Ethical challenges in obtaining informed consent for the genomic study of Rheumatic Heart Disease: a qualitative study

A research dissertation in fulfilment for the requirement of the MSc Med in Bioethics at the University of Cape Town, South Africa

BY

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DECLARATION

I, Francis Masiye, hereby declare that the work on which this 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.

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Abbreviations

AIDS	Acquired Immuno-Deficiency Syndrome
ASAP	Awareness, Surveillance, Advocacy and Prevention
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
DNA	Deoxyribo-Nucleic Acid
ECG	Electrocardiogram
ECHO	Echocardiogram
H3A	Human health and heredity in Africa
HGP	Human Genome Project
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IDI	In-depth interviews
GAS	Group A Streptococcus
GCP	Good Clinical Practice
PO	Participant Observation
OPD	Out Patient Department
REMEDY	RhEuMatic hEart Disease RegistrY
RF	Rheumatic Fever
RHD	Rheumatic Heart Disease

RHDGen	Genomics of Rheumatic Heart Disease
RNA	Ribonucleic acid
WHO	World Health Organization
UCT	University of Cape Town

ABSTRACT

INTRODUCTION: Advances in genetic and genomic research have introduced new challenges in obtaining informed consent for research in low and middle-income settings. However, there are only few studies that have explored challenges in obtaining informed consent in genetic and genomic research in Africa and none in South Africa. To start filling this gap, we conducted an empirical study to investigate the efficacy of informed consent procedures for a genomic study on Rheumatic Heart Disease (RHDGen) at the University of Cape Town in South Africa. The main aim of the study was to understand the ethical challenges in obtaining informed consent in the RHDGen study.

METHODS: We used a qualitative study methodology involving in-depth interviews and participant observations. Our research participants were RHDGen cases and controls as well as research staff involved in the recruitment of RHDGen research participants. In total, we conducted 32 in-depth interviews with RHDGen research participants, 2 in-depth interviews with research staff and 57 direct observations of the consent procedures of RHDGen research participants. The in-depth interviews were conducted in English, audio-recorded and transcribed verbatim. All the data were analysed using thematic content analysis. The study was conducted in 3 sites within Cape Town, South Africa, and these sites were the Groote Schuur Hospital in Observatory, the Vanguard Community Health Centre in Bonteheuwel and the Heideveld Community in the Cape Flats.

RESULTS: Most healthy controls joined the RHDGen study in order to be screened for rheumatic heart disease (diagnostic misconception). Some patients thought the RHDGen study was part of routine clinical care (therapeutic misconception). Some research staff felt unsafe and insecure at one of the recruitment sites. A majority of RHD patients joined the RHDGen study in order to help future RHD patients (altruism). Some research participants were scared of giving blood. There was a potential breach of privacy and confidentiality for RHDGen controls recruited in the van. Some RHDGen research participants had trust in clinicians who were part of the RHDGen research team. Some

research participants had difficulty in understanding genetics, genomics, DNA and data sharing. Finally, research nurses had challenges in explaining genetics, genomics, DNA and data sharing to research participants.

CONCLUSION: Ethical challenges that impacted on obtaining informed consent in the RHDGen study are complex. In this study, the challenges included diagnostic and therapeutic misconception, safety and insecurity, altruism, fear of giving blood, potential breach of privacy and confidentiality, trust and difficulty in understanding genetics, genomics, DNA and data sharing.

1 INTRODUCTION

Recently, there has been an increase in genetic and genomic research in the world. Since the launch of the Human Genome Project (HGP) by the National Human Genome Research Institute of the National Institutes of Health and the US Department of Energy in the 1990s, there have been different research studies involving genetics and genomics. Researchers have been conducting both genetic and genomic studies in order to understand the contribution of both genetics and genomics to health and wellbeing. Genetic and genomic research studies raise slightly different ethical issues from biomedical research studies. While genetic research studies focus on certain genes or certain parts of the DNA that cause specific diseases such as Sickle Cell Disease and Huntington's disease, in which case only that part of the DNA that causes the specific disease would be analysed, genomic research studies focus on the whole genome [1]. In other words, genetic research generates information about a specific disease or condition under study by analysing some aspect of the gene that causes the disease while genomic research provides us with genetic information for a multitude of diseases and traits, including finding out about predispositions to developing other conditions that may be completely unrelated to the disease being investigated in the original study.

Of special interest are genomic epidemiological studies that attempt to understand genetic and environmental causes of complex diseases such as rheumatic heart disease, diabetes, cancer, asthma, malaria, HIV/AIDS and tuberculosis [1]. Such studies gather information about interactions of multiple genes across the whole genome, together with environmental factors in order to understand the causes of the complex diseases. They collect clinical, socio-demographic and genomic data of a large number of different populations and their findings could generate knowledge about the biology of conditions under study, including identifying molecular pathways previously unknown to be involved in the disease. Scientists hope that such knowledge could lead to the development of new interventions or therapies to treat or prevent such diseases. Since genomic epidemiological studies require large sample sizes, sometimes researchers use stored biological samples with the corresponding clinical and socio-demographic data in addition to newly collected samples from both cases and controls and other relevant data.

Two major recent consortia in genomic research in Africa have been the Malaria Genomic Epidemiology Network (MalariaGEN) and the Human, Health and Heredity in Africa (H3Africa). The MalariaGEN was a partnership of malaria researchers in over 20 countries in Africa, Asia and Oceania supported by the Grand Challenges in Global Health Initiative [2]. The H3Africa is a consortium of African scientists funded by the Wellcome Trust and the US National Institutes of Health in partnership with the African Society for Human Genetics whose main aim is to foster genomic research expertise on the African continent with the goal of using genomic methods to address health inequities in both communicable and non-communicable diseases in Africa [3]. The main objective of the H3Africa consortium is to enhance the capacity of African researchers to conduct genomic research among African populations. Most H3Africa research grants are awarded directly to African institutions where principal investigators are based and this allows African scientists to develop and direct their independent research agendas in response to health priorities in their countries. The H3Africa consortium also encourages formation of intracontinental collaborations and development of specific infrastructural elements such as Africa-based bio-repositories and a pan-African bioinformatics network (H3ABio-Net). It also includes training programs aimed at retaining African scientists on the continent to help build a sustainable critical mass of African researchers [3]. Currently, there are 21 H3Africa funded projects, each of which involves collaboration in its own right. Under these projects, genomic research studies on conditions such as cardiovascular diseases, rheumatic heart disease and diabetes are being conducted [4].

1.1 A background of the Genomics of Rheumatic Heart Disease Network (RHDGen) Study

The RHDGen Study is one of the genomic research projects funded by the Wellcome Trust under the H3Africa consortium. Rheumatic heart disease (RHD) is a chronic heart condition that is caused by rheumatic fever (RF). RF is caused by a bacterium called Streptococcus pyogenes that make some people have a sore throat. While some people get better from this infection, others develop rheumatic heart disease. However, the infection can be prevented from developing into rheumatic heart disease by taking antibiotics such as penicillin [5, 6 and 7]. Currently, RHD remains the most common

cardiovascular disease in young people under the age of 25 and it manifests itself with heart failure, stroke, infective endocarditis and pregnancy-related complications [8]. Right now, scientists do not understand why some people with the infection develop RHD while others do not develop the disease. Nevertheless, there is a belief that the reason why some people get better and others develop the RHD is to do with “genetics”. Therefore, the RHDGen study aims at understanding the genetics of RHD. The RHDGen study is recruiting 2500 adult patients with echocardiographically-confirmed RHD and it will compare them with 3500 normal people (healthy population-controls) from 8 sub-Saharan African countries in order to identify genetic factors of risk. The eight countries involved in the RHDGen network are Kenya, Mozambique, Namibia, Nigeria, South Africa, Sudan, Uganda and Zambia. This study on ethical challenges in obtaining informed consent in the RHDGen study was nested in the RHDGen study in South Africa specifically in the Western Cape where both RHD cases and controls are being recruited.

2 LITERATURE REVIEW

Ethical issues in both biomedical research and genomic research have received increasing attention. Both biomedical research and genomic research raise a host of ethical challenges, some of which are unique to Africa and its people while others are similar to ethical challenges raised elsewhere in the world [3]. The main focus of the ethical issues raised has been on the ethical implications of carrying out biomedical and genomic research in low socioeconomic settings. However, in all international ethics guidelines, principles and documents such as the Nuremberg Code, the Declaration of Helsinki, the Council for International Organizations of Medical Sciences (CIOMS), the US National Research Act, the Belmont Report, the Code of Federal Regulations (CFR), the World Health Organization (WHO) and the International Conference on Harmonization Guidelines for Good Clinical Practice (ICH-GCP), informed consent is described as paramount for the ethical conduct of research [9, 10, 11, 12, 13 and 14].

The theory of informed consent originates from the ethical principle of autonomy or respect for persons and it is based on the principle that competent individuals are entitled to choose freely whether to participate in research or not [9, 10, 11 and 12]. In fact, the

CIOMS guideline number four defines informed consent as *a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation* [11]. From this definition of informed consent, there are four main elements that are important in a research setting namely, (1) full disclosure of appropriate information about a research study to a potential research participant; (2) adequate understanding or comprehension of the disclosed information by the potential research participant; (3) legal and mental competence or capacity of the potential research participant to make a decision to participate; (4) and voluntary authorization or voluntariness of the potential research participant to join research with written documentation or an acceptable alternative.

In order to obtain genuine informed consent, researchers are required to meet all the four elements stipulated in the above definition. This means any informed consent is said to be genuine if research participation is adequately informed and understood, and it is voluntarily given by a potential research participant who is competent to do so [2]. Obtaining genuine informed consent is considered as both an ethical obligation and a legal requirement for protection of the basic human rights of research participants. For example, the right to informed consent is a legal requirement in South Africa that is enshrined in the constitution and it is also a legal requirement in many countries in the world. The ethical obligation of respecting the autonomy of potential research participants is met by allowing them to make independent or voluntary decisions to participate in research free of coercion or undue influence and allowing them to withdraw from research participation voluntarily at any time without prejudice while the legal requirement is expressed in the signed consent form or document which is a contract between a researcher and a research participant. Of course, satisfaction of the legal requirement does not necessarily guarantee satisfying the ethical obligation and vice versa. This is so because potential research participants can sign informed consent forms without necessarily making autonomous decisions to participate in research or they can decide to participate in research without necessarily signing informed consent forms. Therefore, obtaining genuine informed consent in practice is difficult because even though the legal

requirements of informed consent may be met, the ethical requirements of informed consent may not necessarily have been achieved in practice [15]. Nevertheless, there is general consensus among researchers, scientists and bioethicists that acquiring genuine informed consent from research participants is a prerequisite for the conduct of an ethically sound study [16]. Despite general agreement on the above essential elements of an informed consent, there are many challenges to achieving genuine informed consent in practice [17] in both biomedical research and genomic research. Obtaining genuine informed consent for biomedical research and genomic research is very challenging regardless of whether the research is conducted in Africa or elsewhere in the world.

2.1 Ethical challenges in obtaining informed consent in biomedical research

Empirical research shows that obtaining genuine informed consent in biomedical research is difficult in practice in both developing and developed countries [3]. Based on various studies on informed consent conducted in both developing countries and developed countries which reported similar findings in both settings, Christine Pace and others as well as Amulya Mandava and others have concluded that there is no compelling evidence for claims that informed consent is worse in developing countries than in developed countries [18-19]. However, there are other studies that have reported that the challenges of getting genuine informed consent are greater in settings with low socioeconomic status than those with high socioeconomic status [15, 20, and 21]. There are various studies that have documented that there are many challenges in getting illiterate participants and participants with low socio-economic status to freely and voluntarily join biomedical research [22 – 34]. The conditions of poverty and illiteracy as well as the history of political oppression in low- and middle income countries make it difficult to obtain genuine informed consent from research participants in research practice because they all present numerous challenges to ensuring research participants' understanding and voluntariness as well as the attainment of quality informed consent.

Language is one of the challenges in obtaining genuine informed consent. Language becomes a challenge especially in the disclosure of information to potential research participants and understanding of such information. This is the case because some languages lack certain words for scientific terms and many cultures cannot readily conceptualize pivotal biomedical and scientific concepts. For example, it is very challenging for researchers to explain to potential research participants the concepts of double-blinding, placebo, vaccine and randomization in a research setting [28 - 34]. Some languages lack precise translations for such scientific terminologies [35], and even in cases where researchers are able to translate scientific concepts into indigenous languages, the translations are usually made using universal language. The resulting translation may not be intelligible to prospective research participants who speak a more colloquial version of the language.

Illiteracy among prospective research participants is another challenge in obtaining informed consent. It may affect both the transmission of research information to prospective research participants and its comprehension [35]. Although verbal communication is an alternative to providing information to illiterate research participants, it still poses a challenge between researchers and research participants who come from different ethnic/language groups. As such, illiteracy may result into low levels of understanding among prospective research participants. Related to this challenge is prospective research participants' exposure to research or their scientific literacy. Researchers have difficulty to convey research aims and methods to prospective research participants who have not previously been exposed to scientific and research concepts [15, 36].

A third challenge in the transmission of information to prospective research participants is the power differential or level of trust between researchers and research participants [37]. In cases where researchers also provide health care to their prospective research participants, the research participants may feel obliged to participate in their medical doctors' research because they trust them. They may also feel that they will not be attended to by the doctors if they refuse to participate in their research projects [37]. Various studies have also found that research participants who participate in their doctors'

research projects have problems in understanding the differences between research and routine clinical care and that therapeutic misconception is very common especially among research participants in resource-poor settings [15 – 25]. Prospective research participants might not differentiate research from the routine care they receive from the same medical doctors who are also researchers and they may think that participation in the research projects is part of routine care.

To overcome the above challenges, some researchers have suggested that scientific jargon and concepts can be adapted to local cultural norms, ideas and idioms [24, 34]. There have been suggestions that local analogies can be used to explain scientific concepts such as placebo and randomization. Researchers have also suggested the use of videos and pictures to explain scientific concepts to prospective research participants during the consent process [15, 34]. Others have proposed a variety of comprehension tests at the end of the consent process to verify research participants' understanding. These can either be self-reported or administered by research staff [38 – 39]. These suggestions have been tried and tested in different research settings but they have proven not to be successful. Other researchers have suggested that community engagement activities should be conducted before implementation of research projects in order to enhance prospective research participants' understanding and deal with any misconceptions prospective research participants might have about research before they are requested to participate in research projects [22, 27 - 28]. Readability tests using Flesh-Kincaid readability scales have also been suggested as a solution to dealing with consent forms that could not have been read and understood by prospective research participants with low literacy levels [40].

2.2 Ethical challenges in obtaining informed consent in genetic and genomic research

The above challenges in obtaining genuine informed consent in biomedical research also exist in genetic and genomic research. Specific ethical challenges in informed consent that have been identified in genetic and genomic research include the difficulty in explaining scientific methods and concepts such as "gene", "genetics", "genomics",

“DNA”, “genetic database” and “data release” in local language during the consent process; the conduct of research in emergency situations which make standard consent processes impracticable especially where patients or their guardians are under stress; therapeutic misconception among research participants who are recruited in clinical settings and who have the widespread conception that research studies result in clinical benefit; and the trust that research participants have in medical doctors who are also researchers [1 - 2 40 - 44]. These ethical challenges are compounded by illiteracy, poverty, socio-cultural barriers and ineffective regulatory mechanisms in developing countries [45].

