results prior to academic publication; and quality also reporting inconsistent across trials(86–88). Challenges have been raised with PPI, which indicates the need for a solid basis of evidence. For example, the research team perceives public contributors as having an excessively narrow or self-serving agenda or if they are not satisfactorily involved, in spite of the opportunity and support provided.

PPI can work well if its objectives are pure, there are well-developed strategies for PPI in a study, and ~~if~~ PPI models are more responsive and managerial (e.g. membership in the trial management group), rather than limited to general supervision (e.g. membership in the trial management committee)(89). Our own study showed that potential trial participants were enthusiastic about giving us advice on how best to manage the recruitment to our adult volunteer database and were open to us accessing their electronic medical records. As the latter is only one part of a person’s medical experience, there may be other gaps in knowledge to be explored, such as how to obtain similar records from the myriad of private practitioners that people consult, and an accurate record of over-the-counter medication use.

A limitation of this study was the low response rate to our advertisements and the significant delays in obtaining electronic medical records for people completing the online questionnaire. Ultimately,only eight medical records were obtained, which limited our ability to explore the differences in the responses to the questionnaire. Furthermore, this delay resulted in a short time in which to conduct face-to-face interviews, also resulting in a small sample size. Finally, the advertisements, online questionnaire, and interviews could only be conducted in English, which will have impacted the generalizability of our findings but may also have hampered the conversations within the interviews with people whose first language was not English.

4.3. Conclusion:

Our study provides some evidence for places to advertise for an adult volunteer database, and optimal wording and format for an advert and an online questionnaire. We provided data to show discrepancies between medical histories obtained through online self-reports questionnaire, electronic public sector medical records as well as face to face interview. More efforts are needed to help the general public understand the meaning of clinical trials. The main reasons for not reporting information in the questionnaires included forgetting, considering it not relevant/important, or because of the questionnaire attributes. We have shown that electronic medical records may be accessed to help understand potential participants' eligibility for trials, but that the feasibility of accessing such data timeously may need further negotiation.

References

1. Klemperer G. Elements Of Clinical Diagnosis. Hansebooks; 2017. Published by BiblioLife.
2. Curran J. The Doctor, his Patient and the Illness. BMJ. 2007 Nov 3; 335(7626): 941.
3. Gul RB, Ali PA. Clinical trials: The challenge of recruitment and retention of participants. J Clin Nurs. 2010 Jan 19(1-2):227-33.
4. Allen EN, Mushi AK, Massawe IS, Vestergaard LS, Lemnge M, Staedke SG, et al. How experiences become data: The process of eliciting adverse event, medical history and concomitant medication reports in antimalarial and antiretroviral interaction trials. BMC Med Res Methodol. 2013 Nov14;13:140.
5. Pocock SJ. Clinical trials : a practical approach. Wiley; 1983. 266 p.Book.1991.
6. FDA. The Drug Development Process - Step 3: Clinical Research. U.S. Food & Drug Administration. Report.2018.
7. The Drug Development Process: 9 Steps From the Laboratory to Your Medicine Cabinet [Internet]. [cited 2019 Oct 14]. Available from: https://www.fool.com/investing/general/2015/01/03/the-drug-development-process-9-steps-from-the-labo.aspx
8. Clinical Development [Internet]. [cited 2019 Oct 14]. Available from: https://www.msd.co.za/msd-research-home/discovery-and-development-process-at-msd/clinical-development/
9. Curtis A. Dickman. How Clinical Trials are Conducted [Internet]. 2019 [cited 2019 Oct 14]. Available from: https://www.spineuniverse.com/clinical-trials/how-clinical-trials-conducted
10. Chalmers TC. The clinical trial. Milbank Mem Fund Q Health Soc [Internet]. 1981 [cited 2019 Oct 14];59(3):324–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7024846
11. Learn About Clinical Studies - ClinicalTrials.gov [Internet]. [cited 2019 Oct 14]. Available from: https://clinicaltrials.gov/ct2/about-studies/learn
12. Wang D, Bakhai A. Clinical Trials: A Practical Guide to Design, Analysis, and Reporting - Book. First edition. March 2006.
13. Types of Cancer Clinical Trials - National Cancer Institute [Internet]. [cited 2019 Oct 14]. Available from: https://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials/types
14. Meadows M. The FDA's drug review process: ensuring drugs are safe and effective. FDA Consum. 2002 Jul-Aug;36(4):19-24.
15. Keyter A, Gouws J, Salek S, Walker S. The Regulatory Review Process in South Africa: Challenges and Opportunities for a New Improved System. Ther Innov Regul Sci. 2018 Jul;52(4):449-458.
16. CHOICES: Understanding Clinical Trials as a Treatment Option - Full Text View - ClinicalTrials.gov [Internet]. [cited 2019 Oct 14]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT00983866?term=understand+clinical+tria

l&rank=5

17. NRC Research Institute | Clinical Trials in Orange County [Internet]. [cited 2019 Oct 14]. Available from: https://www.nrcresearch.com/

18. Clinical Trials Information for Patients and Caregivers - National Cancer Institute [Internet]. [cited 2019 Oct 14]. Available from: https://www.cancer.gov/about-cancer/treatment/clinical-trials

19. Reviewer Guidance Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review [Internet]. 2005 [cited 2019 Oct 14]. Available from: http://www.fda.gov/cder/guidance/index.htm

20. Elizabeth Weeks-Rowe.The CRA's Guide to Monitoring Clinical Research.book. Fourth Edition. June 2016.

21. Arango J, Chuck T, Ellenberg SS, Foltz B, Gorman C, Hinrichs H, et al. Good clinical practice training: Identifying key elements and strategies for increasing training efficiency. Therapeutic Innovation and Regulatory Science. 2016 Jul;50(4):480-486.

22. SAHPRA - South African Health Products Regulatory Authority [Internet]. [cited 2019 Oct 14]. Available from: https://www.sahpra.org.za/

23. What Are Clinical Trials? [Internet]. [cited 2019 Oct 14]. Available from: https://www.breastcancer.org/treatment/clinical_trials/what_are

24. Understanding the Clinical Research Process and Principles of Clinical Research 2 Understanding the Clinical Research Process and Principles of Clinical Research, v1.0. Participant Guide. HIV/AIDS Network Coordination (HANC).Report 102209.2009.

25. Introduction to Clinical Trials | HSA | Health Sciences Authority [Internet]. [cited 2019 Oct 14]. Available from: https://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Clinical_Trials/Overview/Introduction_to_Clinical_Trials.html

26. Strevel EL, Newman C, Pond GR, MacLean M, Siu LL. The impact of an educational DVD on cancer patients considering participation in a phase I clinical trial. Support Care Cancer. 2007 Jul;15(7):829-40.

27. Krishna S, Prasad NP. Ethical issues in recruitment of "healthy volunteers": study of a clinical research organisation in Hyderabad. Indian J Med Ethics. 2014 Oct-Dec;11(4):228-32.

28. Schroeder D, Cook J, Hirsch F, Fenet S, Muthuswamy V, SpringerLink. Ethics Dumping Case Studies from North-South Research Collaborations. SpringerBriefs in Research and Innovation Governance.eBook. 05 December 2017.

29. Resnik DB, McCann DJ. Deception by research participants. N Engl J Med. 2015 Sep 24;373(13):1192–3.

30. Colfax G, Buchbinder S, Vamshidar G, Celum C, McKirnan D, Neidig J, et al. Motivations for participating in an HIV vaccine efficacy trial. J Acquir Immune Defic Syndr. 2005 Jul 1;39(3):359-64.

31. Dhalla S, Poole G. Motivators to participation in actual HIV vaccine trials. AIDS and Behavior. 2014.

32. Nyaoke BA, Mutua GN, Sajabi R, Nyasani D, Mureithi MW, Anzala OA. Volunteer motivators for participating in HIV vaccine clinical trials in Nairobi, Kenya. PLoS One. 2017 Sep 7;12(9):e0183788.

33. Volk JE, Hessol NA, Gray GE, Kublin JG, Churchyard GJ, Mlisana K, et al. The HVTN503/Phambili HIV vaccine trial: A comparison of younger and older participants. Int J STD AIDS. 2014 Apr;25(5):332-40.

34. Burgess LJ, Sulzer NU, Hoosain F, Leverton N, Bliganut S, Emanuel S. Patients' motivations for participating in cardiovascular clinical trials: A local perspective. Cardiovasc J Afr. 2009 Jul-Aug;20(4):220-3.