In addition, advances in genetic and genomic research have introduced new challenges in obtaining informed consent in research practice [46]. These include (1) granting broad or blanket consent for use of samples and data in future research the uses of which are not usually known at the time of giving consent [1,41 - 42]; (2) the difficulty in explaining data and sample sharing with researchers who were not part of the original study in which samples and data were collected; (3) the challenge of protecting the privacy and confidentiality of groups (i.e. families, communities or tribes); (4) the challenge of returning incidental or unrelated findings that were not part of the original research project to research participants [47 -49]; and (5) the difficulty in explaining risks not only to individual genomic research participants but also to their families, communities and even tribes in cases where members share the same genetic mutation associated with increased risk of stigmatization [1 – 2, 41 - 44]. In contrast to the above challenges, Marshall et al and Rotimi et al have found that patients with the genetic disease under study have a higher level of comprehension of the information disclosed during the consent process than healthy people in the control group due to their interaction with the health system because of their disease [43, 50].

Researchers and scientists have tried to suggest solutions to overcoming the above ethical challenges in obtaining informed consent in both genetic and genomic research. For instance, Aceme Nyika observes that prospective research participants do not necessarily have to understand the scientific jargon and concepts used in genetic and genomic research in order to comprehend the potential risks and benefits associated with

it [1]. He suggests that researchers have to be creative enough to explain the scientific jargon and concepts without necessarily explaining in detail the structures of genes and genomes and their processes. De Vries et al and Tekola et al acknowledge that these concepts can be linked to local knowledge of genetics, for example, that particular phenotypic traits are often inherited within families and communities [2, 44]. Other researchers have also suggested that communities involved in genetic and genomic research should be consulted and consented as part of community engagement before implementing any genetic and genomic research studies in their communities in order to address potential risks to such groups and protect their privacy and confidentiality [1, 41].

In order to deal with the challenge of obtaining informed consent in emergency situations, Tindana et al suggest that researchers should observe conditions of prospective research participants and the emotional states of their guardians to ascertain an appropriate time to initiate the consent process [41]. In addressing the issue of sample sharing and data sharing among different researchers, it has been suggested that a governed approach to sample and data sharing should be developed prior to the implementation of genetic and genomic research [52] and the informed consent document should have options for withdrawal from research and data sharing plans [47]. There is also a suggestion that research staff who seek consent should be provided with additional specialized training so that they are able to explain in lay language the scientific concepts and methods used in such complex studies [1, 41 – 44, 50]. Some have suggested that the information sheets should contain a variety of different elements to ensure that research participants easily understand the disclosed information [47]. They say such elements should include a brief description of the research project, the goals of the research, the potential risks and benefits of participation, feedback of results and incidental findings and options for withdrawal from research as well as plans for data sharing.

On the contrary, Chokshi et al have observed that it is difficult to create useful analogies in lay language for scientific methods and concepts to be used during the consent process in genetic research [42]. They argue that although several guidelines suggest that unfamiliar concepts should be explained using analogies during the consent process, there is no practical guidance for creating useful analogies for such unfamiliar concepts

as “gene”, “DNA”, or “genetic database”. Tindana et al have also observed similar challenges in explaining genomics in local language and in extrapolating knowledge of heredity to explain genomics where such research involves population level sampling that does not necessarily involve families affected by the genetic disease under study [41]. Community engagement activities have also shown little evidence of being successful in ensuring group confidentiality and in minimizing group risks in genetic and genomic research [43]. De Vries et al have also observed that ensuring that prospective research participants give informed consent for genomic studies still remains a significant challenge [2]. Although this work had started to highlight some of the complexities around seeking informed consent for genomics research, further empirical work was needed to understand a) how these challenges play out in different research contexts and populations and b) how they can be resolved. In fact, there are quite a few studies that have informed this discussion on ethical challenges in obtaining informed consent in genetic and genomic research and most of the studies reported in literature were theoretical [1 -3, 42 – 43, 46 – 49,53] while only four studies provide empirical data [41, 44, 50 - 51]. Interestingly, there was virtually no empirical work that had been done in South Africa on local genomic research.

2.3 Problem statement and justification

Few studies have explored challenges in obtaining informed consent in genetic and genomic research in Africa, and the majority of these were theoretical not empirical. Such work cannot merely be extrapolated to the South African research context. Interestingly, there is virtually no work that has been done in South Africa on ethical challenges in obtaining informed consent for genomic research in particular. Therefore, to start filling this gap, we conducted an empirical study to investigate the efficacy of the informed consent procedures for a genomic study on Rheumatic Heart Disease that is currently being conducted in the Department of Medicine (FHS 466/2008) at the University of Cape Town.

2.4 AIM AND OBJECTIVES

2.4.1 AIM

The main aim of the study was to understand ethical challenges in obtaining informed consent in the RHDGen study.

2.4.2 OBJECTIVES

The specific objectives of the study were:

1. To explore the ethical challenges in obtaining informed consent from prospective research participants in the RHDGen study.
2. To explore what research participants understood during the consent process.
3. To identify factors that could compromise voluntary decision-making for potential research participants in the RHDGen study.

3 METHODOLOGY

3.1 INTRODUCTION

In the previous chapter, I identified a number of important obstacles to obtaining genuine informed consent, and I observed that only a very limited number of studies on informed consent were conducted in the South African context, none of which examined participant comprehension in genomic research. In this project, I examined research participants' understandings of the informed consent process for the RHDGen project. This chapter describes the research design, the location of research and the methods that were employed during data collection, data processing, data management and data analysis. It also explains the sampling strategies for the study participants, their demographic characteristics, methodological challenges, study limitations and ethical considerations that were encountered in this study.

3.2 RESEARCH DESIGN

The study used a cross-sectional study design to collect data from research participants. This design was appropriate for the study because data was collected from research participants at one point in time thereby allowing the acquisition of data in an open, flexible and inductive manner [54]. Since the main research question was to understand ethical challenges in obtaining informed consent in genomic research, the study was exploratory and descriptive in nature.

3.3 LOCATION OF THE RHDGEN PROJECT

The study participants were enrolled as cases and as controls in the RHDGen, a genomic research project on rheumatic heart disease. The RHDGen research project is recruiting both patients who have rheumatic heart disease and healthy people. Researchers in the RHDGen project are aiming to identify genetic factors of risk in patients who have rheumatic heart disease by comparing them with the genetic material and antibodies of people who do not have the disease. This will help them in designing an effective vaccine to prevent the development of rheumatic heart disease in people who are at risk of

developing the disease. As stated in section 1.1 above, the RHDGen research project is being conducted in 8 sub-Saharan African countries. The eight countries were chosen on the basis of having laboratory facilities for processing of DNA samples and throat swabs, and regulatory provision for export of biological materials for study in another country. These countries have already recruited 1087 unrelated probands with rheumatic heart disease as part of the REMEDY study. The recruitment of South African RHDGen cases and controls happened at four sites within the City of Cape Town in South Africa.

3.3.1 RHDGen recruitment at Groote Schuur Hospital

Groote Schuur Hospital is one of the largest tertiary hospitals of the Western Cape Province and it is a teaching hospital for the Faculty of Health Sciences of the University of Cape Town. The patient community served by this hospital comprises people from all racial backgrounds in South Africa, although the majority of patients are black and mixed ancestry South Africans from the Western Cape Province and largely from Cape Town. The RHDGen research project is recruiting both patients who were enrolled in a prior study, the Global Rheumatic Heart Disease Registry (REMEDY) study and new patients with rheumatic heart disease from the Cardiac Clinic at the Groote Schuur Hospital. Former REMEDY patients are identified through hospital records at the Cardiac Clinic by the research staff who are part of the RHDGen research project and work in the Cardiac Clinic as well. The new patients with rheumatic heart disease are identified by both the research nurse and study doctor who are part of the RHDGen research project and work in the Cardiac Clinic. Both the former REMEDY patients and new patients are approached to take part in the RHDGen research project as cases. The patients who are eligible and show interest to participate in the RHDGen research project are either recruited into the RHDGen research project on the same day they are approached or are booked for recruitment on specific dates at the Clinical Research Centre (J52) of the Old Main Building of the Groote Schuur Hospital. This study on ethical challenges in obtaining informed consent in the RHDGen research project targeted both former REMEDY patients and new patients that were recruited into the RHDGen research project. Participant observations (POs) were conducted during the consenting of the patients for

participation into the RHDGen research project and in-depth interviews (IDIs) were done with some of the patients.

Some controls for the RHDGen research project were recruited at the Clinical Research Centre located in the Old Main Building of the Groote Schuur Hospital. All study procedures for controls such as the consent process, recruitment and study specific procedures at the Groote Schuur Hospital were done in the Clinical Research Centre. The controls for the RHDGen research project came to the Clinical Research Centre in response to advertisements about the study which were posted around the Groote Schuur Hospital. The adverts contained introductory information about the study, the purpose of the study and the eligibility criteria for the study. Potential controls who read the adverts and were interested to participate in the study were invited to come to the Clinical Research Centre (J52) of the Old Main Building of the Groote Schuur Hospital for recruitment. When the potential controls arrived at the Clinical Research Centre, they were taken through the consenting process after their obtaining their consent, the research nurse collected their blood samples in one room.

Demographic information such as age, ethnicity, mother tongue, area of origin, height, weight and blood pressure as well as completion of the case report forms (CRFs) were done by the field officer in the second room. After that, study participants went to the third room where the echo-cardiologist or study doctor performed echocardiograms (ECHOs). When they were done with study related procedures, study participants left the Clinical Research Centre. Some controls recruited at the Clinical Research Centre who were not based at the Groote Schuur Hospital or the Faculty of Health Sciences were given transport refunds to their homes.

3.3.2 RHDGen recruitment at Vanguard Community Health Centre

The Vanguard Community Health Centre is a primary healthcare facility located in Bonteheuwel and serves mostly Xhosa speaking South Africans from the Langa area in Cape Town. Some controls for the RHDGen research project were recruited at the Vanguard Community Health Centre. The consent process, recruitment and study procedures for controls at the Vanguard Community Health Centre were done in a bus

which was previously being used as a mobile van for the Awareness, Surveillance, Advocacy and Prevention (ASAP) program for kids' heart health by the Department of Medicine at the University of Cape Town. The bus/van is divided into three compartments. For the RHDGen research project, the first compartment was used for consenting potential study participants, taking blood samples, weight, height, age, ethnicity, area of origin and mother tongue. The first compartment was also used as a waiting area for study participants before they went to the second compartment. In some cases, it was also used as a waiting area for potential study participants who were yet to be consented and recruited into the RHDGen research project. The second and third compartments were used for performing echocardiograms and electrocardiograms respectively.

Recruitment at the Vanguard Community Health Centre started with a talk which was given by the field officer for the RHDGen research project to patients who were waiting to consult clinicians at the Out Patient Department (OPD) waiting area of the Health Centre. The talk centred on the introduction, purpose, study procedures and the eligibility criteria for controls of the RHDGen research project. At the end of the talk, patients were given a chance to ask questions about the study. Patients were also asked to read an information leaflet about the study which was posted on the notice board of the Health Centre for detailed information. Finally, potential study participants who met the eligibility criteria and were interested to participate in the study were invited to come to the bus for consenting and study related procedures.

3.3.3 RHDGEN recruitment at Heideveld Community

The Heideveld Community is a community of coloured (mixed ancestry) South Africans in Cape Town. Potential study participants for the RHDGen research project at the Heideveld community were identified by a community leader. The community leader together with his assistants wrote down names of potential study participants they identified. The potential study participants were asked to come to the bus, which was normally parked at one of the flats of the community, at a time convenient to them. When the potential study participants arrived, they were given information about the RHDGen research project by either a nurse or the field officer. The nurse or field officer introduced the RHDGen research project to them, explained the study related procedures and

eligibility criteria. The potential study participants were also handed the information leaflets for the study to read and they were asked to consult any of the study staff if they had any questions about the study. Those who expressed willingness to participate in the study entered the first compartment for consenting and other study related activities. They continued with the study related procedures in the second and third compartments in the same way as described earlier. When they were done with the RHDGen study-related procedures, the study participants were given refreshments such snacks and juices.

3.4 RESEARCH PARTICIPANTS

Many genetic and genomic research projects recruit both cases and controls. The rationale for recruiting both cases and healthy controls is to compare samples from patients who have the disease under study with samples from people who do not have the disease. Researchers study the genetic material (DNA and RNA) and antibodies of both groups in order to establish the genetic difference or mutations between the two groups that make some people develop the disease and the other people healthy. This difference in genetic make-up enables researchers or scientists to come up with interventions to mitigate the development of the disease in people who have the genetic mutations and might develop the disease. This is why the RHDGen research project recruits both cases and controls. The current study targeted both RHDGen cases and controls.

3.4.1 RHDGen cases

The RHDGen cases are both REMEDY patients and new patients with rheumatic heart disease recruited from the Cardiac Clinic at the Groote Schuur Hospital. This study has conducted observations of the consent process of the RHDGen cases and in-depth interviews with some of the study participants.

3.4.2 RHDGen controls

As described in section 3.3, controls for the RHDGen research project were recruited at the Vanguard Community Health Centre in Bonteheuwel, the Heideveld Community in the Cape Flats and the Clinical Research Centre of the Groote Schuur Hospital. All the

controls for the RHDGen research project were people who did not suffer from any chronic diseases and did not have any heart problem during the time of recruitment. In this study on informed consent, we conducted observations of the consent process and in-depth interviews with RHDGen study participants across all these RHDGen recruitment sites.

3.4.3 RHDGen staff as key informants

This study also recruited RHDGen staff who were involved in obtaining consent and recruiting both RHDGen cases and controls. The RHDGen staff were recruited and interviewed at the Clinical Research Centre.

3.5 DATA COLLECTION METHODS

A combination of two qualitative research methods – in-depth interviews (IDIs) and participant observations (POs) were employed in the study. An in-depth interview is a dialogue or a conversation between an interviewee and an interviewer in which there are several selected themes of interest based on a pre-determined question guide [55]. During the interview, the interviewer does not need to ask questions in a particular way and the interviewee (respondent) can answer in any way she/he likes and he/she can be probed when it is needed. In a participant observation, the observed are less involved and the observer has the freedom to direct his or her attention in the direction which seems most appropriate [55]. In qualitative studies, observational data is as important as interview data; in fact, the two types of data are closely linked, as qualitative researchers might use interviews to make sense of what they observe, and observation to interpret their interview data [56]. Qualitative researchers also use participant observation as a data collection method when it complements other forms of data collection methods [56].

The qualitative study approach employed in this study allowed the student to derive in-depth information from study participants [57].

3.5.1 IN-DEPTH INTERVIEWS (IDIs)

As described earlier, this study recruited RHDGen cases and controls as well as RHDGen staff involved in the consent process and recruitment of RHDGen cases and controls. Before conducting each IDI, individual written informed consent was obtained from each

of the respondents and a demographic data form was administered to document respondents' age, sex, highest education achieved, occupation, religion, first language, the location where the respondent was living, the type of respondent and the time since the study participant was recruited into the RHDGen research project. These demographic data were important for the student during the analysis process of the interviews because they allowed the student to compare the responses from the different study participants based on their demographic information. The student and a Research Assistant conducted the IDIs with RHDGen controls that were enrolled at the Clinical Research Centre in the Old Main Building of the Groote Schuur Hospital. One of them moderated the interviews while the other took notes, recorded observations and assisted in probing the respondents. Semi-structured interview guides were used in a flexible way to guide the interviews with cases and controls recruited into the RHDGen research project and research staff in order to get in-depth knowledge and experience on the consent process. The interview guides had sets of pre-determined and open-ended questions and the questions were formulated using the study objectives and they were being revised as the data collection progressed. The semi-structured interview guides allowed the student to control the line of questioning, which was especially useful for a qualitative study, and to follow-up on aspects that emerged during the course of the interviews [58].

The IDIs with cases in the Cardiac Clinic of the Groote Schuur Hospital and with controls at the Vanguard Community Health Centre and the Heideveld Community as well as with research staff were conducted by the student. The IDIs were conducted in English and consent was obtained for recordings. The audio-recordings were later transcribed verbatim by the student. Notes were taken and observations were recorded at each interview. All interviews were conducted on the day of enrolment in the RHDGen study.

IN-DEPTH INTERVIEWS WITH RHDGEN CASES AND CONTROLS

Both male and female cases and controls recruited into the RHDGen research project were included in this study. For the RHDGen cases, the IDIs were conducted in the recruitment room located in the Cardiac Clinic of the Groote Schuur Hospital. Twelve (12) IDIs were conducted there with RHDGen cases. For RHDGen controls, IDIs were

conducted either in the front seat of the van which was used for recruitment at the Vanguard Community Health Centre and the Heideveld Community or in the meeting room of the Clinical Research Centre in the Old Main Building of the Groote Schuur Hospital. Twenty (20) IDIs were conducted with RHDGen controls at the Vanguard Community Health Centre (9), Heideveld Community (5) and the Clinical Research Centre in the Old Main Building of the Groote Schuur Hospital (6). In total, 34 IDIs were conducted with RHDGen cases and controls.

IN-DEPTH INTERVIEWS WITH RESEARCH STAFF

The study also targeted research nurses who were responsible for consenting potential RHDGen cases and controls. The research nurses were scheduled for IDIs at the time of their convenience. Two (2) IDIs were conducted with research nurses involved in the consenting and recruitment of RHDGen cases and controls. Both IDIs with research nurses were conducted by the student.

In total, 91 study participants were recruited into the study. Thirty-four (34) respondents took part in the in-depth interviews while 57 participants took part in the observations.

Most of the IDI respondents were female (see table 2 below). This could be attributed to the fact that more women attended the health care facilities than men during the period of data collection. Most of the respondents were within the age range of 18 to 40 and had completed secondary school education. Two-thirds of the respondents were employed and the majority was of the Christian faith. There was an almost equal division between Xhosa and Afrikaans as first language. Those that indicated Afrikaans as first language generally also spoke good English. The study targeted both Xhosa and Afrikaans speakers who could also speak English. Non-English speakers were not included in the study.

Below is a table showing the in-depth interviews conducted with the RHDGen research participants in each site.

Table 1: LIST OF ALL IN-DEPTH INTERVIEWS BY SITE

CASES – GSH (N=12)	CONTROLS – GSH/CRC (N=6)	RESEARCH STAFF GSH/CRC (N=2)	CONTROLS VANGUARD HC (N=9)	CONTROLS HEIDEVELD (5)
CWR 14	COC 05	RS_1	COV 01	COH 26
CWR 15	COC 06	RS_2	COV 02	COH 27
CWR 16	COC 07		COV 03	COH 30
CWR 17	COC 08		COV 04	COH 31
CWNR 18	COC 20		COV 09	COH 32
CWR 19	COC 21		COV 10	
CWR 22			COV 11	
CWNR 23			COV 12	
CWR 24			COV 13	
CWR 25				
CWR 28				
CWR 29				

KEY

COC = Control recruited at the Clinical Research Centre

COH = Control recruited at the Heideveld Community

COV = Control recruited at the Vanguard Community Health Centre (Bonteheuwel)

CWR = Remedy patient (Case) recruited in the Ward at the Groote Schuur Hospital (E17) or at the Clinical Research Centre

CWNR = Non-Remedy patient (Case) recruited in the Ward at the Groote Schuur Hospital (E17) or at the Clinical Research Centre

3.5.2 PARTICIPANT OBSERVATIONS (POs)

In addition to in-depth interviews, we also conducted a large number of participant observations for this project. All POs were conducted by the student. For the POs, the research nurse administering the consent process introduced the student orally before commencing the RHDGen consent process. The student then sought verbal consent from each potential research participant for his presence during the consenting process. All participants in the POs were given an information leaflet to inform them about the study. During the observations, the student took notes which were typed up immediately after the observations. The information obtained in the POs informed the topic guides for IDIs with both RHDGen research participants and research staff. Some of the POs were succeeded by IDIs with both RHDGen cases and controls.

The POs with RHDGen research participants were conducted at the same venues where they were recruited into the RHDGen research project while the IDIs with research staff were conducted at the Clinical Research Centre in the Old Main Building of the Groote Schuur Hospital.

Data were collected from RHDGen research participants and research staff for a period of 5 months from July to November 2014.

PARTICIPANT OBSERVATIONS WITH RHDGEN CASES AND CONTROLS

The student observed 14 consent procedures of RHDGen cases in the Cardiac Clinic at the Groote Schuur Hospital and 43 consent procedures of RHDGen controls at the Vanguard Community Health Centre (21), Heideveld Community (18) and the Clinical Research Centre in the Old Main Building of the Groote Schuur Hospital (4) (see Table 2

below). In total, 57 POs were conducted during the consent procedures and recruitment of both RHDGen cases and controls by the student. The POs were conducted at the venues where informed consent from the RHDGen cases and controls was obtained. The results of this part of the study are reported in the subsequent Chapters of the thesis.

Table 2: OVERVIEW OF RESEARCH PARTICIPANTS RECRUITED

DATA COLLECTION METHODS	**GROOTE SCHUUR HOSPITAL**			**VANGUARD HC** *(CONTROLS)*	**HEIDEVELD COMMUNITY** *(CONTROLS)*	**TOTAL**
	CASES	*CONTROLS*	*STAFF*			
Observations	14	4	NA	21	18	**57**
In-Depth Interviews	12	6	2	9	5	**34**
TOTAL						**91**

Table 3: DEMOGRAPHIC CHARACTERISTICS OF STUDY PARTICIPANTS

DEMOGRAPHIC CHARACTERISTICS	IDI RESPONDENTS (N= 34)
Sex	
Male	10
Female	24
Age	
18 – 40	21

41 - 60	13
First Language	
Xhosa	17
Afrikaans	14
English	3
Occupation	
Employed	23
Not employed	11
Religion	
Christian	26
Moslem	6
Non-religious	2
Highest Education Achieved	
Primary	2
Secondary	24
Tertiary	8

3.6 DATA PROCESSING AND MANAGEMENT

All interviews were conducted in English. The duration of the shortest in-depth interview was 25 minutes while the longest interview lasted 45 minutes. The shortest participant observation took 15 minutes while the longest lasted 30 minutes. The majority of interviews (n=28) were transcribed verbatim by the student. A small number of interviews (n= 6) were not transcribed. These interviews were either very short or did not add insight into the topic of study – for instance, because the respondent only answered 'yes', 'no' or 'I don't know' and some of the respondents seemed not to be interested in answering the questions that were being asked. To ensure that no valuable information was lost, the student listened to all the audio-recordings that were not transcribed when all other interviews were coded hierarchically and took note of any additional important content.

Each transcript had a preamble or summary of the interview followed by a verbatim transcription of the audio-recording with two key letters, I and R to stand for interviewer and respondent respectively. The summary of each interview was informed by the notes that were taken during the interviews. All transcripts were imported into NVivo 10 for analysis.

The student took notes during the POs and typed up the notes immediately after each PO. The written notes from the POs were read thoroughly by the student in order to understand the dynamics in the recruitment and consenting process of the RHDGen participants.

3.7 ANALYSIS OF INTERVIEW DATA

Thematic content analysis was used to analyse interview data. The analysis was iterative and preliminary analysis started when the initial interviews were transcribed. The analysis was inductive. The inductive process involved the following steps:

●Thorough reading of transcripts for familiarization with the data: the student read 10 transcripts from the IDIs as well as field-notes in order to understand what was coming out of the interviews. Issues that emerged and needed elucidation were probed in subsequent interviews.

●Transcripts were imported into NVIVO software and free-coded. The free codes were recorded in the student's codebook. Free codes were discussed with the supervisor, who also read a number of interviews together with the free codes. Based on these discussions and insights from the first round of coding, a coding framework was developed. The coding framework was applied to the transcripts by grouping together similar responses, a process described by Creswell as taking apart texts or qualitative information and looking for categories, themes or dimensions of information [59]. The quotes for each code were reviewed and any excerpts that were not categorized with the coding framework were given a new code. In case of doubt or un-clarity, the codes and their quotes were discussed with the supervisor.

●Searching themes from the initial codes: the free (initial) codes were read again and grouped into hierarchical coding scheme. The higher codes were grouped into main themes with the lower nodes as their sub-themes. The transcripts were re-coded using this new hierarchical coding scheme. Memos were written for each hierarchical code. The quotes for each theme were reviewed and discussed with supervisor.

●Production of data summaries and charting: data summaries were produced from the texts. The data summaries comprised main themes and their sub-themes as well as their quotes as examples from the texts. The data summaries were discussed with the supervisor and from the discussions, a charting framework was developed with linkages to the data. The charts were produced for each main theme and sub-theme. The charts were also compared across all themes. Each chart was given a descriptive account of each theme and had relevant quotes from the study participants.

●Writing of empirical chapters: the charts were used to develop a first account of the empirical data, which was discussed with the supervisor. Subsequent drafts re-examined the data and the charts, and integrated emerging insights into the analysis.

3.8 METHODOLOGICAL CHALLENGES AND STUDY LIMITATIONS

One limitation of the study was the dual role played by the research student. The student was both a member of the RHDGen project team and an ethics researcher on the project. As a team member, he was sometimes asked to assist the research staff in completing

some of the study related procedures for potential research participants such as recording weight and height, explaining the study to potential study participants and completing the enrolment logs for controls. As such, study participants thought that the IDIs and POs were part of the RHDGen research project procedures and this might have affected the way they responded to the questions in the IDIs. They might have also felt obliged to respond to the questions in the interviews although they had to give a separate consent for participating in the interviews. Related to this limitation is the challenge of the research student as an embedded ethicist. The research student assisted the field officer and research nurses in completing some study related procedures for research participants whilst at the same time he was also actively observing how the consent process was being conducted by the other research staff in order to take note of ethical challenges in obtaining consent from the potential research participants. In cases where the research student observed that the consenting process was not properly done or that they were some challenges in obtaining informed consent, he initially sought to discuss these with the research staff to improve practice. However, it became clear that the research student's intervention caused some resentment among some research staff and there was a risk that they would henceforth resist having the research student present during the recruitment process. This was partly resolved by an intervention by one of the project supervisors who intervened by talking to the research staff to explain the purpose of the study and to assure them that the research student was not there to spy on them. From that moment on, the student recorded challenges or shortfalls in the consent process, but did not intervene or comment on the quality of the consent process to the study staff. However, balancing this tension between on the one hand knowing, from literature and experience, how the consent process ought to be conducted, and on the other hand observing imperfect processes remained a challenge throughout this project. In the results section of the thesis, I will give an account of the challenges encountered by research staff in patient recruitment.

A second limitation was that we did not recruit people who refused to participate in the RHDGen research project to understand why they refused to participate. This was outside of the scope of this study since our aim was not to understand why some people refused to participate in the RHDGen research project.

A third important limitation is that interviews were conducted in English. Some of the study participants who had said that they could speak English were in fact not very fluent in English, and for others speaking in a second language may have complicated explaining issues relating to genomics. This was mostly a problem among Xhosa speakers that were recruited at the Vanguard Community Health Centre.

3.9 ETHICAL CONSIDERATIONS

Ethics approval was obtained from the Human Subjects Research Review Committee in the Faculty of Health Sciences at the University of Cape Town. Written individual consent was obtained from each of the study participants prior to their participation in the IDIs while verbal consent was obtained from all the participants who participated in the participant observations. Verbal consent was obtained from the potential research participants to have the consent process observed because the student did not interact with the study participants during the consent process other than observing the consent process. However, individual written informed consent was sought from each of the research nurses administering the consent procedures once before the first participant observation was conducted. All the participants in the study were given codes to ensure privacy and confidentiality and the data collected were kept in the student's office and computer located at the Clinical Research Centre in the Old Main Building of the Groote Schuur Hospital.

One of the ethical concerns in this study was that two RHDGen controls recruited from the Heideveld Community refused to put their signatures on the consent documents despite the fact that they were literate and they had given their consent to participate in the study. Instead the student urged the study participants to thumb-print the consent document but they also refused. When the student asked the study participants why they did not want to put their signatures on the consent documents, they explained that they wanted to stick to what the student had told them about confidentiality and the fact that they did not want to have their names written on the consent documents. As such, the student documented in the consent form that the participants had consented to taking part in the study but that they refused to sign the consent form.

Another challenge was that some RHDGen cases in the Cardiac Clinic at the Groote Schuur Hospital and controls at the Vanguard Community Health Centre were in a hurry and they did not want to spend much time during the consent process and the IDIs. Such study participants wanted to sign the consent document immediately after being introduced into the study since they felt that they had already heard about the study and that the consent process and interview might take much of their time as they were on queues waiting to see doctors. In order to address this issue, the student asked such potential study participants to suggest the time they would be free to go through the consent process and to have the interviews. In most cases, such potential study participants agreed to go through the consent process and granted the interviews though they did not participate fully in the interviews.

3.10 SUMMARY

In this study exploring perspectives on and comprehension of the RHDGen consent process, the research student conducted in-depth interviews and participant observations with research participants in the RHDGen project. A total of 34 IDIs and 57 POs were conducted with RHD patients and healthy population controls. Data from these two methods were analysed inductively using computer-assisted thematic analysis. In the next chapter, I will describe my analysis from the participant observations before moving on, in Chapter 5, to a description of the interview data.

4 OUTCOMES OF PARTICIPANT OBSERVATIONS OF THE CONSENT PROCESS OF RHDGEN CASES AND CONTROLS

4.1 Introduction

As described in the methods chapter, observations of the consent process of both RHDGen cases and controls were conducted in the Cardiac Clinic and Clinical Research Centre at the Groote Schuur Hospital, the Vanguard Community Health Centre and the Heideveld Community. This chapter discusses the different contexts where recruitment

and consent of RHDGen research participants took place and the ethical challenges that arose in these different recruitment contexts. It also describes how the different recruitment contexts impacted on the RHDGen research staff's ability to seek proper informed consent and the research staff's attitudes to both RHDGen cases and controls.

4.2 Different recruitment contexts of RHDGen cases and controls

The recruitment of RHDGen participants was conducted in both health facility and community settings. As described in section 3.3 of the methods chapter, the recruitment happened across all the four sites within the City of Cape Town in the Western Province of South Africa, all of which had very different features.