35. Almeida L, Azevedo B, Nunes T, Vaz-Da-Silva M, Soares-Da-Silva P. Why healthy subjects volunteer for phase I studies and how they perceive their participation? Eur J Clin Pharmacol. 2007 Nov;63(11):1085-94.

36. Kass NE, Myers R, Fuchs EJ, Carson KA, Flexner C. Balancing justice and autonomy in clinical research with healthy volunteers. Clin Pharmacol Ther. 2007 Aug;82(2):219-27.

37. Shedlin MG, Decena CU, Mangadu T, Martinez A. Research participant recruitment in hispanic communities: Lessons learned. J Immigr Minor Heal. 2011 Apr;13(2):352-60.

38. Miller KL, McKeever P, Coyte PC. Recruitment issues in healthcare research: The situation in home care. Heal Soc Care Community. 2003 Mar;11(2):111-23.

39. Velott DL, Baker SA, Hillemeier MM, Weisman CS. Participant Recruitment to a Randomized Trial of a Community-Based Behavioral Intervention for Pre- and Interconceptional Women. Findings From the Central Pennsylvania Women's Health Study. Women's Heal Issues. 2008 May-Jun;18(3):217-24.

40. Smith LJ. How ethical is ethical research? Recruiting marginalized, vulnerable groups into health services research. J Adv Nurs. 2008 Apr;62(2):248-57.

41. Patel MX, Doku V, Tennakoon L. Challenges in recruitment of research participants. Adv Psychiatr Treat. 2003 2003;9:229–38.

42. Northouse LL, Rosset T, Phillips L, Mood D, Schafenacker A, Kershaw T. Research with families facing cancer: The challenges of accrual and retention. Res Nurs Heal. 2006 Jun;29(3):199-211.

43. Treweek S, Pitkethly M, Cook J, Fraser C, Mitchell E, Sullivan F, et al. Strategies to improve recruitment to randomised trials. Cochrane Database of Systematic Reviews. 2018 Feb 22;2:MR000013.

44. Vijayananthan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. Biomedical Imaging and Intervention Journal. 2008 Jan;4(1):e5.

45. Wray RJ, Stryker JE, Winer E, Demetri G, Emmons KM. Do cancer patients fully understand clinical trial participation? A pilot study to assess informed consent and patient expectations. J Cancer Educ. 2007 Spring;22(1):21-4.

46. Hartgerink BJ, McMullen P, McDonough JP, McCarthy EJ. A guide to understanding informed consent. CRNA. 1998 Nov;9(4):128-34.

47. Clinical Trials: What Patients Need to Know | FDA [Internet]. [cited 2019 Oct 14]. Available from: https://www.fda.gov/patients/clinical-trials-what-patients-need-know

48. Schlademann S, Hüppe A, Raspe H. [Results of a randomised controlled trial on the acceptance and the outcomes of a counselling on medical inpatient rehabilitation in gainfully employed members of statutory health insurances with rheumatoid arthritis (clinicaltrials.gov identifier NCT00229541)]. Gesundheitswesen 2007 Jun;69(6):325-35.

49. Dessai R.Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa. book. Second edition. Department of Health, 2006.

50. Informed Consent in Cancer Clinical Trials - National Cancer Institute [Internet]. [cited 2019 Oct 14]. Available from: https://www.cancer.gov/about-cancer/treatment/clinical-trials/patient-safety/informed-consent

51. Burgess LJ, Sulzer NU. The role of print advertising in clinical trial recruitment: Lessons from a South African site. Open Access J Clin Trials. 2010:(2) :83-87.

52. Why Do Some Patients Enroll in Clinical Trials and Others Don't? [Internet]. [cited 2019 Oct 14]. Available from: https://forteresearch.com/news/patients-enroll-clinical-trials-others-dont/

53. Burgess LJ, Sulzer NU. Clinical trials in South Africa: Need for capacity building and training. South African Med J.2010;100(7):402.

54. Archibald MM, Munce S. Challenges and strategies in the recruitment of participants for qualitative research qualitative research. Univ Alberta Heal Sci J. 2015 Nov (1), 32-37.

55. Melnyk B, Morrison D. Intervention Research and Evidence-Based Quality Improvement. Book. Second edition. Springer Publishing Company; 2018.

56. Cirelli D, Thompson TE, Dufour MC, Gabriella Newes-Adeyi MPH, Sanjeev R, Chiung M, et al. Evaluation of Patient Recruitment Strategies-Phase I Feasibility Study Final Report [Internet]. 2006 [cited 2019 Oct 14]. Available from: www.csrincorporated.comwww.csrincorporated.com

57. Lawrie TA, Betrán AP, Singata-Madliki M, Ciganda A, Hofmeyr GJ, Belizán JM, et al. Participant recruitment and retention in longitudinal preconception randomized trials: Lessons learnt from the Calcium And Pre-eclampsia (CAP) trial. Trials. 2017 Oct 26;18(1):500.

58. Caine KJ, Davison CM, Stewart EJ. Preliminary field-work: Methodological reflections from northern Canadian research. Qual Res. 2009 Sep (4) 489–513;

59. Clark T. "We're over-researched here!": Exploring accounts of research fatigue within qualitative research engagements. Sociology. 2008 Oct 42(5), 953–970.

60. Highlights from CISCRP's 2017 Perceptions & Insights Study - Center for Information & Study on Clinical Research Participation [Internet]. [cited 2019 Oct 14]. Available from: https://www.ciscrp.org/headline-perceptions-insights-study-march-2018/

61. Munce SEP, Webster F, Fehlings MG, Straus SE, Jang E, Jaglal SB. Perceived facilitators and barriers to self-management in individuals with traumatic spinal cord

injury: A qualitative descriptive study. BMC Neurol. 2014 Mar 13;14:48.

62. Archibald MM, Caine V, Ali S, Hartling L, Scott SD. What is left unsaid: An interpretive description of the information needs of parents of children with asthma. Res Nurs Heal. 2015 Feb;38(1):19-28.

63. Kelstrup AM, Juillerat P, Korzenik J. The accuracy of self-reported medical history: A preliminary analysis of the promise of internet-based research in inflammatory bowel diseases. J Crohn's Colitis. 2014 May;8(5):349-56.

64. Tam VC, Knowles SR, Cornish PL, Fine N, Marchesano R, Etchells EE. Frequency, type and clinical importance of medication history errors at admission to hospital: A systematic review. CMAJ. 2005 Aug 30;173(5):510-5.

65. Brener ND, Billy JOG, Grady WR. Assessment of factors affecting the validity of self-reported health-risk behavior among adolescents: Evidence from the scientific literature. Journal of Adolescent Health. 2003 Dec;33(6):436-57.

66. Kim H, Lee K, Chang S, Kang G, Tak Y, Lee M, et al. Factors affecting the validity of self-reported data on health services from the community health survey in Korea. Yonsei Med J. 2013 Jul 1; 54(4): 1040–1048.

67. Eze-Nliam C, Cain K, Bond K, Forlenza K, Jankowski R, Magyar-Russell G, et al. Discrepancies between the medical record and the reports of patients with acute coronary syndrome regarding important aspects of the medical history. BMC Health Serv Res. 2012 Mar 26;12:78.

68. Weisskopf M, Bucklar G, Blaser J. Tools in a clinical information system supporting clinical trials at a Swiss University Hospital. Clin Trials. 2014 Dec;11(6):673-80.

69. Huang Y, Fried LF, Kyriakides TC, Johnson GR, Chiu S, Mcdonald L, et al. Automated safety event monitoring using electronic medical records in a clinical trial setting: Validation study using the VA NEPHRON-D trial. Clin Trials. 2019 Feb;16(1):81-89.

70. Yamamoto K, Yamanaka K, Hatano E, Sumi E, Ishii T, Taura K, et al. An eClinical trial system for cancer that integrates with clinical pathways and electronic medical records. Clin Trials. 2012 Aug;9(4):408-17.

71. Osler M, Hilderbrand K, Hennessey C, Arendse J, Goemaere E, Ford N, et al. A three-tier framework for monitoring antiretroviral therapy in high HIV burden settings. Journal of the International AIDS Society. 2014 Apr 28;17:18908.

72. Long DR, Strauss A, Corbin J. Basics of Qualitative Research: Grounded Theory Procedures and Techniques. Book. SAGE Publications, Second edition Sep 1990.

73. Auerbach C, Silverstein LB. Qualitative data: An introduction to coding and analysis. Qualitative Data: An Introduction to Coding and Analysis. Book. NYU Press; First edition Sep 2003.

74. Chandler C. Qualitative methods for international health intervention research · Publications · ACT Consortium. 2014 [cited 2019 Oct 14]; Available from: http://www.actconsortium.org/publications.php/72/qualitative-methods-for-international-health-intervention-research.html

75. Ohmann C, Deimling A. Attitude towards clinical trials: Results of a survey of persons

interested in research. Inflammation Research. 2004 Aug 53(2); 142-147.

76. Agrawal M, Grady C, Fairclough DL, Meropol NJ, Maynard K, Emanuel EJ. Patients' decision-making process regarding participation in phase I oncology research. J Clin Oncol. 2006 Sep 20;24(27):4479-84.

77. Catania C, De Pas T, Goldhirsch A, Radice D, Adamoli L, Medici M, et al. Participation in clinical trials as viewed by the patient: Understanding cultural and emotional aspects which influence choice. Oncology. 2008 Aug 74(3-4):177-87.

78. Watson JM, Torgerson DJ. Increasing recruitment to randomised trials: A review of randomised controlled trials. BMC Medical Research Methodology. 2006 Jul 19;6:34.

79. Caldwell PHY, Hamilton S, Tan A, Craig JC. Strategies for increasing recruitment to randomised controlled trials: Systematic review. PLoS Med. 2010 Nov 9;7(11):e1000368.

80. Townsend A, Cox SM. Accessing health services through the back door: A qualitative interview study investigating reasons why people participate in health research in Canada. BMC Med Ethics. 2013 Oct 12;14:40.

81. Kim ES, Bernstein D, Hilsenbeck SG, Chung CH, Dicker AP, Ersek JL, et al. Modernizing eligibility criteria for molecularly driven trials. J Clin Oncol. 2015 Sep 1;33(25):2815-20.

82. Gore L, Ivy SP, Balis FM, Rubin E, Thornton K, Donoghue M, et al. Modernizing clinical trial eligibility: Recommendations of the American society of clinical oncology-friends of cancer research minimum age working group. J Clin Oncol. 2017 Nov 20;35(33):3781-3787.

83. Steffen MW, Murad MH, Hays JT, Newcomb RD, Molella RG, Cha SS, et al. Self-report of tobacco use status: Comparison of paper-based questionnaire, online questionnaire, and direct face-to-face interview - implications for meaningful use. Popul Health Manag. 2014 Jun 17(3); 185-189.

84. Körner M. Patient-centered care through internal and external participation in medical rehabilitation. Health (Irvine Calif). 2013;05(06):48–55.

85. Bagley HJ, Short H, Harman NL, Hickey HR, Gamble CL, Woolfall K, et al. A patient and public involvement (PPI) toolkit for meaningful and flexible involvement in clinical trials – a work in progress. Res Involv Engagem. 2016 Apr 27;2:15.

86. Mathie E, Wilson P, Poland F, Mcneilly E, Howe A, Staniszewska S, et al. Consumer involvement in health research: A UK scoping and survey. Int J Consum Stud. 2014 Jan 38(1); 35-44.

87. Buck D, Gamble C, Dudley L, Preston J, Hanley B, Williamson PR, et al. From plans to actions in patient and public involvement: Qualitative study of documented plans and the accounts of researchers and patients sampled from a cohort of clinical trials. BMJ Open. 2014 Dec 4;4(12):e006400.

88. Gradinger F, Britten N, Wyatt K, Froggatt K, Gibson A, Jacoby A, et al. Values associated with public involvement in health and social care research: A narrative review. Heal Expect. 2015 Oct 1;18(5):661–75.

89. Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, et al. A

Systematic Review of the Impact of Patient and Public Involvement on Service Users, Researchers and Communities. Patient. 2014 ;7(4):387-95.

Appendix 1 - Collecting quantitative and qualitative data - nested in an existing adult volunteer database

Protocol Number: MCRG AVDB01

Building and maintaining an adult volunteer database for future clinical trials

Author:	**Elizabeth Allen**
Version number:	**1.2**
Release date:	**07 April 2014**

Investigator Signature Page

I have read the protocol and agree that it contains all necessary details for carrying out the screening of applicants for inclusion in an adult volunteer database as described. I will conduct this protocol as outlined therein and supervise staff that conduct the screening and maintain the database.

I agree to inform all applicants that their involvement is not for any particular clinical trial and I will ensure that the requirements related to screening volunteers and obtaining informed consent are in accordance with ICH and South African Guidelines for Good Clinical Practice (GCP), including the Declaration of Helsinki (2008 and 2013) where applicable.

I will not make any changes to the protocol without the Faculty of Health Sciences Human Research Ethics Committee's (HREC) approval, except when necessary to minimise apparent immediate harm to volunteers. I agree to promptly report to the HREC any changes in the research activity and unanticipated problems involving risk to the participants in accordance with their standard operating procedures.

I agree to maintain adequate and accurate records and make those records available in accordance with GCP and local requirements, where applicable.

_____ Date: _____

Karen I Barnes

Principal Investigator

Division of Clinical Pharmacology

Department of Medicine

University of Cape Town (UCT)

K45 Old Main Building

Groote Schuur Hospital

Observatory 7925

South Africa

Tel: +27 21 406 6294 / 4070 / 6996

Fax: +27 21 650 3726

Mobile: +27 82 440 2542

Email: karen.barnes@uct.ac.za

Protocol Synopsis

Protocol number	AVDB01
Protocol title	Building and maintaining an adult volunteer database for future clinical trials
Principal Investigator	Professor Karen Barnes Division of Clinical Pharmacology University of Cape Town K45 Old Main Building Groote Schuur Hospital Observatory 7925, South Africa Tel: +27 21 406 6294 Fax: +27 21 448 1989 Email: karen.barnes@uct.ac.za
Objective of screening	To determine the eligibility of adult volunteers for future clinical trials to be conducted by the MCRG
Eligibility criteria	**Inclusion Criteria** • Written informed consent • Male and female, aged at least 18 years old • Body weight of at least 50 kg and a body mass index (BMI) within the range of 18-32 kg/m^2 • Good peripheral venous access • An ability to communicate well with the research staff, such that they are likely to understand and comply with future trial-specific requirements • Agrees to stay in contact with the MCRG for the foreseeable future, and no current plans to move away from the study area **Exclusion Criteria** • A history of hypersensitivity to any drugs • A history of anaphylaxis or severe allergic reaction • Resting vital signs (measured after 5 minutes in the supine position) outside of the following ranges: oral body temperature between 35.0 and 37.5 °C, systolic blood pressure from 90 to 140 mm Hg, diastolic blood pressure from 50 to 90 mm Hg, pulse rate from 40 to 90 bpm • Orthostatic changes in blood pressure and heart rate measurements greater than: 20 mm Hg drop in systolic blood pressure, 10 mm Hg

	drop in diastolic blood pressure, 20 bpm increase in heart rate [Orthostatic changes will be assessed by comparing supine measurements (after at least 5 minutes in the supine position) to measurements taken 3 minutes after standing up from the supine position] • A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening: PR >210 ms, QRS complex >120 ms, QTcF >450 ms or shortened QTcF less than 340 ms or a family history of long QT syndrome or sudden death, second or third degree atrioventricular block, incomplete, full or intermittent bundle branch block, abnormal T wave morphology, left ventricular hypertrophy with repolarisation abnormalities, right ventricular hypertrophy • A history of malignancy of any organ system (other than localised basal cell carcinoma of the skin), treated or untreated, within the past five years, regardless of whether there is evidence of local recurrence or metastases • Pregnant or lactating women • Fertile males and females, defined as physiologically capable of conceiving offspring, UNLESS agreeing to comply with two highly effective contraceptive methods during any subsequent clinical trial, including a follow-up period of possibly up to 12 weeks (e.g. oral contraceptives, injectable contraceptives, or intra-uterine device) • Use of tobacco products in the previous three months or a urine cotinine level ≥500 ng/ml, if conducted • Haemoglobin below 9.5 g/dl, if known • Clinically significant abnormalities on urine dipstick, if conducted • Recent (within the last three years) and/or recurrent history of autonomic dysfunction (e.g. recurrent episodes of fainting, palpitations, etc.) • Recent (within the last three years) and/or recurrent history of acute or chronic bronchospasm (including asthma and chronic obstructive pulmonary disease, treated or not treated) • A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody test result, if conducted • A history of endocrine disease, in particular, adrenal disorders such as Cushing's syndrome or Addison's disease, or diabetes mellitus (or a clinically abnormal fasting glucose) • A history of any food allergies

	• Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardise the safety of the participant in likely future clinical trials. The investigator should make this determination in consideration of the participant's medical history and/or clinical or laboratory evidence, including any of the following: Inflammatory bowel disease, ulcers, gastrointestinal or rectal bleeding in the last six months; major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection; or pancreatic injury or pancreatitis in the last six months. • Evidence of urinary obstruction or difficulty in voiding at screening • A history of drug or alcohol abuse within the 12 months prior to screening or a positive urine drug screen or breath alcohol result, if conducted • Any clinically significant mental disorder that could limit the validity of informed consent or the participant's ability to comply with a future trial's protocol requirements
Identification and pre-selection	Volunteers will be sourced from those who have been screened for (and/or enrolled in) our clinical trials and the general public. The former group will be asked at the time they finish participation in a clinical trial for consent to be included in the database. The latter group will be targeted through advertising and pre-screened by telephone.
Screening process	For those identified through pre-screening, each applicant will be asked for informed consent to join the database at a screening visit by a suitably qualified and trained member of staff. HIV tests will require separate written informed consent accompanied by adequate pre- and post-test counselling. HIV tests, however, will not be necessary for those who declare themselves to be HIV positive. Screening will involve the following assessments, the results of which are recorded in paper-based participant files. Only if applicants are eligible, will the results of these assessments be entered into the database. Should it be necessary, applicants will be invited back to discuss results of any tests and for referral to an appropriate practitioner: - Demographics, relevant medical and surgical history / current medical conditions, dietary allergies, intolerances and preferences, whether a blood donor. - Physical examination, vital signs, electrocardiogram (ECG), height and weight - Laboratory evaluations (should funds allow):

	- Blood (haemoglobin, fasting glucose, hepatitis B, HIV [not required for those declaring themselves to be HIV positive]); - Urine: semi-quantitative urine dipstick analysis (specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes and blood); urine cotinine; a toxicology screen for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates); pregnancy (women only) - Alcohol breath test Should a repeat value remain outside of the required range for eligibility, the applicant will be excluded from enrolment.
Withdrawal from the database	Volunteers may request to be removed from the database at any time for any reason. The database can also be terminated at any time for any reason by the Principal Investigator. Should this be done, all enrolled volunteers will be contacted to inform them of the decision as soon as possible.
Safety of volunteers	The Principal Investigator has a personal responsibility to closely monitor screened participants and take whatever measures necessary to ensure their safety. He/she also has the authority to terminate, suspend or require changes to the screening for safety concerns and may prohibit enrolment of a participant in the database if he/she has some suspicion that taking part in a subsequent clinical trial may place a volunteer at significant risk. Although enrolled volunteers are not yet part of a clinical trial, there may be some risk to them by being screened for, or included in, the database (e.g. bruising from blood tests). Although all reasonable efforts will be made to ensure confidentiality, there may be inadvertent problems relating to the loss of privacy. The research team managing the database will adhere to the FHS HREC policy: "Unanticipated Problems Involving Risks to Research Participants and Others Including Adverse Events".
Data storage and management	Source paper files will be kept in a secure location only accessible to the research team. Data management will be performed in accordance with regulatory requirements, including the Protection of Personal Information (POPI) Act (when implemented), and HREC requirements. Direct access to source data/documents will be allowed if required for subsequent trial-related monitoring, audits, ethics committee reviews, and regulatory inspections, as is explicit in the informed consent.
Ethical considerations	There will be no payments of R50.00 made to those screened or enrolled. However, those attending a screening will be offered refreshments. Should applicants or enrolled participants be requested to come back to the unit for subsequent visits (e.g. for a repeat laboratory test or counselling), these will also be recompensed at R50.00 per visit to cover transport costs and inconvenience.

	A description of the setup and maintenance of the database may be submitted for publication in due course; no information that could disclose the identity of any volunteer will be included in such a publication.

INTRODUCTION AND RATIONALE FOR THE ADULT VOLUNTEER DATABASE

This protocol describes an adult volunteer database that will be built and maintained by UCT's Malaria Clinical Research Group (MCRG). The decision to develop this database was prompted by the MCRG's experiences in screening participants for previous clinical trials. It was found that, for instance, approximately 400 people had to be pre-screened to screen 69, in order to ultimately enrol 26 healthy volunteers for a recent Phase 1 trial. Each stage of this process was lengthy and labour-intensive, possibly because the local population is not familiar with the concept of healthy volunteer studies and does not necessarily have a good knowledge of their health. For subsequent trials involving adult volunteers, it is critical that the process of screening is more efficient and cost-effective. By starting to build a database before our next trial is approved, our aim is to develop a strong pool of potential participants who can then be invited to trial-specific screening. However, the protocol is not intended to only include *healthy* adult volunteers as the group will likely conduct trials with other participant populations, for example, otherwise-healthy HIV positive participants to study antimalarial and antiretroviral drug interactions.

This database could also potentially be shared with others in the Faculty of Health Sciences (FHS) once sufficient safeguards about data protection are in place. This could ultimately prevent duplication of efforts by different departments as regards advertising, recruitment, and screening of trial participants for what are possibly very similar protocols. Implementation of this standard process could facilitate the cost-effective conduct of clinical trials in the faculty while maintaining good quality processes and protection of the participants involved. However, the group will contact the HREC to discuss the plan should it decide to go this route.

OBJECTIVE OF SCREENING FOR THE ADULT VOLUNTEER DATABASE

The objective of this protocol is to determine the eligibility of adult volunteers for future clinical trials to be conducted by the MCRG.

TARGET POPULATION

The target population for the database is adult, male and female volunteers. Eligibility will be based on the inclusion and exclusion criteria described below.

Inclusion Criteria

1. Written informed consent
2. Male and female, aged at least 18 years old
3. Body weight of at least 50 kg and a body mass index (BMI) within the range of 18-32 kg/m^2
4. Good peripheral venous access
5. An ability to communicate well with the research staff, such that they are likely to understand and comply with future trial-specific requirements
6. Agrees to stay in contact with the MCRG for the foreseeable future, and no current plans to move away from the study area

Exclusion Criteria

1. A history of hypersensitivity to any drugs
2. A history of anaphylaxis or severe allergic reaction
3. Resting vital signs (measured after 5 minutes in the supine position) outside of the following ranges: oral body temperature between 35.0 and 37.5 °C, systolic blood pressure from 90 to 140 mm Hg, diastolic blood pressure from 50 to 90 mm Hg, pulse rate from 40 to 90 bpm
4. Orthostatic changes in blood pressure and heart rate measurements greater than: 20 mm Hg drop in systolic blood pressure, 10 mm Hg drop in diastolic blood pressure, 20 bpm increase in heart rate [Orthostatic changes will be assessed by comparing supine measurements (after at least 5 minutes in the supine position) to measurements taken 3 minutes after standing up from the supine position]
5. A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening: PR >210 ms, QRS complex >120 ms, QTcF >450 ms or shortened QTcF less than 340 ms or a family history of long QT syndrome or sudden death, second or third degree atrioventricular block, incomplete, full or intermittent bundle branch block, abnormal T wave morphology, left ventricular hypertrophy with repolarisation abnormalities, right ventricular hypertrophy
6. A history of malignancy of any organ system (other than localised basal cell carcinoma of the skin), treated or untreated, within the past five years, regardless of whether there is evidence of local recurrence or metastases
7. Pregnant or lactating women
8. Fertile males and females, defined as physiologically capable of conceiving offspring, UNLESS agreeing to comply with two highly effective contraceptive methods during any subsequent clinical trial, including a follow-up period of possibly up to 12 weeks (e.g. oral contraceptives, injectable contraceptives, or intra-uterine device)
9. Use of tobacco products in the previous three months or a urine cotinine level ≥500 ng/ml, if conducted
10. Haemoglobin below 9.5 g/dl, if known (based on the lower limit of grade 1 anaemia in the US National Institute of Allergy and Infectious Diseases toxicity tables, although future studies in HIV-negative healthy volunteers may require higher Hb levels)
11. Clinically significant abnormalities on urine dipstick, if conducted
12. Recent (within the last three years) and/or recurrent history of autonomic dysfunction (e.g. recurrent episodes of fainting, palpitations, etc.)
13. Recent (within the last three years) and/or recurrent history of acute or chronic bronchospasm (including asthma and chronic obstructive pulmonary disease, treated or not treated)
14. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody test result, if conducted

15. A history of endocrine disease, in particular, adrenal disorders such as Cushing's syndrome or Addison's disease, or diabetes mellitus (or a clinically abnormal fasting glucose)
16. A history of any food allergies
17. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardise the safety of the participant in likely future clinical trials. The investigator should make this determination in consideration of the participant's medical history and/or clinical or laboratory evidence, including any of the following:
    - Inflammatory bowel disease, ulcers, gastrointestinal or rectal bleeding in the last six months;
    - Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection; or
    - Pancreatic injury or pancreatitis in the last six months.
18. Evidence of urinary obstruction or difficulty in voiding at screening
19. A history of drug or alcohol abuse within the 12 months prior to screening or a positive urine drug screen, or breath alcohol result, if conducted
20. Any clinically significant mental disorder that could limit the validity of informed consent or the participant's ability to comply with a future trial's protocol requirements

Justification of Inclusion and Exclusion Criteria

The inclusion and exclusion criteria have been selected to minimise risk to the wellbeing of participants in likely future clinical trials while also allowing for various patient populations to be identified.