4.2.1 Recruitment and consent process of RHDGEN cases in the Cardiac Clinic and the Clinical Research Centre at the Groote Schuur Hospital

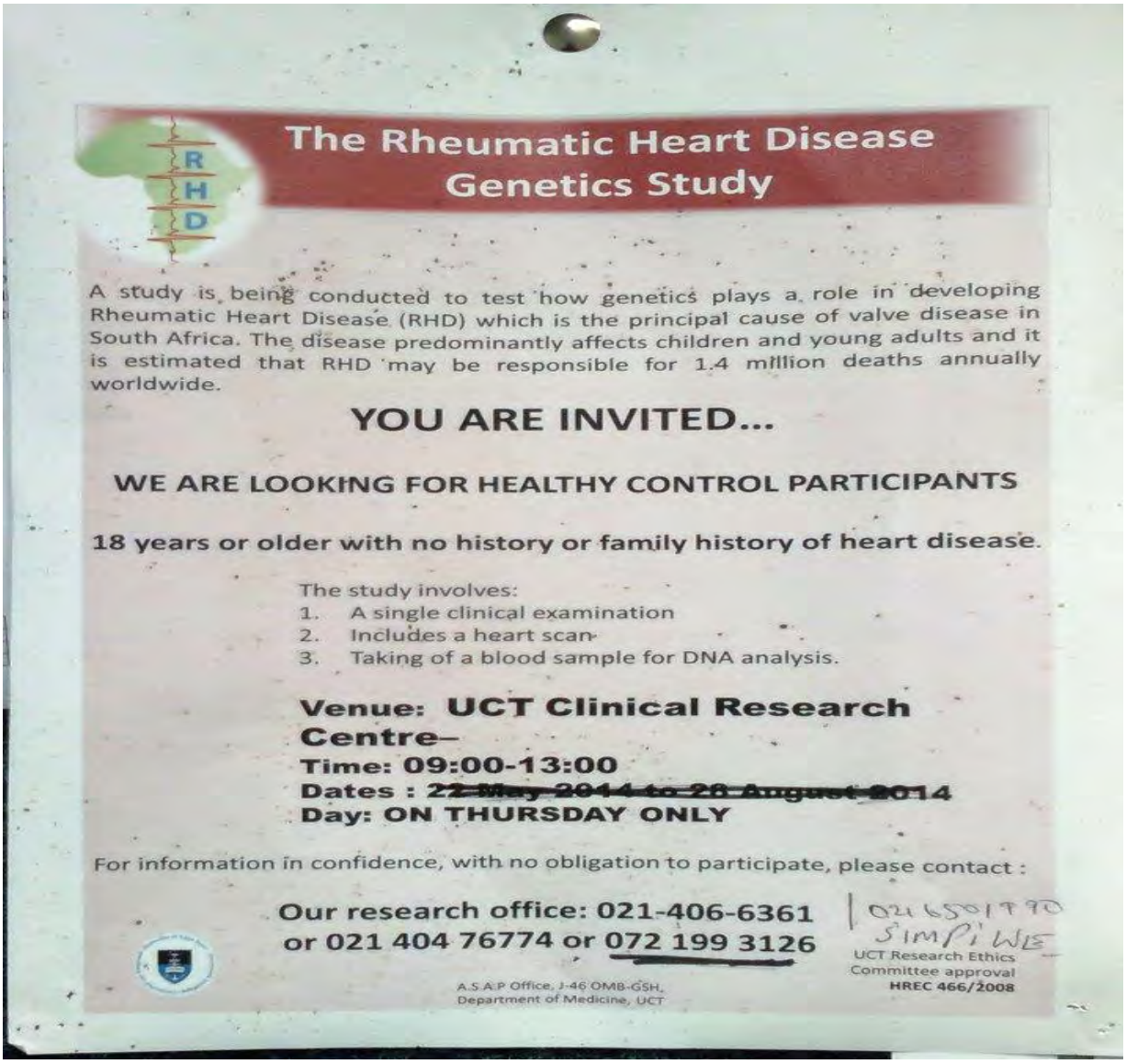
Recruitment of RHDGen cases in the Cardiac Clinic and the Clinical Research Centre was done by the RHDGen research nurse and study doctor. At the beginning of each consent procedure, the research nurse or study doctor provided information about the RHDGen research project to prospective research participants. She/he explained the purpose of the RHDGen research project, the potential benefits, foreseeable risks and study-related procedures such as collection of blood samples, blood pressure, height and weight as well as performance of ECHOs and electrocardiograms (ECGs) to scan the heart. Most research participants appeared to have understood the information which was provided. She/he also gave an opportunity to the research participants to ask questions or seek any clarifications about the study. The information provided to the prospective research participants by the research nurse or study doctor in the Clinical Research Centre was similar to the information which was provided to prospective research participants in the Cardiac Clinic. However, the research nurse or study doctor took much more time to discuss the RHDGen research project with prospective research participants in the Clinical Research Centre than in the Cardiac Clinic. In the Clinical Research Centre, she was able to articulate the study-related procedures and the rationale for the different procedures. In the Cardiac Clinic prospective research participants were to consult their doctors whom they had come to see on appointment and they were sitting in a queue

when the research nurse or study doctor approached them to take part in the RHDGen research project. Some had already been informed of the study telephonically. Unlike in the Cardiac Clinic, prospective research participants in the Clinical Research Centre were at ease and patient to go through the consent and recruitment process because they had come solely for the consent and recruitment process into the RHDGen research project. These facts impacted on how the research nurse and study doctor conducted the consent and recruitment process. In the Cardiac Clinic, they had to conduct the consent and recruitment process quickly so that the prospective research participants could go back to their queue while in the Clinical Research Centre, they took their time to take the prospective research participants through the consent and recruitment process.

4.2.2 Recruitment and consent process of RHDGen controls at the Clinical Research Centre of the Groote Schuur Hospital

Study procedures for RHDGen controls at the Clinical Research Centre were the same as those for RHD patients recruited in the Clinical Research Centre. The controls came to the Clinical Research Centre in response to adverts about the study which were posted around the Groote Schuur Hospital (refer to figure 1 below) and after being informed by their friends or colleagues about the study. The posters had introductory information about the RHDGen research project including the purpose of the study, eligibility criteria and study-related procedures. Prospective research participants, who read the posters or were informed by friends and colleagues about the study and got interested to join the study, came to the Clinical Research Centre (J52) of the Old Main Building of the Groote Schuur Hospital for recruitment.

Figure 1: Advert about the RHDGen study on the notice board of the Groote Schuur Hospital



In contrast to the recruitment of patients (cases) in the Cardiac Clinic at the Groote Schuur Hospital, there was no oral information provided to prospective research participants (controls) enrolled at the Clinical Research Centre because the prospective research participants had already heard about the study from either their friends/colleagues or the adverts that were posted on the notice boards at the Groote Schuur Hospital. Instead when the prospective research participants arrived at the Clinical Research Centre, they were taken through the consenting process by the research nurse who also collected

blood samples for genetic tests in one room. After that, the recruited research participants went to the second room where the field officer obtained demographic information such as age, ethnicity, and mother-tongue, area of origin, height, weight and blood pressure. From the second room, the research participants went to the third room where the echo-cardiologist or study doctor performed ECHOs and ECGs. When they were done with all study related procedures, the research participants left the Clinical Research Centre. The research nurse had enough time to explain the RHDGen study to prospective research participants and most research participants seemed to be educated and understood what a genetic study meant. Most prospective research participants were also inquisitive to learn what the RHDGen research project was all about. Unlike controls that were recruited at the Vanguard Community Health Centre and the Heideveld Community, controls that were recruited at the Clinical Research Centre and were not based at the Groote Schuur Hospital or the Faculty of Health Sciences were given transport refunds.

4.2.3 Recruitment and consent process of RHDGen controls at the Vanguard Community Health

A third location of participant recruitment was at the Vanguard Community Health Centre. Before recruitment and consent process of controls at the Vanguard Community Health Centre, the RHDGen field officer introduced the RHDGen research project to prospective research participants who came as patients to access services at the Vanguard Community Health Centre. The talks were given at the waiting area in the Out Patient Department where patients waited to see clinicians at the Health Centre and they were done in both Xhosa and English. During the talks, the field officer introduced himself and explained that a study was being conducted that targeted healthy adult people to find out if they had rheumatic heart disease (RHD). He referred them to the posters on the walls of the Health Centre which had information about the RHDGen research project. He went on to explain the benefit of participating in the study as being that study participants would know whether they had a rheumatic heart disease or not. He also highlighted that ECHOs and ECGs were being performed as part of the study to confirm rheumatic heart disease. He articulated that the ECHOs and ECGs were expensive at private hospitals or clinics and that the study was providing such services free of charge. He also alluded to the fact

that community members always complained about health services not being made available to them and that the UCT Groote Schuur Hospital was bringing such services to their doorsteps at the Vanguard Health Centre. He also explained that patients who would be confirmed to have RHD during the ECHOs and ECGs would be referred to the Groote Schuur Hospital for further treatment. Finally, he invited prospective research participants who were interested to participate in the study to go to the van which was parked outside the Health Centre close to the main entrance of the Hospital for recruitment.

After going through all the study-related procedures, each recruited research participant left the study site (van) and the research nurse or field officer proceeded with consent/recruitment of other prospective research participants.

Figure 2: Picture of the bus at the Vanguard Community Health Centre

4.2.4 Recruitment and consent process of RHDGen controls at the Heideveld Community

Prospective research participants for the RHDGen study at the Heideveld Community were identified by a community leader. The community leader together with his assistants wrote down names of prospective research participants they identified. The potential research participants were asked to come to the bus/van, which was normally parked at one of the Flats of the community, at their convenient time. When the prospective research participants arrived at the van, they were given information about the RHDGen study by either the research nurse or the field officer. The research nurse or field officer introduced the RHDGen study to them, explained the study related procedures and the eligibility criteria. The potential research participants were also handed the information leaflets for the study to read and they were asked to consult any of the research staff if they had any questions about the study. There was no detailed information provided to the prospective research participants at this stage because most of them had already heard about the RHDGen study from their community leader and the adverts that were distributed in their community prior to recruitment. Those who expressed willingness to participate in the study entered the first room for consenting and other study related activities in the same way as they did at the Vanguard Community Health Centre. They continued with the study related procedures in rooms B and C. When they were done with the study procedures, the research participants were given refreshments such as snacks and juices. Almost all the recruited research participants at the Heideveld Community were coloured or of mixed ancestry.

Figure 3: Picture of the bus at the Heideveld Community

4.3 Specific ethical challenges with the informed consent process of RHDGen cases and controls in the different recruitment sites

4.3.1 Fear of giving blood

Research participants recruited in the Cardiac Clinic felt that the volume of blood which was being collected by the research nurse and study doctor for the RHDGen study was too much. The research nurse and study doctor collected 9 mls of blood from each research participant in three EDTA tubes of 3 mls each. Some research participants felt this amount of blood was a lot. This was because during their appointments with doctors in the Clinic, doctors also took 5 mls of blood for clinical purposes. As such, some research participants were afraid to give their blood for the RHDGen study. In some cases, these concerns led to some potential participants not being enrolled into the

RHDGen study although they had already given their consent to join the study and had gone through the other study-related procedures.

4.3.2 Trust and familiarity with research staff

Most patients recruited in the Cardiac Clinic seemed to trust clinicians (doctor and nurse) who were part of the RHDGen research team because of their familiarity with them in the clinic. It was evident during the consent process that the prospective research participants had trust in the study doctor and study nurse and did not pay attention to the disclosure of information about the study. Some prospective research participants even told the study nurse and study doctor to proceed with the study related procedures before she/he finished providing information about the study. Familiarity with the field officer who was part of the RHDGen research staff also played a role in the recruitment of controls at the Vanguard Community Health Centre. Some controls knew the field officer personally while others used to see the field officer in their community. Because of their familiarity with the field officer, most prospective research participants willingly presented themselves to the van for recruitment after he had provided them with information about the study.

4.3.3 Diagnostic misconception among prospective research participants

According to the observations, most prospective research participants came to the van and the Clinical Research Centre for recruitment because they wanted to be screened for rheumatic heart disease and other heart conditions. They wanted to access the free ECHO and ECG services that were available to prospective research participants since they were informed that such services were quite expensive in private hospitals. It was clear from the observations that most prospective research participants did not pay attention to the information which was being disclosed to them during the consent process and they were very eager to go through the ECHOs and ECGs. After the heart scans, most research participants were very happy that they did not have any heart problems. They were so happy that one could think they had passed an examination. It was also observed that some prospective research participants were motivated by the information that they would be referred to the Groote Schuur Hospital if they were found to have

rheumatic heart disease or any heart conditions during the ECHO and ECG services. From the information provided by the field officer, some prospective research participants might have also thought the study was a health service brought to their communities to know whether they had a RHD or not. This observation was common among research participants recruited at the Heideveld Community. From the information provided by the community leader to the prospective research participants in Heideveld Community, it was clear that prospective research participants thought the study was a health service brought to their community in order to screen them for RHD. It was evident from the prospective research participants that the members of the research team had gone to their community to screen them for rheumatic heart disease. However, the community leader's role was to mobilize prospective research participants to come to the recruitment site where they would be provided with detailed information about the study before being recruited into the RHDGen study.

4.3.4 Privacy and confidentiality

As explained above, consent and collection of personal information from prospective research participants at the Vanguard Community Health Centre and the Heideveld Community were done in the presence of other prospective research participants and recruited research participants in the van. This might have compromised privacy and confidentiality of research participants. In fact, the van did not provide physical space that would respect privacy and confidentiality of prospective research participants. This was due to the limited space which was available for conducting study related activities in the two sites.

4.3.5 Pressure during the recruitment process

In most cases, the research staff were under pressure to recruit the potential research participants because they would normally come in their large numbers and queue for recruitment. There was pressure on the research nurses obtaining consent to do the process as quickly as possible because the prospective research participants were always eager to go back to the clinic to see their clinicians in the case of Vanguard Community Health Centre and they did not want to be delayed further with the recruitment

process. As such, in some cases, the consent process was done hurriedly and the prospective research participants were not provided with sufficient/adequate information about the study in order for them to make an informed decision. This might have affected prospective research participants' comprehension of the information about the study and could have compromised their voluntary decision-making process. Of course, research participants' understanding of the study and their voluntary decision-making were explored further in the in-depth interviews that were conducted with the research participants as part of this study on informed consent.

Due to the queues, research participants waited for long to go through the study related procedures i.e. blood draws, BP measurement and record of their height and weight. Due to the long waiting times, some recruited research participants decided to leave before completing the study procedures because they became impatient and tired of waiting since they had gone to the van before they had consulted the clinicians at the Health Centre and felt they were being delayed further or would miss being seen by the clinicians at the Health Centre. Some research participants I talked to expressed this dissatisfaction with the long waiting times. However, there was no way the research staff could have hurried the study related procedures for the research participants.

4.3.6 Undue inducement to participate in the RHDGen research project

As stated above, prospective research participants in the Heideveld Community were identified by the community leader or his assistants. The community leader was asked to identify a specific number of prospective research participants to be recruited in the community on each day of recruitment. Having talked to some of the prospective research participants and from the information provided by the field officer, it was apparent that prospective research participants thought that the study was a health service being provided to them to know whether they had RHD or not. The prospective research participants confirmed that the community leader informed them that doctors from the Groote Schuur Hospital were coming to screen people in the community for rheumatic heart disease and most prospective research participants who came to the site wanted to know whether they had RHD or not and they were motivated by the fact that the ECHOs and ECGs were free and that these services had been brought to their community.

Information and emphasis on free health service and referral to the GSH for further treatment for prospective research participants with confirmed RHD could have also unduly induced prospective research participants to join the study. Some of the features that were observed in this community that might have contributed to this ethical challenge were the high levels of unemployment and crime among the residents as well as poverty and limited access to health care.

4.3.7 Refusal to disclose names and sign consent documents

Some of the research participants in the Heideveld Community refused to provide their names and sign the consent documents during the consenting process although they had given their verbal consent to participate in the study. This was common among young men who came to be enrolled into the RHDGen study. When they were asked why they refused to give their names and sign the consent documents, they explained that they do not give their names nor provide their signatures or thumb prints on any documents. In such cases, the research nurse or field officer had to document in the consent forms that the individuals had agreed verbally to participate in the study.

From the observations, it was clear that some of the people who refused were gangsters and they did not want to put any of their identifiable information on documents. As described in chapter 2 above, potential research participants can decide to participate in research without necessarily signing informed consent forms. In the Heideveld Community, this might have to do with poverty, crime and prison experience as stated in chapter 5, section 5.3. This was a unique challenge because the consent documents required the names and signatures or thumb prints of the recruited research participants.

4.3.8 Security and safety of research staff

The research staff felt insecure during the days of recruitment at the Heideveld Community. This was so because of the cases of gangsterism in the community and the ongoing gunshots that were heard during the recruitment days. Despite this, the community leader assured research staff that they were safe as long as he was present at the recruitment site. The community leader knew all the people who were coming for recruitment at the site. He himself, also had inscriptions on his arms that were similar to

those of the youngsters who were suspected to be gangsters who displayed prison gang tattoos. He also exposed signs of wealth, for instance, he had golden teeth and a large golden watch. These observations combined with his apparent ability to ensure the safety and security of research staff. The feeling of insecurity was an issue among research staff who are not used to such unsafe environments and this might have affected the way they conducted the recruitment exercise. Some research staff had to ask to be escorted to their vehicles upon completion of recruitment on each recruitment day. The issue of safety and insecurity among research staff was explored further in the in-depth interviews and the results of the interviews are reported in chapter 5, section 5.3 below.

4.4 Conclusion

This chapter has attempted to describe the different recruitment contexts and highlighted the specific ethical challenges that arose during the consent and recruitment process of prospective research participants in the different contexts. From the descriptions, it is clear that the different recruitment settings presented different ethical challenges for the RHDGen research staff and the research participants themselves. In the successive results chapter where findings from in-depth interviews are given, there is detailed explanation about the different ethical challenges that emerged in these different settings from the research participants' points of view.

5 FINDINGS FROM INDEPTH INTERVIEWS WITH RHDGEN RESEARCH PARTICIPANTS

5.1 DIAGNOSTIC AND THERAPEUTIC MISCONCEPTIONS IN THE RHDGEN STUDY

Diagnostic misconception is defined as failure to appreciate the difference between research and diagnosis by research participants [60]. It can also be defined as expectations of receiving personal health information as a fringe benefit of health research participation [61]. Therapeutic misconception has been extensively studied and addressed within clinical trials while diagnostic misconception has been identified as an equivalent of therapeutic misconception in the genetic research context [60]. According to literature, diagnostic misconception occurs when potential research participants consider research participation as an opportunity to be checked or diagnosed for diseases [62 - 63]. In some cases, research participants may believe that they are being enrolled in research in order to be checked for the disease under study while in other cases, research participants may believe that they are being enrolled in research in order to receive individualized information about medical diagnoses and future disease risks [60 - 61, and 64]. This is contrasted with therapeutic misconception that occurs in clinical trials when research participants either misunderstand or fail to appreciate the key differences between research and clinical care [65 – 66]. Currently, there is not much empirical data on diagnostic misconception in genetic studies and none in genomic studies. Therefore, this particular finding of this study contributes to the body of literature on diagnostic misconception in genomic studies.

In this chapter, I will seek to demonstrate that most RHDGen research participants had beliefs related to diagnostic misconception. These beliefs of diagnostic misconception were more common among RHDGen controls than RHDGen cases.

Most RHDGen controls who participated in the IDIs described that they joined the RHDGen study in order to be screened for rheumatic heart disease. They indicated that they were interested to be screened for heart disease because this was a free service

which was brought to their communities. Most of them mistakenly considered the RHDGen study as a screening program for rheumatic heart disease. As witnessed during the participant observations, many participants were full of joy and happiness after going through the screening program and after being told that they did not have rheumatic heart disease. Some came out of the bus with their arms in the air, saying “I have passed the test!” The quotation from one of the study participants below supports this finding:

The thing that motivated me was to know if I have a heart disease and I wanted to see my heart beating too (IDI # COV 02).

Most controls in the IDIs also said that they decided to participate in the RHDGen study because the screening for rheumatic heart disease was a free service and that such free services were rarely available in their communities. They observed that the Field Officer informed them during the introductory talk about the RHDGen study that the screening was very expensive in private hospitals and that they considered this as a motivation for them to be screened for rheumatic heart disease. For instance,

I think the other reason is that this is a free service and such free services are rarely found here. So, I thought it was necessary to have the service (IDI # COV 04).

These services are free and they benefit us because they say the scanning of the heart is very expensive (IDI # COV 11).

We don’t have check-ups for heart problems here and sometimes they don’t test our blood when we are sick. So, with these free check-ups, I decided to come (IDI # COV 10).

Most controls recruited at the Heideveld Community also noted that they were requested to come for the screening for rheumatic heart disease by their community leader. They indicated that the community leader announced to the community that there was going to be a free screening program on rheumatic heart disease by doctors from the Groote Schuur Hospital. This motivated the community members to come for the screening. Thus the research participants said the following:

I was asked to come by our chairman. He announced two days ago that doctors from the Groote Schuur Hospital will come today and every Monday to screen people for rheumatic heart disease. So, that is why I came today (IDI # COH 26).

The community leader announced to everybody that you would be coming to this community to check people for rheumatic heart disease (IDI # COH 32).

Peer pressure also played a role in motivating some controls to participate in the RHDGen study. The control participants explained that they decided to join the study after seeing fellow community members participating in the study and that they did not want to be left out. The quotation below highlights this:

It was ok because everybody was being screened for the disease and I didn't want to be left out (IDI # COH 26).

A majority of controls also said they joined the RHDGen study because they wanted to know the conditions of their hearts. They expressed that they made the decision to join the RHDGen because they were informed that they would have heart scans and the doctor would be able to tell them if they had any heart problems or conditions. The two quotations below highlight this finding:

Hahaha (respondent laughs) I just wanted to check my heart if I had a problem or not (IDI # COV 01).

The main reason why people decided to come is because of the screening for heart problems. We were told you had those machines for screening people and since most of us do not know whether we have heart problems or not, it was necessary to come for the screening (IDI # COH 30).

An interesting contributory factor lending further support to the importance of the diagnostic misconception in the RHDGen enrolment is that many controls also described that they joined the RHDGen study because of stories they had heard of people who had heart complications and died because of ignorance about the status of their heart conditions, for instance,

Because another thing that made me get interested, my sister in law died of a heart disease. She had a heart problem and so that's what interested me to know if I have a heart problem. I was also scared of passing away from such a disease (IDI # COV 02).

Some of the controls indicated that they were very happy when they were informed that they had no heart problems after the heart scans. In fact, the controls regarded the heart scans as an exam or test one had to undergo and they considered it as one of the benefits of the RHDGen study as explained by the two controls below,

I was interested to know if I have a heart problem and I am happy that I don't have any heart problem (IDI # COV 04).

Yes, it is helpful because people are able to know whether they have a heart problem. For me I was happy when the doctor told me that I don't have any heart problem (IDI with study participant # COC 21).

Some controls also said that they decided to participate in the RHDGen study in order to have access to ECHO and ECG services. These services enabled them to have the conditions of their hearts checked and some of them were happy to see inside their hearts. The quotation below demonstrates this:

The doctor put something on my chest and I could see my heart moving and he recorded everything on that machine. After that, I went to the third room where I could see the beating of my heart and the lady there told me that I don't have any heart problem and my heart condition is fine. Obviously, I was happy to hear that because I was worried about my heart since I feel pain at the chest at times (IDI # COH 30).

Some controls were also interested to join the RHDGen study because of their previous experience working with researchers in clinical trials and the fact that they also wanted to see the echocardiograms of their hearts. Thus two study participants said:

I was also interested to see the echocardiogram of my heart. Yah I also work with pathological specimens and I was curious to see inside of my own heart (IDI # COC 21).

Well I work for an organization that runs clinical trials. So, it was quite interesting to be the participant and decided to consent and to be informed about this study. I came partly because I was quite keen to have an ECHO and an ECG; for me, it was a way of testing my heart to see if it was healthy but also I wanted to contribute to science (IDI # COC 20).

One of the RHDGen research staff who participated in the in-depth interviews noted that lack of understanding due to language barriers might have contributed to the misconception that the study was a screening program for heart conditions. She also observed that some of the participants had already made up their mind to have the screening before they went through the consent process and that it was difficult for such participants to understand that this was a research activity and not a screening program. Thus she said:

Ok I think the first challenge is probably the language barrier because I don't speak Xhosa. And so, that's a big challenge to some patients, although they might speak English but their English isn't good. Another challenge is some patients come when they have already made up their mind to be screened for heart conditions. So, even when you give them information that this is research, they seem not to understand (IDI # RS 02).

In addition to people joining the study in order to know about their hearts, participants also described that they joined in order to know more about their health status. These participants indicated that they expected that they would be told the results of their blood tests and that the tests would tell them if they had any diseases in their bodies. In fact, they regarded the RHDGen study as a general medical check-up and they expected that they would receive medical diagnoses at the end of the study. For instance,

Yaah and any disease they can find in it. In fact I smoke and sometimes I cough. So if they find anything in my blood I will be happy to know it (IDI # COH 26).

As I have said I just wanted to know about health and I am gonna be happy if they want to test anything in my blood because I really want to know about my health (IDI # COV 01).

Most of the RHDGen controls also believed that they would be referred to clinicians for treatment if they were diagnosed with severe health conditions during the study. This belief (misunderstanding) among controls suggests that there is a link between diagnostic misconception and therapeutic misconception. Below are quotations from some of the controls on this:

Aah she said if the doctor finds you with a problem, he will give you an appointment to see doctors at the hospital. That guy also explained the same. So, I will tell my husband to come and that if they find him with a heart problem, he will be given an appointment to go to the Groote Schuur Hospital to see doctors for further treatment (IDI # COV 04).

Yes because if they find you with a problem, they will send you to the hospital to see doctors there (IDI # COV 11).

I think it is both because everybody is checked and if you have the disease, they ask you to go to the Groote Schuur Hospital for treatment (IDI # COH 32).

But it was not altogether wrong because if research participants' echo were abnormal, they were referred to clinicians for treatment and this could be the origin of therapeutic misconception. On the issue of diagnostic misconception with regard to taking blood samples and performing blood tests, one of the nurses who took part in the IDIs clarified that it was not unexpected for the research participants to ask for results of their blood tests because they are always provided with results of their blood tests whenever they go for clinical care and their blood sample is taken. She said:

So, usually when they are in the hospital and somebody takes their blood, it's for a reason and they get their results. And now they need to understand that they are giving us blood for research purposes and they need to understand that it's not part of their standard of care; it's only for research (IDI # RS 01).

Some controls explained that they joined the study because they wanted to know their blood pressure. They indicated that their blood pressure is rarely checked and that their participation in the RHDGen study provided them with an opportunity to have their blood pressure checked. They observed that many people collapse and die of blood pressure

because of ignorance about their blood pressure levels. The fear of sudden death because of ignorance of their blood pressure levels was a motivating factor for such controls. They felt it was important for them to join the study in order to be checked for blood pressure since research participants were being checked for blood pressure as one of the study procedures. Below are the quotations from the controls on this particular finding:

And the most important thing was to know if I have high blood pressure (IDI # COV 02).

…I was happy also when the guy told me that my blood pressure is fine (IDI # COV 04).

I also wanted to know my blood pressure because sometimes you don't know that you have high blood pressure and people do collapse and die because of not knowing that they have high blood pressure (IDI # COH 32).

A majority of the RHDGen cases who participated in the IDIs also stated that they decided to join the RHDGen study in order to help find better drugs for treating patients with rheumatic heart disease in the future. The research participants noted that the current drugs that are being given to patients with rheumatic heart disease such as warfarin can have devastating side effects and they felt that through the RHDGen study, doctors and scientists would be able to develop better drugs for the current RHD patients and other patients in the future.

Thus the research participants said;

I think it will also help doctors to come up with new and better medications for this disease because they will understand what happens in the body when one has the disease by studying the DNA. In such a way, patients with rheumatic heart disease will be treated better and other patients with this disease will not have complications in the future (IDI # CWR 18).

Aah I think the issue of finding better drugs for people who suffer from this disease is important (IDI # CWR 15).

As I said they may also develop better medicines to treat the disease (IDI # CWR 18).

I joined because this study is useful. As I said it will help in developing better treatment and prevention for people with the sore throat, fever and those with the disease (IDI # CWR 15).

DIAGNOSTIC AND THERAPEUTIC MISCONCEPTION: DISCUSSION

From the findings of this study, it is evident that the majority of controls chose to participate in the RHDGen study because they were motivated by knowledge about heart disease, heart conditions, blood pressure, general health status and other medical conditions. These beliefs related to diagnostic misconception could be attributed to the fact that most of the controls who joined the study were healthy participants who considered the RHDGen research participation as an opportunity to be checked for various diseases including rheumatic heart disease. This was due to deprivation or limited health care access, poverty, unemployment and crime especially among controls that were recruited at the Vanguard Community Health Centre and Heideveld community.

These findings are consistent with findings of an observational bio-specimen research conducted among Latino communities on the US-Mexico border by Knerr et al [61]. In situations of limited health care, poverty and unemployment, medical diagnoses in research settings are described in favourable terms and it is not surprising. In the communities where the RHDGen study was conducted, there are health facilities that provide free health care, however, the quality of health care is characterized by overcrowding and long waiting times. According to Emmanuel, Wendler and Grady, the specification and enhancement of potential benefits to individual research participants should consider only health-related potential benefits derived from research [67]. In this case, participants joined the RHDGen study in order to obtain individual health benefits even whilst they acknowledged that this was research and they apparently understood that they were participating in research. Although their expectations are related to diagnostic misconception, which some may call an “ethical worry” in research participation, arguably, it was acceptable for them to enrol in the RHDGen study with medical diagnoses as reasons for their participation since they made their decisions autonomously.

Furthermore, some RHDGen cases reported that the drugs that would be developed from this study could help them in improving their own health. Such patients may have anticipated that they would derive direct personal benefit in form of better treatment from the RHDGen study. This motivation has been described as 'therapeutic misconception'. Therapeutic misconception depicts the hope that research participants may experience when previous clinical treatments have failed to help them adequately and hope to obtain better treatment by participating in research. Understandably, some patients in the RHDGen study have had complications and undergone surgery to implant artificial heart valves. Such patients are put on warfarin and they may not have benefitted from penicillin, which is the current prophylaxis for rheumatic heart disease. Hence, their hope for a new and better drug for rheumatic heart disease is justifiable.

Finally, one needs to appreciate the social context in which these people come from before making any judgments. Given the high levels of unemployment, poverty and, limited health care in the recruitment contexts, it was arguably not unethical for people to choose to participate in the RHDGen study in pursuit of individual health benefits. In fact, the participants themselves admitted that they were not forced by anybody to participate but chose to take part on their own. In my view, these were rational decisions by the research participants. In addition, this was a minimal risk study which did not expose participants to excessive discomforts and risks.

5.2 ALTRUISM IN THE RHDGEN STUDY

Altruism is defined as loving others as oneself or just as helping others. Auguste Comte coined the word *altruism* in 1851 *(www.altruists.org)*. In Comte's description, altruism means self-sacrifice for the benefit of others. Here, the word "others" can refer to members of the general population, fellow community members, friends and family members. In fact, evolutionary scientists speculate that altruism has such deep roots in human nature because helping and cooperation would promote the survival of our species [68]. Indeed, Charles Darwin argued that altruism, which he called sympathy or benevolence, is an essential part of the social instincts [69]. Darwin's claim is supported

by some neuroscience studies, which have shown that when people behave altruistically, they experience pleasure and reward, similar to when they eat chocolate or have sex [70].

In clinical trials, qualitative studies conducted with research participants have demonstrated that participants are often altruistically motivated to join clinical trials [71 - 74]. One motivational factor in clinical trials is the desire to help others in the future. For instance, a study conducted in India reported that the most common motivation among healthy participants was altruism [74]. And a recent qualitative study conducted in South London also found that the main reason for research participants to join clinical research was believed to be altruism [76].

Some research participants in genomic studies have also indicated that they were motivated to participate in genomic studies by altruism. In a genomic study conducted in Washington DC and Baltimore in the US by Facio and others, it was reported that one of the main reasons for participating in genomic research was a conviction to altruism in promoting research [77]. In another genomic research also conducted in the US by Sanderson and others, it was also found that altruism was one of the reasons for research participants' willingness to participate in genomic research [78]. However, there is a dearth of data from empirical research on altruism as a motivating factor for genomic participation in Africa. In this section, I will explore the extent to which considerations of altruism also motivated participation in the RHDGen study. I am going to demonstrate that most research participants decided to join the RHDGen study because of altruistic motives. The issue of altruism as a motivation for joining the RHDGen study was more common among RHDGen cases than RHDGen controls.

Most RHDGen research participants who took part in the in-depth interviews described that they joined the RHDGen study in order to help other people in future so that they might not suffer from heart disease. They indicated that they joined the RHDGen study in order to help doctors and scientists in coming up with prevention strategies against the development of rheumatic heart disease. Below are the quotations of the research participants on this finding;

Well, I want to help other people so that they cannot suffer from this disease. In fact, the nurse said the study may help other people in the future to be prevented from suffering from this disease and I think it is a good idea to help other people not to suffer from this disease in the future (IDI # CWR 14).