HOW VOLUNTEERS WILL BE IDENTIFIED

Volunteers for the database will be sourced from those who have been screened for (and/or enrolled in) our clinical trials and from the general public. Those from the former group who have been identified as fulfilling the database eligibility criteria will be asked at the time they finish participation in the clinical trial for consent to be included in the database. Those from the general public will be pre-selected and screened according to the process below:

VOLUNTEER PRE-SELECTION PROCESS

Advertising

Adult volunteers will be recruited from within Cape Town and its surrounding areas. Advertising may be in print (e.g. newspapers, posters, leaflets, and website) and/or radio/television appearances. The text for printed adverts is given in Appendix 1, and the questions and answers presented in the information and consent document (Appendix 2) will be used on the website. Press releases/radio/television appearances will be discussed on an individual basis with the HREC.

Pre-screening

A log of the name and contact details of any applicant will be maintained. A suitably trained member will contact each applicant and complete a brief pre-screening form (Appendix 3). Those who appear suitable for screening will be assigned the next available date/time for a visit to the Clinical Research Centre. He/she will be given directions and briefly advised what to expect in terms of the screening process. He/she will be requested to bring an ID document as this is critical to ensuring that those pre-screened are the same as those subsequently screened, and ultimately enrolled, in the database and any subsequent clinical trial. Those who appear ineligible will be advised as such.

VOLUNTEER SCREENING PROCESS

On the day of screening, each applicant will be asked for informed consent to join the database (Appendix 2). The information will be given in written and verbal forms by a suitably qualified and trained member of staff and will be available in three local languages (English, Xhosa and Afrikaans). The information may be given to many applicants at the same time (e.g. with a PowerPoint presentation) but each applicant will have the opportunity to meet individually with staff to confirm consent. A simple comprehension test will be done by asking the applicant to explain certain parts of the database information as per the HREC's guidelines.

HIV tests will require separate written informed consent accompanied by adequate pre- and post-test counselling (Appendix 4). HIV tests, however, will not be necessary for those who declare themselves to be HIV positive.

After informed consent, the screening visit will continue with the following assessments, the results of which are recorded in paper-based participant files. Only if applicants are eligible, will the results of these assessments be entered in the database. Should it be necessary, applicants will be invited back to discuss results of any tests and for referral to an appropriate practitioner.

Demographics: Date of birth, age, gender and race/predominant ethnicity (recorded for the purposes of potential pharmacogenetic studies and to reflect the demographics of disease burden).

Relevant medical and surgical history / current medical conditions: A detailed medical and surgical history and record of any medication taken for ≥ 4 weeks at any point in the last five years and any medication taken within the past six months. Medication includes over-the-counter, alternative and traditional medicines, as well as nutritional supplements and investigational products.

Diet: Dietary allergies, intolerances, and preferences, including the use of grapefruit and caffeine.

Blood donation: Whether a blood donor and, if so, the date of the last donation.

Physical examination: General appearance, skin, neck (thyroid), ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems. If indicated as a result of the participant's medical history, rectal, external genitalia, breast, and/or pelvic exams may be performed with the applicant's verbal consent.

Vital signs: Body temperature, heart rate and blood pressure assessments. Systolic and diastolic blood pressure will be measured with an appropriately sized cuff, after the applicant has been supine for at least five minutes. Orthostatic changes to blood pressure and heart rate will also be assessed; he/she will be requested to stand after completion of the supine measurements, and blood pressure and heart rate will be recorded after three minutes in the standing position.

Electrocardiogram (ECG): Standard 12-lead ECGs. Participants will rest in a supine position for at least ten minutes prior to the start of recording. Special attention will be given to changes in QT- and QRS-intervals from baseline, T-wave morphology changes and dysrhythmias.

Height and weight: Height in centimetres (cm) and body weight (to the nearest 0.1 kg in indoor clothing, but without shoes).

Laboratory evaluations: Evaluations of limited laboratory parameters will be performed should funds allow. Results that fall outside of the specified eligibility criteria may be repeated once prior to enrolment in the database to exclude a possible laboratory error. Should the repeat value remain outside of the required range for eligibility, the applicant will be excluded from enrolment in the database. Laboratory results that fall outside of the normal reference range but are not considered clinically significant will be reviewed by the Principal Investigator who will confirm whether or not the participant is eligible for inclusion. Laboratory assessments (should funds allow) will include:

- Blood: Haemoglobin, fasting glucose, hepatitis B, HIV (HIV testing is not required for those declaring themselves to be HIV positive). Appropriate pre- and post-test counselling will be part of the separate informed consent for HIV testing and HIV positivity will be confirmed by an ELISA.
- Urine: A semi-quantitative urine dipstick analysis on a midstream urine sample to assess specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes and blood; urine cotinine levels; a toxicology screen for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates); pregnancy (women only).
- Alcohol breath test

VOLUNTEER IDENTIFICATION IN THE DATABASE

During screening, applicants will be allocated a unique sequential screening number S00001, S00002. All eligible volunteers who agree to be enrolled in the database will then be allocated a unique sequential enrolment number. This will be three digits prefixed by the letters 'AVDB' (i.e. AVDB 001, AVDB 002, AVDB 003, etc. in ascending order) and will be the primary identifier to ensure consistency of reporting from the time of enrolment.

WITHDRAWAL FROM OR CLOSURE OF THE DATABASE

Enrolled volunteers may request to be removed from the database at any time for any reason. The database can also be terminated at any time for any reason by the Principal Investigator. Should this be done, all enrolled volunteers will be contacted to inform them of the decision as soon as possible.

ENSURING THE SAFETY OF DATABASE PARTICIPANTS

The Principal Investigator has a personal responsibility to closely monitor screened participants and take whatever measures necessary to ensure their safety. He/she also has the authority to terminate, suspend or require changes to the screening for safety concerns and may prohibit enrolment of a participant in the database if he/she has some suspicion that taking part in a subsequent clinical trial may place a volunteer at significant risk.

Although enrolled volunteers are not yet part of a clinical trial, there may be some risk to them by being screened for, or included in, the database (e.g. in terms of bruising from blood tests). In addition, although all reasonable efforts will be made to ensure confidentiality, there may be inadvertent problems relating to the loss of privacy. Therefore, the research team managing the database will adhere to the FHS HREC policy: "Unanticipated Problems Involving Risks to Research Participants and Others Including Adverse Events".

DATA STORAGE AND DATABASE MANAGEMENT

Source documents (paper files) will be kept in a secure location only accessible to the research team. These will consist of notes containing demographic and medical information, laboratory results, ECG traces, and reports.

The database itself will only include information about volunteers who are enrolled. A designated data manager will review the data entered for completeness, and request the research team make any required corrections or additions. Data management will be performed in accordance with regulatory requirements, including the Protection of Personal Information (POPI) Act (when it is implemented), and the HREC requirements for the "Collection and Storage of Data or Biological Specimens for Research Purposes" and/or "Databases, registries and repositories" (where relevant). The Principal Investigator will, however, provide direct access to source data/documents if required for subsequent trial-related monitoring, audits, ethics committee reviews, and regulatory inspections. This will be made explicit in the informed consent documents.

ETHICAL CONSIDERATIONS

Regulatory and Ethical Compliance

The development of an adult volunteer database will be conducted, where relevant, according to the ethical principles set forth in the Declaration of Helsinki 2008 and 2013, ICH-GCP, South African Good Clinical Practice Guidelines, and other local regulatory requirements (including those relating to data protection as mentioned above).

Compensation

There will be no payments of R50.00 made to those screened or enrolled in the database to cover their travel expenses. However, those attending a screening visit will be offered refreshments. Should applicants or enrolled participants be requested to come back to the unit for subsequent visits, these will be recompensed at R50.00 per visit to cover transport costs. Trial-related screening visits will be recompensed according to each trial's approved rate.

Publications

A description of the setup and maintenance of the database may be submitted for publication in due course; no information that could disclose the identity of any volunteer will be included in such a publication.

RESEARCH TEAM

The Principal Investigator will ensure that the research team is suitably qualified and/or experienced in order to play their role, as detailed in their CV, training records and a delegation of tasks document kept

on file by the MCRG. Screening and database processes will also be described in standard operating procedures in which the team will be trained and there will be periodic oversight of the process by a senior member of the team.

VOLUNTEER INFORMATION LEAFLET & CONSENT FORM

DATE OF FIRST INFORMED CONSENT DISCUSSION: ☐☐/☐☐/☐☐☐☐

(dd/mm/yyyy)

RESEARCH INSTITUTION:

Clinical Research Unit, J51 (J floor) Old Main Building, Groote Schuur Hospital, Observatory, South Africa.
Tel: 021 406 6294/ 4070/ 6996 Fax: 021 650 3726

Database team member conducting informed consent interview: _____

Introduction

You are invited to join our clinical research volunteer database. Before you agree to join, you need to understand why we have a database and what will happen. Please read this leaflet carefully and ask us if anything is not clear or if you need more information. Please don't agree to take part until you are happy that you understand what will happen, and any possible risks (dangers).

Why do we have a volunteer database?

Before a new medicine is allowed to be given to patients, it has to be tested to see if it is safe and works properly, and what the best dose would be. The medicines are tested in clinical research studies. We have a volunteer database, where we type some of your details into a computer so that we can keep records of people who have said that they would like to be part of future clinical research studies.

What are clinical research studies (also called clinical trials)?

These are experiments where we find out about new treatments for various illnesses. Volunteers come into a research centre and take the new treatment for a short time while being closely looked after by doctors and nurses. A number of tests are done in these studies to see how their bodies react to the new treatment.

Do I have to have an illness to take part?

No, not always. In fact, many studies are done with completely healthy volunteers. As they are not ill, the new medicine is not going to treat any illness. Therefore these volunteers will not get any medical help from the medicine. Instead, they help others by helping us develop new medicines. Sometimes we ask people with some illnesses to take a new treatment that is not for their illness but for something else. These volunteers will also not get any medical help from the medicine.

Why would I want to join the volunteer database?

It is because of volunteers that we are able to make new medicines for those who need them. You may not be helped by the medicine if you are not ill. Once the medicine is found to be safe, people with the illness take it to see if it helps them.

What happens if I want to part of the volunteer database?

- To join our volunteer database you need to visit us for 3-4 hours. We will explain what is going to happen and then you will have a physical examination by qualified medical staff. You will also answer questions, including about your health and what medicines you normally take.
- We may then take a blood or urine sample for some tests (to check if is safe for you to consider taking part in future clinical research studies) and, if so, may ask you back for another visit to give you the results or do a repeat test, for which we will give you R50.00 to cover any transport costs. These tests could include checking the level of your blood or sugar and if you are infected with HIV, hepatitis B or C. You will need to sign a separate informed consent form for us if we test you for HIV. You may decline the HIV test, but this will mean you will not be able to participate in some studies. If you already know you are HIV positive, then you do not need to do another test.
- If you are a woman, we may check if you are pregnant as it would not be safe for you or your baby to be in our clinical research studies.
- You may be asked to give a urine sample so that we can make sure you are not using any drugs that can be abused (cocaine, amphetamine, opioids, dagga, benzodiazepines and barbiturates) and will also test for any abnormalities in your urine by dipping a plastic strip into the urine sample.
- We may also do an alcohol breath test and/or a urine test to check if you smoke.
- We will also measure if you have any heart problems by doing an electrocardiogram (ECG). This is done by putting stickers on your chest to which wires will be attached to measure how your heart beats for a minute or two. You will have to remove the clothes from your chest and lie still for a few minutes during the test. It is not painful but may be uncomfortable.
- If you agree to join the database and we think it is safe for you to take part in future clinical research studies, we will keep your details safe in our files.
- If our tests show that you have some problem we will, with your permission, refer you to an appropriate healthcare facility.
- It is very important for us to make sure that it is safe for you to join a study in the future. So we ask that you please tell us everything about your health, medicines and habits (e.g. smoking).
- If you have a regular doctor that you visit, please provide us with his or her contact details. With your permission, we would like to contact him or her to make sure that you do not have any illness that may affect your safety in our future clinical research studies.
- We also need to know that we can contact you if we need to so please keep us informed if you change contact details or decide to move away from Cape Town.

Will my personal details be kept private?

Your records will be seen by some of the research staff, and by authorized persons, such as from the University Ethics Committee, who checks to see that the database is being carried out correctly. If you give permission to be part of the database we will type your records into the computer and they may also be seen by staff from future clinical research studies. However, we will ask for your permission for that at the time of the future study. All those people have to keep your details confidential. Your identity will also not be given in any publication.

What happens if I want to join a research study?

If we have a research study for you in the future, we will ask you to come back ~~in~~ to us for another visit. We will explain what the new study is and what will happen, how long the study will take, how many times you need to come in, if you need to stay overnight in our ward and what tests you will have. You may also have to stop using certain foods and drinks while you are in some studies. We will also tell you what we know about the medicine and what the risks (possible dangers) are for you.

What are the risks (possible dangers) of being in the database or a future research study?

For the database, there may be small problems, such as bruising from the blood tests you may have.

For future research studies, we have to follow strict rules and there are also people who look at our plans and decide whether they are safe enough. Before you join a research study in the future we will explain what we know about the medicine so you can choose whether to take part. The medicine you take in these studies may not help you if you do not have the illness the new medicine is for. There may, however, be some risks because we don't know enough about the medicines yet.

Will I be paid to take part?

You will not be paid to take part in the database. However, you will be offered refreshments and a sum of R50.00 to compensate for travel expenses. Should you be asked to come back to the unit for subsequent visits, you will be paid R50 per visit to cover transport costs.

What if I don't want to be a volunteer?

You can decide not to join our volunteer database or to be taken out of the database or any research study at any time and for any reason. You can also go home and think about joining and talk to others like your family. We can also stop the database if we decide to - if we do this, we will let you know.

What if I have any questions?

If you have any questions or wish to report any problems you have experienced related to the study, please contact the lead investigator, Dr Phumla Sinxadi (phumla.sinxadi@uct.ac.za or at 021 650 4096) or the study principal investigator, Prof Karen Barnes (karen.barnes@uct.ac.za at 021 406 6294). If you have any concerns regarding your rights and welfare as they relate to this study you can contact the University of Cape Town Human Research Ethics Committee Chairperson, Professor Marc Blockman (Room E52-24 Old Main Building, Groote Schuur Hospital, Observatory, 7925, +2721 406 6338).

Signature page

Protocol no: MCRG AVDB01

Protocol title: Building and maintaining an adult volunteer database for future clinical trials

I have received a copy of this information leaflet and consent form about the volunteer database.

The database has been fully explained to me and I have been given the opportunity to ask any questions or discuss joining with others like my family. I know that I am free to leave the database at any time for any reason. I know that my personal records will be looked at by the database staff, and authorized persons who check to see that the database is being carried out correctly. However, my records will not be shown to anyone else without my permission and my name will not appear in any report. I agree to be part of the database. I understand that I have not given permission to be in any clinical research study as this will be discussed with me if a suitable study comes along.

Print volunteer's name: _____	Home address: _____	Work Address: _____
Signature: _____		Date: _____
Print witness's name: (if volunteer gives oral, not signed consent) _____	Signature: _____	Date: _____
Print presenter's name: (who presented/explained the document) _____	Signature: _____	Date: _____
Print Investigator's name: _____	Signature: _____	Date: _____

Appendix 2: Advertisement

HEALTHY VOLUNTEERS NEEDED FOR CLINICAL RESEARCH STUDIES/TRIALS

The University of Cape Town's Clinical Research Centre at Groote Schuur Hospital is looking for volunteers to join an Adult Volunteer Database which helps match potential research volunteers to future clinical studies/trials.