Well, rheumatic heart disease is a disease that is affecting quite a good number of people and since it is an inherited disease, many more people may suffer from it in the future and when I saw the advert, I felt it was important for me to take part in the study so that I might help others in the future so that they may not suffer from the disease. That's what I meant when I said it's for a good cause (IDI # COC 21).

Whereas for many RHDGen research participants the "others" that their altruism was targeted at were not described, some participants linked altruism more directly to their family members now and in the future. The research participants observed that they did not want their own children and grandchildren to suffer from rheumatic heart disease and that they decided to join the study in order to assist doctors and scientists in finding ways of preventing the disease from developing prophylaxis which would benefit their own children and grandchildren. For instance,

And at the end, may be it will benefit my own children and grandchildren from not suffering from rheumatic heart disease. I don't want them to go through the suffering I have gone through (IDI CWR 29).

A few RHDGen research participants who took part in the IDIs stated that they joined the RHDGen study because of the care shown by researchers. They indicated that they felt encouraged by doctors who are conducting further research on rheumatic heart disease with the intention of finding better treatment for RHD patients in future. Thus one participant said;

Another thing is that we feel encouraged when we see doctors doing further research on this disease because we know that they care about us and they will be able to treat patients better in the future (IDI CWNR 23).

ALTRUISIM: DISCUSSION

From the above findings of this study, it is clear that altruism was a motivating factor for participation in the RHDGen study. The majority of the research participants were motivated by the hope that others would benefit from the development of prophylaxis and better drugs for treating rheumatic heart disease which would result from the RHDGen study. Some research participants also indicated that they decided to join the study in order to help their own children and grandchildren not to develop rheumatic heart disease. These findings are consistent with findings of a study conducted among Americans in genomic research and a whole-genome sequencing study, both in the US, by Sanderson and others [78] as well as Facio and others [77] respectively. These studies found out that individual research participants affected with a specific genetic condition reported participating in genetic studies for altruistic reasons, for example, to help others who have or are at-risk for disease. Similarly, in the RHDGen study, altruism was more common among the RHD patients than the healthy volunteers. Of course, it is not surprising for the RHDGen cases to have been motivated by altruism to participate in the RHDGen study. Historically, the social good and compassion for others, which are characteristics of altruism, have been virtues that human beings value. In fact, genetic scientists such as William Hamilton have discovered that there are certain genes in humans that are associated with altruistic behaviour [68]. Individuals with such genes express sympathy and compassion for others and studies have revealed that patients who carry such genes do not want others to suffer from the diseases that they have suffered from [79 – 80]. Research also suggests that practicing altruism enhances our personal well-being—emotionally, physically, romantically, and perhaps even financially. It is also necessary for stable and healthy communities as well as the well-being of the human species as a whole (http://www.greatergood.berkeley.edu/topic/altruism/definition).More importantly, patients feel more compassionate towards their blood relatives including their own children as they do not want them to suffer from the pain and suffering they go through as a result of diseases which have affected them [69]. Indeed, altruism is part of human nature and it plays a role in alleviating the sufferings of others and improving people's health in the world including developing countries such as Africa.

5.3 SAFETY AND INSECURITY OF RESEARCH STAFF IN THE RHDGEN STUDY

Research staff play a very vital role in the recruitment of research participants in the field. They are an integral part of the research process and they are primarily responsible for implementing 'ethically appropriate' practices during recruitment in the field [82]. As such, any challenges they encounter in the field can affect recruitment and the implementation of other study related procedures in the field. As Gikonyo et al and Giessler et al report, implicit day to day social relations and engagements during data collection between community members and field staff are fundamental to the research process and they can impact on recruitment of research participants [37; 83].

Research staff in the RHDGen study complained about safety and security in one of the recruitment sites in Cape Town. Specifically, the issues of security and safety were raised at the Heideveld Community where some of the RHDGen controls were recruited. The concerns were raised because gunshots were heard during the period of data collection and police men were seen patrolling in the community. On the first days of recruitment, research staff had to leave the community under cover. Upon inquiring about the gunshots and the presence of policemen in the community, it was reported that they had to do with gangs in the area.

Gangsterism has been identified as one of the common issues in the urban ghettos of the Cape Flats in Cape Town and it is believed to account for almost 70% of all crimes in Cape Town [85]. According to Mncube and Madikizela-Madiya, gangs range from scavenger types that are involved in petty crimes, territorial types that are well organized with initiation rites and to corporate gangs which conduct illicit activities and have distinct names and symbols attached to their names [84]. Recently increased gang activities have been reported in Manenberg, Delft, Belhar, Hanover Park, Mitchells Plain, Lavender Hill, Heideveld and Athlone [81]. Bowers-Du Toit and others have reported that gangsterism

is rampant in the Cape Flats because of poverty, un-employment and over-crowding [81]. Most gangs are involved in crime and violence as a result of drug and alcohol abuse.

As such, I made an attempt to find out the extent of gangsterism in Heideveld from the research participants who participated in the in-depth interviews. My questions centred on the impact of gang-related activities to safety and security in the community.

In this section, I am going to present the responses of the research participants to the concerns about safety and security that were related to gangsterism in the community. In response to the question about safety and security, most of the research participants explained that there was security in the community. When they were probed on why gunshots were often heard and policemen were seen patrolling in the community, the research participants stated that the gunshots were targeted at members of rival gang groups and that the policemen came to the community to provide security because there were always fights among the different rival groups of gangsters. They also stated that the gangsters trade in illicit drugs and the policemen came to deal with the illicit drug trade among the gangsters in the community. For example, one research participant said;

We have gangs here that fight quite often and most of the gangsters trade and take drugs. So, they always shoot each other. That's why the police always come here. But they don't attack people who are innocent (IDI # COH 26).

The concerns about safety and insecurity for research staff were also raised by one of the research nurses who took part in the IDIs. The research nurse raised the concerns because she was part of the research team that was involved in the recruitment of research participants at the Heideveld Community. She however observed that she did not feel insecure because she was used to working in such environments. The research staff said;

And there was also a concern about security at Heideveld. Some of our staff felt that they were not safe to work in that community though I am personally used to working in such communities (IDI # RS_02).

However, the research participants assured the research staff that there is always security in the community. They explained that the gangsters usually attack members of their rival groups and strangers who come to the community without their knowledge. Thus;

Yes generally, it is safe. However, sometimes there are these groups of gangsters that fight and they usually fight among themselves and sometimes when there are strangers, they can also fight them especially if they are not known around here and they don't know why they are here (IDI # COH 30).

In your case you are not strangers here. Your coming was announced by our community leaders and we knew that you were coming. So, there is no way anybody can harm or shoot you (IDI # COH 30).

Yes, you are very safe because they respect Mr. X. They know you are here for our own health and they cannot attack you (IDI # COH 26).

No, no, you don't have to fear. Mr. X and our leaders are here. So, nobody can harm you. You are very safe (IDI # COH 30).

Aaah if you are not part of the gangsters they cannot attack you. They usually attack each other and sometimes they also attack intruders in this community. So, in a way, they also protect people who live in this community (IDI # COH 26).

It's because the law doesn't allow people to shoot each other like that and it is illegal to trade or take drugs. So, they come here for that (IDI # COH 26)

The research participants also explained that the gangsters may attack strangers if they suspect that they have been sent by the police to spy on them and their illicit trade. They also observed that the gangsters provide "protection" to the community by attacking people who intrude into the community. For instance;

Yah they try to protect the community too. Sometimes they are people who come to disturb or spy on the gangsters and if they feel threatened they shoot them. You know most young people here take and sell drugs and the cops usually come here to catch

those youths. So, when a stranger comes, they feel may be he is a spy sent by the cops. That's why they shoot (IDI # COH 30)

The respondents also revealed that the gangsters use symbols which represent their groups and that they are able to identify each other through the symbols. One of the respondents said;

Those are the different symbols the gangsters use to identify each other. In fact, they know each through those symbols (IDI # COH 26)

One of the research participants did not want to name the groups involved in drug dealing as gangsters. Instead he explained that the policemen who were seen patrolling in the community had come to look for drug dealers. However, the research participant had tattoos that resembled those of the gangsters and it is possible that he did not want to acknowledge that there were gangsters in the community. He said;

(Laughs) Yes, this community is safe. There is no problem with security here. Those cops come here to look for drug dealers and sometimes they shoot them (IDI # COH 31).

The research participant observed that the drug dealers earn their living by selling drugs and he did not identify the drug dealing as an illicit trade. When the respondent was asked if drug dealing was a big problem in the community, he responded;

Not really, but there are some people who are doing it and they earn a living by selling drugs. Otherwise, there is tight security here (IDI # COH 31).

He also emphasized that the research staff were very safe in the community and that they would not be attacked by anybody. For instance;

But you don't have to be afraid; nobody can shoot you or attack you (IDI # COH 31)

Yah, do your work freely because our leaders are all here and nobody can cause problems here (IDI # COH 31).

SAFETY AND INSECURITY: DISCUSSION

From the findings of this study, research staff were concerned about the issues of safety and security related to gangsterism in the Heideveld Community. The research staff felt unsafe and insecure because of the gunshots that were heard during the recruitment process. These concerns about safety and security might have affected the consent process and other study related procedures. Lack of safety and security could have also eroded the morale of research staff. As noted in 4.3.8 above, the research staff were assured of safety and security by the community leader and members who were involved in the recruitment process. However, as Sassy Molyneux et al have noted, research staff need to work in a safe and secure environment in order for them to implement 'ethically appropriate' practices during recruitment in the field [82]. But for them to feel safe and secure, there is need for appropriate engagement with community members and ensuring that community members are part and parcel of the research process. For example, despite concerns about safety and security during the recruitment of RHDGen research participants at the Heideveld Community, research staff were assured that they would be safe and secure during data collection in the community because community leaders and members were involved in the recruitment process and they were present throughout the period of data collection. This ensured the smooth conduct of the RHDGen study in the Heideveld Community.

As noted by one of the research staff, familiarity with the recruitment context may also help in understanding individuals involved in the research process. For example, the understanding that gangsterism was common in the community because of poverty, un-employment and over-crowding made the research staff to appreciate the day to day problems that community members were facing that forced them to resort to crime and violence. Understanding that gangs targeted members of rival groups and strangers that might have come to spy on the activities of the gangsters also helped research staff to feel safe and secure.

Finally, community engagement has been identified as an ethical requirement for research involving human beings, particularly marginalized populations [11]. It is believed that genuine community engagement in community-based research offers the hope of enhancing recruitment, safety, security and satisfaction of both research participants and research staff [86]. However, I do not know how best community engagement could work in the Heideveld Community where gangsterism is very rampant.

5.4 FEAR OF GIVING BLOOD IN THE RHDGEN STUDY

Fear of blood is also known as blood phobia and it is defined as the extreme and irrational fear of giving blood [87]. People may fear to donate blood to others for blood transfusions or they may fear to provide blood for research purposes in biomedical research. This section examines reasons why people fear to give their blood samples for use in biomedical research and it is informed by in-depth interviews that were conducted with research participants recruited into the RHDGen study.

Previous studies have documented reasons why research participants are afraid of giving their blood samples for research purposes [88 – 91]. In a qualitative study conducted in Zambia by Zulu and others, it was reported that research participants were afraid to give their blood samples in biomedical research because of the belief that the blood could be used for satanic practices [88]. Research participants in the study were scared of giving their blood samples for research purposes because they had heard rumours in their communities that blood drawn during research activities was being used for Satanic practices. These beliefs about using blood for Satanic practices in the Zambian context are similar to beliefs among Gabonese that blood drawn from research participants is sold by medical staff to the Rosicrucian Order, a semi-secret society affiliated with the Free Masons of Western Europe and the United States [92].

However, in another qualitative study conducted by Boahen and others in Ghana, it was reported that research participants feared to give their blood for research purposes because of their discontent with the quantity of blood that research participants were requested to give [89]. The research participants in the Ghanaian study viewed the blood samples being drawn as too much for their liking. In the same Ghanaian study, it was also

reported that some research participants did not understand why blood would be drawn from healthy people and this was another reason why participants were unwilling to provide their blood. Some research participants in the same study had the opinion that researchers could use the blood for rituals while others talked about having unpleasant experiences following blood draws [89].

The fear of pain was also reported as one of the main reasons why research participants hesitated to give their blood for research use in an Indian study [90]. And in another study conducted among health professionals in India, it was reported that research participants had negative attitudes that blood draws could lead to weakness, anaemia and reduced immunity [91].

Therefore, in this section, I am going to demonstrate that some RHDGen research participants had various reasons for fearing to give their blood for study-related tests.

A majority of the RHDGen research participants who were afraid of giving blood explained that they were scared of giving blood samples because they felt that the quantity of blood draws was too much. They observed that three (EDTA) tubes of blood samples that were being collected from them were a lot and they became scared. For instance;

It's just my fear and I think when I saw the nurse taking blood from that other guy, I thought it was a lot of blood and I was afraid of that (IDI # COH 26).

Aah for the blood, I don't know why the nurse is taking too much blood, perhaps she should be explaining to people why she is taking too much blood (IDI # COH 32).

I was not happy with the amount of blood she took; it's too much because when we go to the hospital, they don't take much blood as she is doing but I had no courage to ask her why she took 3 tubes of blood from me (IDI # COH 31).

The blood they are drawing is too much. They could reduce it to may be one tube instead of the three tubes of blood they are getting from us (IDI #CWR 15).

On the quantity of the blood draws, the RHDGen cases complained that it was too much for them to give such a volume of blood because they were also required to give blood

samples for clinical purposes on the same days they were recruited into the RHDGen study. The main reason for their fear on the amount of blood draws was that they did not have enough blood and they could become anaemic. Below are quotations from the research participants on this;

I think it was too much considering that the doctors also collect blood from us every time we come. So, I am afraid that I may become anaemic if I have to give this amount of blood every time I come to the hospital (IDI # CWR 18).

Aah may be the other thing is the blood. I think she took a lot of blood from me and I was not happy with that because I can become anaemic. I think they should reduce the amount of blood they take from people because it can scare some people from participating in this study (IDI # CWR 28).

I think it is still too much considering that some of us don't have enough blood (IDI # CWR 14).

A good number of RHDGen research participants were afraid to give their blood because of concerns they had about the use of left-over blood samples. They explained that they heard stories circulating in their communities that some doctors who sell blood to *Sangomas* which they use for *muthi.* Because of these rumours, the research participants suspected that doctors in the RHDGen study could abuse the sell the left-over blood samples by selling them to *Sangomas.* Other research participants stated that community members think researchers sell blood to other people without specifying who the other people were. The quotations below highlight these;

Not really, but we always become suspicious when doctors collect a lot of blood from us because we don't know what happens when the blood is left over. Of course, in the past I heard about rumours that some doctors were selling blood to Sangomas for muthi (IDI # COH 32).

*Eeh they think you are going to sell some blood to other people (*IDI # *COH 32)*

The speculations about doctors selling blood to *Sangomas* have not been verified and they might be misconceptions that community members have about what happens to left-

over blood in both clinical and research settings. In this study, we attempted to find out examples of cases where doctors were found or caught selling left-over blood samples to Sangomas, but none of the research participants who talked about it came up with examples. Thus;

People talk about it but I have never seen a doctor selling blood to Sangomas. May be in the past it was happening and that is why people talk about it (IDI # COH 32).

Some research participants were afraid to give blood because they were afraid of the pain that is associated with needle injection when nurses are drawing blood. They observed that application of spirit before injecting the needle lessens the pain. One research participant said;

For me she just used cotton and the needle without applying any spirit and maybe that's why I felt pain. I know that when I go to the hospital, they apply spirit and the nurses do it gently in such a way that I don't feel pain. But today the needle was painful and I felt very painful (IDI # COH 26).