Future studies/trials that are suitable for healthy volunteers may involve you taking a new medicine that has not been taken by people before, or has only been taken by a few people. These medicines are NOT treatments for any illness you may have, so you will not get any medical help from them. Instead, you will be helping others by helping us develop new medicines.

We need adult (18 years or older) men and women to join the Adult Volunteer Database. To qualify you need to be/have:

- NOT pregnant or breast feeding
- NO high blood pressure
- NO heart problems
- NO cancer
- NO stomach or bowel problems
- NO medicine or food allergies

If you are interested in joining our database please complete an [online form] with your contact details and a simple health and medicine questionnaire. We may then contact you in the future to discuss the possibility of taking part in a clinical research study/trial.

Appendix 3: Online pre-screen checklist adapted from existing adult volunteer database protocol.

Your records will be kept in our computer and only be seen by our research staff, and possibly other specially authorised persons, such as from the University Ethics Committee who oversee our work. If there is a clinical study which we feel may be suitable for you we will not share your records with that study team until we have your permission. Your identity will never be given in any publication.

We would like to request your medical health records from the Western Cape Department of Health Data Centre, directly, so that we can compare the information that health providers collect to the information that you provide to us during any subsequent interview. This will help us to understand similarities and differences between various sources of health information, including how patients and healthcare workers understand health issues

University of Cape Town	Pre-screen eligibility checklist	Date :
Name		
Gender		
ID number		
Date of birth or age		
Language(s) spoken (indicate any language you speak/read)		
Home address		
Phone number & Email		
Alternative contact person		
1. General health. Have you ever suffered from?	☐ **High blood pressure** ☐ **Sugar diabetes** ☐ **Asthma** ☐ **Tuberculosis** ☐ **HIV** ☐ **Muscle or joint problems** ☐ **Heart condition** ☐ **Epilepsy (sometimes called seizures or fits)** ☐ **Other medical conditions (link to many fields)** ☐ **None**	
2. Have you had surgical operations before? Yes/No	Describe:	
3. Are you using any medication or treatments at the moment?	Describe	
4. How tall are you in cm if known?		
5. How much do you weigh in kgs if known?		
6. Have you ever tried any recreational drugs? Yes/No	Describe:	
7. Are you smoker? Yes/No	How many cigarettes do you smoke a day?	
8. Do you drink alcohol? Yes/No	How much alcohol do you drink per week?	
9. Have you ever participated in a clinical study/trial before? Yes/No	When did the study end (date)?	
10. When was the last time you went to see a doctor?	Date and why?	

Declaration:

By submitting this form I give permission for the information above to be stored in case of future clinical studies/trials.

I give permission for the database team to request my medical records from the Western Cape Department of Health (to understand similarities and differences between various sources of health information, including how patients and healthcare workers understand health issues [If not selected, will go to a box to record reason]

Appendix 4: In-depth interview

Participant ID:

Facilitator's initials:

Co-facilitator's initials:

Date (dd/mm/yy):

Warm up

Tell me a bit about yourself; where do you live, how long have you lived in this community, do you work?

Part I - Health status and treatments taken prior to the interview

Introductory

How did you come to hear about this database?

What did you understand the advert to be for?

What do you understand about the database? What is it about? Tell me what you think clinical studies/trials are about.

What do you think your role is in this research?

Which clinics do you normally attend? /Do you ever see any other doctors/other healthcare workers?

Wait for full response and take notes of any relevant illness/treatments mentioned

Medical/drug history

How is your health at the moment?

When did you last see a doctor? (Probes: what was that for? What did he/she recommend? Mention clinics, doctors reported above)

Are you taking, or have you taken, any medicines in the past month? (Probes: when did you start? Have you had them before?)

What are you taking these for? (Probes: when did that start? Have you had this before?)

Have you had any times in your life when you were quite ill? (Probes: when was that? What treatment did you have for that? When was the last time you experienced that? What treatment did you receive?)

What other illnesses did you have as a child? (Probes: when was that? What treatment did you have for that?)

And as an adult? (Probes: when was that? What treatment did you have for that?)

Have you taken/used anything [else] for any other reason? For example, anything to prevent ill health / just for general good health/contraception/vitamins, traditional/alternative medicines.

Who do you normally see for your health issues? (Probes: some people [also] speak to their family/friends/a pharmacist /shopkeeper/a sangoma/alternative health practitioner)

When was the last time you spoke to any of these people about your health (go through each)? (Probes: what brought you to see that person? What did they recommend?)

Do you have any medication at home from any past visits to a hospital, general practitioner or day clinic? *Probe if yes*

Do you have a medical record, follow up card or hospital card? *Probe, if yes.*

Part II - Reasons for differences in reporting depending on the method and help in accessing all information (probe all references to health/treatments)

Thank you so much for completing the online questionnaire. So, let's look together at what you said in that (and also what your medical records contain) and what we have discussed today. I'd really like your help finding the best way for us to collect this information.

It does not matter if we find there is a difference between what you said in the questionnaire and (what is in the medical records or) with what we have discussed today – there is no right or wrong and you will not be in any trouble either way.

Browse different data sources together, if discrepancy:

Why do you think we didn't get [information in medical records and/or interview] at the time you completed the questionnaire? (Probes: did we ask the right questions? What are the right questions?

What helps you remember some things better than others?

Were there any things on the questionnaire you weren't sure about?

What makes you feel that you needed to/didn't need to mention x?

For each answer try to probe further e.g. if he/she says something was not important to report ask why, and which things are important to report/which are not)

If no access to electronic records:

If not addressed already: What helps you remember some things better than others?

Were there any questions on the online questionnaire you weren't sure about?

How do you feel about us accessing your medical records from hospitals, clinics, doctors? How should we go about finding those records? (Probes, public, private, pharmacies)

Would we find anything different to what you have mentioned about your health today and in the questions you completed on the computer for us with those records? Why is that?

If we want to get the most information on the health and treatments of people who want to take part in databases like this, how would you suggest we do this? (Probes: diaries, pictures of medicines, who should ask them the questions (doctor, nurse, community health worker, traditional healer), what type of questions)

Can you recommend ideas for us for where we can find other people to consider joining the volunteer database for future clinical trials? (Posters, leaflets – where? Newspapers, online?)

What wording do you think we should use to invite those people?

What do people need to know about clinical trials?

Discuss any misunderstanding about the intention of the database, particularly as regards clinical trials.

Closing

We are now coming to the end of our talk. Is there anything else anyone would like to add about the discussion, your health, treatments and how we can get the most accurate information in our databases?

- *Summarise*
- *Thank participant*

Appendix 5: Informed consent

Study: A mixed method study of the factors influencing the validity of medical and medication histories obtained from potential healthy adult clinical trial participants

Investigator: Dr. Hanan Ltayef

Organization: Division of Clinical Pharmacology-Faculty of Health Sciences Groote Schuur Hospital, University of Cape Town

I would like to ask if you would consider talking to me about the questionnaire you completed recently to join our adult volunteer database for future clinical trials. We will sit down together for about an hour so that we can discuss what you understand about the database, and about your health and use of medicines/treatment. I would also like to do some basic measurements including your weight, height, temperature, blood pressure, heart and breathing rates. If I notice anything concerning about your health I will be happy to help you obtain the required care, though cannot provide this care myself.

As this talk is quite long I need to record what we all say so that I don't forget anything. This recording will be written into a computer so that I can easily compare what you tell me with what other people tell me.

We promise to keep your personal information you completed online, those we got from your medical records, and what you have said to me today, safe. You will only be identified by a code and not by name in any report that is published, though people who might see your personal information includes others involved in this project, and those from the UCT Human Research Ethics Committee (who has approved the plan for our talk and this form). If you have questions about your rights in research, you may call The Chairperson of the ethics committee on tel. 021 406 6626.

It is entirely up to you whether you want to have this discussion or not and you can stop it any time without it affecting your care by the staff here or at any other clinic. We do not feel that you will have any risks in taking part in this talk. The benefits to us are that any important information you tell us could help us build these kinds of databases better. We will cover transport and inconvenience you may have by attending this interview with R75 and will supply drinks and a snack while we talk.

Thank you for taking the time to consider my request. If you would like, please take some time to think about it or discuss it with your family. Do you have any questions for me?