On the pain that some research participants felt during the blood draws, they explained that the research nurse had difficulty to find the right vein to draw blood from and this caused pain to the research participants as the nurse to inject the needle on various veins before she could find the right vein to draw the blood from.

It was painful because she could not find a vein where she could draw blood. So, she tried to collect it from different veins and I felt pain (IDI # COH 32).

As I said the nurse took a lot of blood and felt pain on both arms because she had difficulties to get the blood (IDI #CWR 14).

And I also felt pain when she was taking the blood because she couldn't find where to take the blood. Maybe she couldn't find the right vein where she could draw the blood. She tried on both arms and she has problems to get the blood (IDI # COV 10).

Yooh it's too much and it was painful when she was taking it because she couldn't find the right vein to collect the blood. So, she tried on both of my arms and I am still feeling pain (IDI # CWR 18).

Some research participants stated that they felt blood is life and it is part of them. As such, they would not like to give blood for research purposes. They also noted that they would not want to share their life with "foreigners" when they were informed that the blood samples could be shared with other researchers who would want to do future research. One research participant suggested that instead of taking blood, they could get urine or saliva and do the tests. They stated that whenever blood is being drawn from them, they feel like part of them was being removed.

For me, I don't like giving blood. I gave the blood because the nurse said everybody has to give the blood. But if it was possible, they could check the disease may be in urine or saliva instead of blood because blood is life. (IDI # COH 26).

My brother as I have said, blood is life and you cannot share it with foreigners because these people cannot share their blood with us (IDI # COV 11).

I just become irritated with it. I feel like a part of me is being removed (IDI # COH 27).

Some research participants said they did not like giving blood samples. When they were quizzed as to why they did not like giving blood, they did not provide any reason. They said they were either scared or did not like giving blood at all. For instance;

I don't think there are any risks except that personally I don't like giving blood (IDI # COH 27).

Yooh, she took too much blood from me and I didn't like it (IDI # COV 04).

Am always scared to have my blood taken (IDI # COH 30).

Despite their fears, all the RHDGen research participants provided their blood samples for the study because they were told that they would be excluded from the study if they did not provide blood samples. Since blood draw was one of the final study procedures

recruited into the RHDGen study, the research participants felt obliged to provide the blood samples despite their fears. Thus

Yaah I accepted because she said she would not include me if I did not give blood (IDI # COH 26).

I was forced to give the blood because the nurse said I will not be part of the study if I refused to give my blood (IDI # COV 13).

FEAR OF GIVING BLOOD: DISCUSSION

From the findings of this study, there were various reasons why some RHDGen participants were afraid to provide their blood for this study. The reasons included that; the quantity of blood draws was too much; they were afraid of becoming anaemic as a result of too much blood draws; they had fear that their left-over blood samples would be sold to *Sangomas* for *muthi*; they were afraid of pain associated with needle injection during blood draws; and they had the perception that blood is part of one's life and cannot be removed from someone.

Consistent with the Ghanaian study and Zambian studies conducted by Boahen and others, Zulu and others as well as Kingori and others, RHDGen research participants were not happy with the amount of blood that was being collected from them and they thought that the left-over blood could be sold to *Sangomas* who would use it for *muthi* [88 -89 and 93]. There was a strong feeling among research participants that there was too much blood that was being drawn from them and they thought that it might have been done intentionally so that the researchers could sell the left-over blood to traditional healers. However, the actual amount of blood which was being drawn was equivalent to 30 mls in three EDTA tubes of 10 mls each. This amount of blood was just enough for carrying out study- related tests. The main reason for the participants' fears could be attributed to the fact that they were able to see their blood in the EDTA tubes and they thought it was a lot of blood.

In addition, the fear of pain as a result of needle injection during blood draws is also consistent with the findings of the study conducted by Uma and others in India [88]. However, unlike in the Indian study, in this study the pain came about mostly because of the failure of the research nurse to find the right vein where she could draw blood at the first attempt. This resulted in the injection of the needle on several parts of the arm that might have caused some pain to the research participants.

Furthermore, similar to the findings of the Indian study conducted by Desai and others, the RHDGen research participants were afraid that the perceived excessive blood draws could lead to anaemia [91]. This was common among RHDGen cases because they were required to provide extra blood samples for routine clinical care on the same days they were recruited into the RHDGen study. Perhaps the story would have been different if these research participants were recruited on separate days from the clinic days in which they had to give extra blood for clinical purposes.

Moreover, RHDGen research participants observed that blood is life and it is part of one's body. This finding is about the perceptions of most Africans about blood and bodily integrity. In most African cultures, blood has a symbolic value and strength as highlighted by De Vries and others in their discussion paper [94]. Blood is also considered as a life-giving force by most Africa cultures as reported in the studies conducted by Grietens and others in Gabon [92]. Therefore, it is not surprising that some research participants were afraid of providing their blood to the RHDGen research since they consider blood as life and part of their body. As one of the research participants observed, giving blood was perceived as removing a part of one's body.

Finally, to counter all these fears about giving blood for research purposes, there is need to provide adequate information to potential research participants about the blood samples that are collected from them. Potential research participants need to be adequately informed about the purposes for collecting blood samples and how the samples are used in research settings.

5.5 COMPREHENSION OF INFORMATION ABOUT THE RHDGEN STUDY

Comprehension or understanding of information disclosed during the consent process is one of the main elements of valid consent. Potential research participants are required to understand information that is provided to them about any study before they make their voluntary decision to participate in the study. Research participants' understanding of the study entails that they are aware of the both the benefits and risks of the study as well as all the study procedures and what is required of them during their participation in the study. However, evidence indicates that research participants often do not fully understand the studies for which they have volunteered. Various studies that have examined the process of obtaining informed consent for research and participant comprehension and satisfaction with the research have reported that there are challenges both in the provision of information to potential research participants by research staff and in the research participants' understanding of the disclosed information [35; 45;44; 97; 41; 50; 95 - 96]. The studies have reported several challenges that affected understanding of information that was provided to potential research participants during the consent process. One main challenge that affected comprehension of information disclosed to potential research participants during the consent process is language [44; 97; 95]. Language becomes a hindrance to understanding information about a study by potential research participants because some languages lack certain words for scientific terms and scientific concepts that are used in research and researchers may fail to translate such terms and concepts into the vernacular language spoken by potential research participants [35]. For instance, in a study conducted in Ethiopia, Tekola and others reported that the language levels used in information sheets and consent forms were not comprehensible to potential research participants even after the forms were read to them by research staff [44]. Tindana and others have also reported that it becomes difficult in genetic and genomic research to explain scientific terms and concepts such as "gene", "genetics", "genomics", "DNA", "genetic database" and "data release" in local language during the consent process [41]. They observed that the difficulty in explaining these scientific terms and concepts may be compounded by illiteracy in developing countries

[41, 46]. Tindana and others also reported that both research participants and research staff responsible for obtaining consent did not understand fully the methodologies employed during genomic research and their implications [41]. In an empirical study conducted in India, Kumar-Patra and Faulkner have demonstrated that the research staff did not understand that the data collected during the genetic study could be used in future secondary research [45]. In addition, in her discussion paper on informed consent for HIV cure research in South Africa, Ciara Staunton has noted that research participants in clinical trials do not understand the basic concepts in the informed consent process [96]. Staunton raises a concern about therapeutic misconception among future HIV research participants due to their failure to understand the basic elements of future clinical trials that are aimed at curing HIV/AIDS and confusing such clinical trials with clinical care. Marsh and others in Kenya have also reported that field workers in the Kilifi Genetic Birth Cohort Study had challenges in explaining genetics and genomics to potential research participants [97]. Instead the field workers had to use their own explanations about the study without referring to the information sheets which had such scientific terms as genetics and genomics. They also emphasized on screening for sickle cell disease more than talking about the genomic research [97].

In this section, I am going to explain the challenges research staff had in explaining the scientific terms and concepts of genetics, DNA and data sharing to potential research participants that affected research participants' understanding of these terms and concepts. I will also explain the difficulties potential research participants had in understanding these terms and concepts. Research staff were asked to explain the difficulties they had in the disclosure of information to research participants and the challenges they had in explaining some of the scientific terms and concepts used in the RHDGen study. Research participants were asked to explain what they understood by genetics, DNA and data sharing as well as why they would allow data sharing in the RHDGen study.

The RHDGen research staff reported that they had difficulty in explaining genetics and data sharing to potential research participants. According to the research staff, some potential research participants had never heard of the word "genetics" before and it was

taking a lot of time for the research staff to explain it to them. In some cases, research participants would still show that they did not understand it even after explaining it to them several times. The research staff said the difficulty in explaining data sharing came about firstly because some potential research participants did not understand what data meant. Secondly, the research participants did not understand that researchers could read their information from their blood and let alone that researchers could share data of their research participants among themselves. Due to the difficulty in explaining the concept of data sharing to potential research participants, the research staff had to take a lot of time to explain it with the aid of pictures of a library and with reference to computers. However, they were still some research participants that could not understand all the information provided to them about genetics and data sharing. For example;

I think most of our patients have never heard of genetics; it's a new word to them. And the other difficult part of this study is trying to explain to them that some of their bloods will go to Canada and other doctors are going to look at them and they can also read their information. Yaa that's something that also takes a bit of time to explain to the patients (IDI # RS 01).

Aah first of all they don't always understand what data is. I have to explain to them that what we are reading from them is the information they give us and what we get from their blood which doctors want to learn from them and that's what we call data. And if they don't know what data sharing means, I have also to explain to them. I tell them that like computers, everybody can log in and access the computer – I have got pictures of a library and it's like a library where people can access information and share knowledge – we share knowledge in the library. But still some participants would not understand all this (IDI # RS 01).

The research staff also highlighted that the information leaflet for the RHDGen study had explained the concept of data sharing by stating that *"it is now common that genetic information is shared with researchers around the world and that we would also like to*

share your genetic information and some of the clinical information with other researchers for other projects after we finish our study." However, they observed that some potential research participants kept asking questions as to why their genetic information would be shared with other researchers around the world and they would express fears that the researchers might decide to clone them and make other people. Much as the research staff would try to justify data sharing by stating that it would benefit many researchers who might want to use the same information for different research projects and that they would not use their blood to clone them, some research participants would not be convinced and they would still refuse to have their genetic information shared with other researchers around the world. The research staff attributed the research participants' refusal to have their data shared with other researchers to the research participants' misunderstanding of the concept of data sharing.

Some participants refused to have their data shared with other researchers. Of course, we had to respect their decision although I think that it had to do with their misunderstanding about what I explained to them about data sharing (IDI RS 02).

*Aaah so, when I have gone into the genetics side of the study, I always get questions related to the genetic side of things. So, I often get asked the researchers gonna not clone me and make other people. You know they are hearing these stories from the movies. Yaah I get asked questions about that. And then they also ask more questions about their disease and their condition. Can their children catch it from them? You know all those general kind of questions and because of not understanding my explanations, they refuse to have their data shared (*IDI # RS 01).

We have had very few people, mostly Moslem patients, who refused to have their blood sent overseas on religious grounds. It was more of not allowing their blood samples to leave the country, they wouldn't want some of it to leave the country (IDI # RS 01).

The RHDGen research staff also noted that some research participants lacked understanding of the information which was provided to them because of language barriers. They noted that some of the Xhosa speaking research participants had difficulty

in understanding English and in cases where the research staff who were involved in consenting potential research participants did not speak Xhosa, it was difficult for such research participants to understand the explanations about genetics, DNA and data sharing. Thus;

Ok I think the first challenge is probably the language barrier because I don't speak Xhosa. And so, that's a big challenge to some patients, although they might speak English but their English isn't good. Of course, I tried to explain to them what genetics and DNA mean. I even spent time to explain to them that their genetic information will be shared other researchers in future. But even though I gave them all this information, they seemed not to understand (IDI # RS 02).

Sometimes I had difficulties to explain the study to Xhosa speaking patients because I don't speak Xhosa. Of course, I would try to explain genetics, DNA and data sharing but I could still see that they did not understand what I was saying because of the language (IDI # RS 01).

Another challenge was about the difficulty for research participants to understand the link between genetics and rheumatic heart disease. The information leaflet had translated genetics as "genetic material" or "the building block of our bodies, and that it is information that is passed on from one's mother and father to you, and it is shared between family members." However, it appeared that some healthy controls did not understand why genetic tests would be done on their blood. Their (mis)understanding was that genetic test would establish whether they had inherited a heart disease from their parents. The misunderstanding came about because their blood samples were taken after the Cardiologist had already performed ECHOs and ECGs and informed them the results. As such, in the in-depth interviews some healthy controls kept asking why the research staff were interested in collecting their blood which had the genetic material when they had been told that they did not suffer from the rheumatic heart disease. For example;

My understanding is that genetics is about what we inherit from our parents such as our appearances and characters too. For example, I am coloured because I inherited these genes from my parents and I maybe short tempered because I inherited their short

temperament from my father. And the sister also explained the same thing. But I don't understand why the sister took my blood to study genetics while the doctor told me that I don't have any heart disease (IDI # COH 27).

I told the sister that I don't have this heart disease. So, I don't know why she decided to take my blood and do genetics to see if I have the heart disease when the machine did not find it. I don't really know how they will identify the disease in my blood by doing the genetic test (IDI # COV 13).

The research staff reported that they would not enrol potential research participants if they had feelings that they did not understand what the study was about. After disclosing information about the RHDGen study, the research staff would assess the prospective research participants' understanding of the information disclosed and if they were convinced that the prospective participants did not understand what the study was about, they would repeat the information session until they were convinced that the prospective research participants understood it. If after the repetition the prospective research participants seemed not to understand what the study was about, they were excluded from the study. However, the research staff did not assess prospective research participants' understanding of the scientific concepts and terms of "genetics", "DNA" and "data sharing". They also observed that there were some patients who would think that the research study was part of their routine care and for such patients, the research staff would also refuse to enrol such patients into the study. Thus;

Well, I don't enrol the patient if I get the feeling that they have no understanding of it because often they think it's part of the care they receive. They are coming to see the doctor today and they think it's just part of that. And I see that they think it's part of care of seeing the doctor and if I find that they think it's part of seeing the doctor and management of the day, then I don't enrol them. Yaa sometimes it takes me much longer to repeat myself to explain to them and I often ask them to repeat what I have explained to them. I often ask them what do you understand about what I have just told you about what we are doing. And from what they tell me, I will either go over and over again. But if I can clearly see that they don't just understand and think it's just for the management of today, I don't enrol them (IDI # RS 01).

The research staff observed that they had challenges in explaining the RHDGen study to research participants because it was a genetic study. They noted that it was time consuming to explain the scientific terms and concepts used in genetic studies because the terms and concepts were very unfamiliar to most research participants and the research staff had to repeat the explanations several times in order to get the message across. They acknowledged that this was the most difficult study they had ever participated in as far as the explanation of information about the study to research participants was concerned. Thus;

Yaah if I compare it to other research projects I have done before and explaining research concepts to research participants, I think the consenting of patients into this genetic study has been one of the most difficult and my most consuming time to get the message across to the patients, because it takes much longer to explain to the patients and it's something that is unfamiliar to a lot of patients. It's something they have never heard before. While if you are just explaining blood taking or that you are testing a new drug, they have heard that before. (IDI # RS 01).

They recommended that research staff who are involved in recruiting research participants in genetic studies need to be provided with adequate training about the consent process and the protocol. Below is what they said;

Well, I definitely think the person taking the consent, the research nurse or the doctor, they must be trained in the consent process before they start consenting patients; they must have a good understanding of the study and know what they are having to tell the patients. Yaah they must have a good understanding of the study because if they don't have a good understanding, how can they explain it to patients. *Because I must say I took a long time to actually data sharing and what we were really doing with the blood. So, Research Staff need adequate training before they can relay any message to patients* (IDI # RS 01).