1	I understand the information given to me by Elizabeth Allen and this form	
2	I was given time to ask questions. I had these answered to my liking	
3	I was given time to consider this, and discuss taking part with others	
4	I understand that I can stop at any time being affected	
5	I understand what we discuss may be seen by other staff from this project, the UCT Human Research Ethics Committee but my name will not appear in a report.	
6	I agree freely to take part in the discussion mention above	

		dd	*mm*	*yyyy*
Signature: Participant	Print all initials and surname	Date		
		dd	*mm*	*yyyy*
Signature: Witness	Print all initials and surname	Date		
		dd	*mm*	*yyyy*
Signature: Interviewer	Print all initials and surname	Date		

Version 2.0 7th October 2018

Appendix 6: Ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

05 July 2018

HREC REF: 415/2018

Dr E Allen
Division of Clinical Pharmacology
K47.22
OMB

Dear Dr Allen

PROJECT TITLE: A MIXED METHOD STUDY OF THE FACTORS INFLUENCING THE VALIDITY OF MEDICAL AND MEDICATION HISTORIES OBTAINED FROM POTENTIAL CLINICAL TRIAL PARTICIPANTS-(MPhil Candidate - Dr Hanan Ltayef) Study linked to 007/2014

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 July 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Hanan Ltayef will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

signature removed to avoid exposure online

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HUMAN RESEARCH ETHICS COMMITTEE
10 OCT 2018
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)			
☑ Approved	☑ Type of review: Expedited	☐ Full committee	
This serves as notification that all changes and documentation described below are approved.			
Signature Chairperson of the HREC	signature removed	Date	10/10/2018

Note: All major amendments must include a local **PI Synopsis** justifying the changes for the amendment. Please note that incomplete amendment submissions will not be reviewed.

Comments from the HREC to the Principal Investigator:
Note: The approval of this protocol amendment does not grant annual approval. Please complete the FHS016 / FHS017 form for annual approval at least one month before study expiration.

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	7th October 2018
HREC REF Number	415/2018
Protocol title	A mixed method study of the factors influencing the validity of medical and medication histories obtained from potential healthy adult clinical trial participants
Protocol number (if applicable)	N/A
Principal Investigator	Dr E Allen
Department / Office Internal Mail Address	Division of Clinical Pharmacology, Department of Medicine

1.1 Is this a major or a minor amendment? (see FHS006hlp) Major (tick box) Minor (tick box)	☐ Major	× Minor
1.2 Does this protocol receive US Federal funding?	☐ Yes	× No
1.3 If the amendment is a major amendment and receives US Federal Funding, does the amendment require full committee approval? **Note:** Any protocol amendments for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please email an electronic copy to hrec-enquiries@uct.ac.za)	☐ Yes	☐ No

2. List of Proposed Amendments with Revised Version Numbers and Dates

Please itemise on the page below, all amendments with revised version numbers and dates, which need approval. This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.
Protocol version 2 (7th October 2018)

3. Protocol status (tick ✓)

✓	Open to enrolment
☐	No participants have been enrolled
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only

4. Proposed changes will affect: (tick ✓ all the categories that apply)

	Protocol
✓	Study objectives, design (including investigator's brochure, clinical activities, study length)
☐	Study instruments, questionnaires, interview schedules
☐	Sample size
☐	Recruitment methods
✓	Eligibility criteria (inclusion and exclusion criteria)
☐	Drug/device (composition, amount, schedule, route of administration, combination with other drugs/devices, safety information)
☐	Data collection/ analysis
☐	Principal Investigator. (Please attach revised conflict of interest and PI declaration statements. Refer: sections 7 and 8.4 in the New Protocol Application Form FHS013)
☐	Consent form and information sheet
☐	Recruitment materials (e.g. advertisements)
☐	Administrative (e.g. change in sponsor's name, change in contact information)

☐	Other. Please specify:

4.1 In your opinion, will there be any **increase** in risk, discomfort or inconvenience to participants?	☐ Yes	✓ No
If yes, please provide a detailed justification/explanation:		

4.2 What follow-up action do you propose for participants who are already enrolled in the study?	
☐	Inform current participants as soon as possible
☐	Re-consent current participants with revised consent/assent forms (append)
✓	No action required
☐	Other. Please describe:

5. Detailed description of the change(s)

Please attach, for each amendment, a summary of all changes which clearly indicates:

i. Old wording (e.g. ~~strikethrough~~ text, CHANGED FROM and CHANGED TO)

ii. New wording (e.g. *italicized*, **bold**, tracked)

iii. Detailed rationale/ justification/ explanation for each change

6. Ethics Review Levy – cost including vat

Cost for Major Amendments - R3 659.10

(Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from charges)

For invoicing purposes, please provide:	
Sponsor's name	
Contact person	
Address	
Telephone number	
Email Address	

7. Signature

My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.

Signature of PI	signature removed to avoid exposure online	Date	8th Oct 2018

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)		
☑ Approved	☑ Type of review: Expedited	☐ Full committee
This serves as notification that all changes and documentation described below are approved.		
Signature Chairperson of the HREC	signature removed	Date 22/11/2018

Note: All major amendments must include a local **PI Synopsis** justifying the changes for the amendment. Please note that incomplete amendment submissions will not be reviewed.

Comments from the HREC to the Principal Investigator:
Note: The approval of this protocol amendment does not grant annual approval. Please complete the FHS016 / FHS017 form for annual approval at least one month before study expiration.

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	22nd October 2018
HREC REF Number	415/2018
Protocol title	A mixed method study of the factors influencing the validity of medical and medication histories obtained from potential healthy adult clinical trial participants
Protocol number (if applicable)	N/A
Principal Investigator	Dr E Allen
Department / Office Internal Mail Address	Division of Clinical Pharmacology, Department of Medicine

1.1 Is this a major or a minor amendment? (see FHS006hlp) Major (tick box) Minor (tick box)	☐ Major	× Minor
1.2 Does this protocol receive US Federal funding?	☐ Yes	× No
1.3 If the amendment is a major amendment and receives US Federal Funding, does the amendment require full committee approval? **Note:** Any protocol amendments for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (Please email an electronic copy to hrec-enquiries@uct.ac.za)	☐ Yes	☐ No

2. List of Proposed Amendments with Revised Version Numbers and Dates

Please itemise on the page below, all amendments with revised version numbers and dates, which need approval. This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.
Appendix 3 version 3 (22nd October 2018)

3. Protocol status (tick ✓)

✓	Open to enrolment
☐	No participants have been enrolled
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only

4. Proposed changes will affect: (tick ✓ all the categories that apply)

	Protocol
☐	Study objectives, design (including investigator's brochure, clinical activities, study length)
☐	Study instruments, questionnaires, interview schedules
☐	Sample size
☐	Recruitment methods
☐	Eligibility criteria (inclusion and exclusion criteria)
☐	Drug/device (composition, amount, schedule, route of administration, combination with other drugs/devices, safety information)
☐	Data collection/ analysis
☐	Principal Investigator. (Please attach revised conflict of interest and PI declaration statements. Refer: sections 7 and 8.4 in the New Protocol Application Form FHS013)
☐	Consent form and information sheet
✓	Recruitment materials (e.g. advertisements)
☐	Administrative (e.g. change in sponsor's name, change in contact information)

☐	Other. Please specify:		
4.1 In your opinion, will there be any **increase** in risk, discomfort or inconvenience to participants?		☐ Yes	✓ No
If yes, please provide a detailed justification/explanation:			

4.2 What follow-up action do you propose for participants who are already enrolled in the study?	
☐	Inform current participants as soon as possible
☐	Re-consent current participants with revised consent/assent forms (append)
✓	No action required
☐	Other. Please describe:

5. Detailed description of the change(s)

Please attach, for each amendment, a summary of all changes which clearly indicates:

i. Old wording (e.g. ~~strikethrough~~ text, CHANGED FROM and CHANGED TO)

ii. New wording (e.g. *italicized*, **bold**, tracked)

iii. Detailed rationale/ justification/ explanation for each change

6. Ethics Review Levy – cost including vat

Cost for Major Amendments - R3 659.10

(Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from charges)

For invoicing purposes, please provide:

Sponsor's name	
Contact person	
Address	
Telephone number	
Email Address	

7. Signature

My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.

Signature of PI	signature removed	Date	22 Mar 2018

Appendix Version 3 22Oct2018

New wording

We would like to request your medical health records from the Western Cape Department of Health Data Centre, directly, so that we can compare the information that health providers collect to the information that you provide to us during any subsequent interview. This will help us to understand similarities and differences between various sources of health information, including how patients and healthcare workers understand health issues

New declaration:

I give permission for the database team to request my medical records from the Western Cape Department of Health (to understand similarities and differences between various sources of health information, including how patients and healthcare workers understand health issues [If not selected, will go to a box to record reason]