I think the problem with this study is that we did not have proper training of the protocol and the consent process. If we were properly trained and practiced before we started recruiting research participants, we would not have faced these problems in explaining the study to participants (IDI # RS 02).

Consistent with what the research staff had said, some research participants reported that they had difficulty to understand some of the scientific terms and concepts used in the RHDGen study. Thus the research participants said;

I don't really know anything about genetics and DNA. The nurse explained them to me but these words are very new to me but I don't I understood clearly what she said (IDI # COC 21).

I have never heard about genetics and DNA. It was my first time to hear about these words and I was not attentive when the sister was explaining. So, I cannot remember what they mean (IDI # COH 32).

No, I didn't understand what she said about DNA. She just said that they are going to do DNA tests but she didn't explain what it means. She also talked about genetics and genes but she didn't explain what genetics, genes are (IDI # COC 20).

The research participants also disclosed that they did not understand what genetics and DNA meant because the research staff did not explain what they meant. They explained that the research staff mentioned genetics and genes without defining what they meant. They also noted that research staff mentioned that DNA tests would be performed on their blood but they did not explain what they meant by DNA. They cautioned research staff not assume that potential research participants understand these scientific concepts but that they should always explain these scientific concepts and terms to research participants. The following quotations highlight this;

Certainly they have to explain what they mean by genetics and DNA because this is a genetics study. There are people who don't know what genetics or genes mean let alone DNA. So, it is not good to take things for granted. The research nurses need to explain these things to participants (IDI COC 20).

She didn't explain what DNA is. She just said that they are going to do DNA tests but she didn't explain what it means. She also talked about genetics and genes but she didn't explain what genetics, genes are (IDI # COV 10).

Yaah they have to explain in a summary what these terms mean. I know that these terms are quite new to some people who have not gone through the high school or college. So, explaining them won't do any harm (IDI # COV 13).

No, I don't know genetics and DNA (IDI # COV 01).

Ooh I can't remember what DNA means but I learnt it when I was doing Biology. Unfortunately, the nurse did not explain it (IDI # COV 04).

However, some research participants seemed to have understood what DNA and genetics meant. They were able to explain in their own words what they understood by genetics and DNA and it was clear from their explanations that they had understood what the research staff had explained to them about these terms. Some of the research participants also explained that they acquired knowledge about these scientific terms and concepts from Biology classes at High School while for most patients recruited in the Cardiac Clinic, they might have got information about genetics and DNA from clinicians during their routine clinical visits. For instance;

I think I have explained that the DNA has genes which we inherit from our families or parents. So, genetics deals with the genes we inherit from our parents. Any child who is born shares genes from both the mother and father and this also applies to the diseases we inherit from them (IDI # CWR 14).

DNA and genes have to do with genetics or what we inherit from our fathers and mothers (IDI # CWR 18).

Aaah she said they will check the genetic material in the DNA which is in the blood and they will inform us what they will find … DNA is the genetic material that is found in the blood. (IDI # COH 26).

Genetics is about what we inherit from our parents… I learnt this at school (IDI # COV 04).

Genetics is the study about genes in the body. We inherit genes from both our parents (IDI # CWR 15).

Aaah genes are things we are born with in a particular composition I guess which are switched on and off as we get old and so that's what I understand by genes. And some people may have a predisposition to rheumatic fever depending on who their parents are and the environmental factors under which people are born while others don't have it. Yaah I think genes are found in the DNA and I assume that is why they will do DNA tests on the blood (IDI # COC 21).

According to the biology I did during my O Level studies, genes are found in the blood and we inherit some genes from both our father and mother (IDI # COC 03).

The research participants also reported that they had difficulty to understand the concept of data sharing. Their lack of understanding was based on the fact that research staff did not explain what it meant and in some cases, it appeared the research participants did not pay attention to the explanations that were given by the research staff about data sharing. Here is what they said;

I do not understand what you mean by data sharing…the nurse did not explain what you are talking about (IDI # COH 26).

I don't know what the nurse was talking about when she mentioned data sharing. It was not clear to me why these doctors want to share our information with other researchers. This is the first that I am hearing that doctors can share patients' blood with other doctors (IDI #COV 12).

She mentioned something about it but I did not get it. I think there is no reason for these people to share our blood (IDI # CWNR 23).

Despite the lack of understanding of the concept of data sharing, most research participants accepted to have their data shared with other researchers in the world. They

expressed that they would not have any problems in sharing their data and noted that further research on their data might benefit other people in the future.

Certainly, I would not have any problems with them sharing my data as long as they would do it to continue further research that will benefit other people in future (IDI # COC 20).

She explained that they share data and blood samples in genetic studies and they do that to allow other researchers to use the same data and blood samples in their research. So, I told her that I have no problem with that (IDI # COV 03).

Yes, I don't have a problem with that because I will not need the blood. They can do whatever they want to do with it (IDI #COV 04).

Of course, there were a few research participants who did not want their data to be used for research studies on different diseases from rheumatic heart disease. They pointed out that they would rather allow the sharing of their data to researchers who are conducting studies on rheumatic heart disease since they would be able to develop better treatment that might benefit other patients in future. They also expressed the fear that other researchers can use their blood to do studies on sensitive diseases such as HIV/AIDS which they cannot consent to. For example;

No, I wouldn't allow them to use it for research on other diseases because I provided the data and blood specifically for a genetic study on rheumatic fever and I wouldn't be comfortable for them to use my blood for doing let's say HIV research because this genetic study is not related to HIV and HIV is a very sensitive disease (IDI # COC 20).

I can allow the doctors to share my blood with researchers who are doing other researches in rheumatic heart disease. But I can't allow them to use it for research in other diseases. What I want is that doctors or researchers should find better treatment for patients who have this disease (IDI #CWR 29).

Finally, some research participants said that they were not willing to share their data with researchers outside South Africa. Their preference was that the blood should be shared with South African researchers and their reasoning was that blood is life and it cannot be shared with foreigners. They also expressed fears that such researchers could not share

their blood with South Africans and they could abuse the blood for their own benefit. Of course it is not very clear whether these sentiments were raised by the research participants because of their lack of understanding about data sharing although some research participants who refused to have their data shared appeared to have understood this concept.

First of all, I will be happy to know where the researchers are because blood is life and you cannot share it with anybody even with people who are outside the country because these people cannot share their blood with us. I would be comfortable if the blood is shared with South African researchers because they are my own brothers and sisters who will use it for this country (IDI # COV 03).

No, I cannot allow them to share it with other researchers or the whole world. I cannot be happy to see my data being used by people who are in the UK or Canada. In short, I cannot allow researchers from other parts of the world to use my data (IDI #COH 26).

No, I would not want any other people or doctors or whoever you call researchers to have my information. What if they make it public on the internet? I cannot allow them to use my information because I don't know them. I have given my information to the nurse because I know that it will be used by doctors here and I know the nurse. I am afraid that some doctors I don't know can use my blood for something else and that's my worry (IDI #CWR 28).

COMPREHENSION: DISCUSSION

From the findings of this study, it is very clear that research staff had difficulty in explaining the scientific concepts and terms of genetics, DNA and data sharing to research participants. It is also clear that some research participants had difficulty to understand the scientific terms of genetics and DNA as well as the concept of data sharing in genetic studies. From the findings of the study, it is also very clear that literacy levels and language played an important role in understanding scientific terms of genetics, genes and DNA as well as the concept of data sharing. However, it is not very clear whether some research participants refused to have their data shared with other researchers

because of their lack of understanding of data sharing though a few of them explained the reasons why they refused to have their data shared.

Similar to the findings of a qualitative study conducted by Marsh and others in Kenya on the Kilifi Genetic Birth Cohort Study [97], RHDGen research staff had challenges in explaining genetics, DNA and data sharing to potential research participants. As Tindana and others have observed [41], research staff might not have understood the scientific concepts used in genetic research and their implications which made it more difficult for them to explain the concepts comprehensively to potential research participants. Although the information leaflet of the RHDGen study provided simple explanations of genetics, DNA and data sharing, it was still a challenge for the research staff to explain the concepts to the research participants. In fact, the research staff themselves acknowledged that this genetic study was one of the most difficult studies to explain to research participants. Of course I do not agree that protocol training and training in the consent process would have improved manner in which research information was provided to potential research participants and enhance research participants' understanding of the disclosed information. I feel there is need to do further empirical research to understand why research staff find it difficult to explain scientific terms and concepts of genetics, DNA and data sharing to potential research participants despite the fact these terms and concepts are explained in lay language in study information sheets. There is also need to investigate why some research participants are not willing to share their data with other researchers in genetic studies – I am of the opinion that there might be some other reasons why some research participants might refuse to share their data with other researchers outside their country and these need to be unearthed through empirical studies which aim at understanding community members' perceptions and attitudes towards genetic studies. As Tindana et al have suggested, it is important for researchers to understand the cultural sensitivities surrounding data sharing and to try to find better ways of explaining data sharing as well as obtaining culturally appropriate consent for the exportation and sharing of data [98]. Denny et al have also recommended that the disclosure of information about data sharing should include information about the possible benefits and harms of data sharing to potential participants so that participants who give their consent to have their data shared make informed decisions [100]. Indeed,

as Parker and Bull report, calls for data sharing should be supported by explanations of potential benefits of such sharing to the participants who provide the data and their communities [99].

6 DISCUSSION OF THE FINDINGS

When this project was conceived, there was virtually no published empirical work describing ethical challenges in obtaining informed consent for health research in South Africa in general, and for genomic research in particular. Therefore, this study was the first study that attempted to understand the ethical challenges in obtaining informed consent in genomic research in the South African context. Specifically, this study has attempted to understand ethical challenges in obtaining informed consent in the RHDGen study. It explored what research participants understood during the consent process into the RHDGen study and it identified factors that could compromise voluntary decision-making for research participants in the RHDGen study. In-depth interviews and participant observations were conducted with research staff and research participants in the RHDGen research project in order to understand these issues and specific ethical challenges in obtaining informed consent in the different recruitment contexts. A total of 34 in-depth interviews and 57 POs were conducted with RHDGen research staff, RHD patients and RHDGen healthy population controls.

One major finding of this study was that most healthy controls recruited at the Vanguard Community Health Centre, the Heideveld Community and the Clinical Research Centre of the Groote Schuur Hospital decided to participate in the RHDGen study in order to be screened for heart conditions. In the ethics literature, this concept is called diagnostic misconception and it is defined as failure to appreciate the difference between research and diagnosis by research participants [60]. It is also defined as expectations of receiving personal health information as a fringe benefit of health research participation by research participants [61]. RHDGen research participants considered their participation in the RHDGen study as an opportunity to be diagnosed for heart diseases and they thought this study was a screening program for heart diseases. This has been the first study to report diagnostic misconception among research participants in Africa and in South Africa in particular. According to this finding, the RHDGen healthy controls were motivated by knowledge about heart disease, heart conditions, blood pressure, general health status

and other medical conditions. These beliefs among the research participants could be attributed to the fact that most of the controls who were recruited into the RHDGen study were healthy research participants who considered their research participation as an opportunity to be screened for various health conditions. They may have had these beliefs due to deprivation or limited health care access, poverty and unemployment as well as the fact that these free screening services were not readily available in their communities. In situations of limited health care, poverty and unemployment, ancillary care that is provided to research participants during their participation in research is described as the best treatment by research participants. Because of the generally good health treatment they receive during research participation, most research participants who are patients in resource limited settings do not refuse to participate in biomedical research. In the case of the RHDGen study, the research participants accepted to join the study in order to be scanned for heart conditions and be referred for specialist treatment free of charge if they were found to have heart problems. Although some of the study participants were identified by their community leader and his assistants as potential participants for the RHDGen study, they were free to refuse to participate in the study after being provided with detailed information about the study by the RHDGen staff who obtained their individual written consent. The same was true for potential research participants that were provided with information by the field officer at the Vanguard Community Health Centre prior to the consent process into the RHDGen study. In fact, some of such potential participants decided to leave the recruitment site when they felt that the study procedures were taking too long. However, most of those who accepted to join the study did so because they wanted to know their heart conditions. In my opinion, the research participants were not unduly induced to participate in the RHDGen study. Instead, they made their rational and autonomous decisions to participate in the study because they wanted to be screened for heart conditions. For example, in the communities where the RHDGen study was conducted, there are health facilities that provide free health care, however, the quality of health care is characterized by overcrowding and long waiting times. According to Emmanuel, Wendler and Grady, the specification and enhancement of potential benefits to individual research participants should consider only health-related potential benefits derived from research [67]. In this case, research participants joined the

RHDGen study in order to obtain individual health benefits although they acknowledged that this was research and they apparently understood that they were participating in research. Though their expectations are related to diagnostic misconception, arguably, it was acceptable for them to enrol in the RHDGen study with medical diagnoses and specialist treatment as reasons for their participation since they made their decisions autonomously. In my opinion, diagnostic misconception in this particular context was not an 'ethically worrisome undue inducement' to the research participants because these were good decisions made by the research participants and the RHDGen study did not expose them to any "unreasonable risks' [101].

Additionally, some RHDGen cases recruited in the Cardiac Clinic at the Groote Schuur Hospital reported an expectation that the drugs that would be developed from this study could help them in improving their own health. Other patients anticipated that they would derive direct personal benefit in the form of better treatment from the drugs that would be developed from the results of the RHDGen study. The expectation to receive better treatment because of their participation in the RHDGen study has been described as 'therapeutic misconception' in the ethics literature. Therapeutic misconception depicts the hope that research participants may experience when previous clinical treatments have failed to help them adequately and hope to obtain better treatment by participating in research [77]. Nobile et al have identified diagnostic misconception as an equivalent of therapeutic misconception in the genetic research context [62]. Understandably, some patients in the RHDGen study have had complications and undergone surgery to implant artificial heart valves. Such patients might have thought that they would benefit from drugs or any interventions that would be developed from the results of the RHDGen study. To further understand why both healthy controls and patients recruited in the RHDGen study were motivated by diagnostic misconception and therapeutic misconception respectively, one needs to appreciate the social context from whence participants came. Indeed, due to the high levels of unemployment, poverty and limited health care in the recruitment contexts, it was rational for people to choose to participate in the RHDGen study in pursuit of individual health benefits. They made rational decisions because screening services for heart problems are not readily available in their communities and participants who were diagnosed with heart problems were referred to their nearest health facilities and

the Groote Schuur Hospital for treatment. As such, it was ethical for them to decide to participate in the RHDGen study in order to access such free services. Whether the research participants were adequately informed about the RHDGen study or not, they made their voluntary and autonomous decisions to participate in the RHDGen study and their decisions were rational and acceptable in the circumstances. Moreover, the research participants themselves admitted that they were not forced by anybody to participate in the RHDGen study but chose to take part on their own after being motivated by the free screening services for heart problems and referral for treatment. In my view, these were rational decisions made by the research participants and both diagnostic misconception and therapeutic misconception in this context could not be classified as “undue inducements” [102]. Therefore, the consent to participate in the RHDGen study, though given in the context of diagnostic misconception and therapeutic misconception, was genuine.

Another major finding of this study was that some research staff felt unsafe and insecure at the Heideveld Community where some healthy controls were enrolled. The issues of safety and security in this community were related to gangsterism that is prevalent in the Heideveld Community. I described how concerns about safety and security impacted on the consent process and other study related procedures for healthy controls recruited in this community. The concerns about safety and security also eroded the morale of research staff and in some cases research staff had to conduct the study procedures hurriedly in order to do away with the gangsters who had come for recruitment. Although the research staff were assured of safety and security by the community leaders and members who were involved in the recruitment process, it was evident that research staff were affected by these concerns. As Sassy Molyneux et al have noted, research staff need to work in a safe and secure environment in order for them to implement ‘ethically appropriate’ practices during recruitment in the field [82] and they have recommended that appropriate engagement with community members should be undertaken to ensure that community members are part and parcel of the research process in cases where research staff feel insecure and unsafe. Community engagement has been identified as an ethical requirement for research involving human beings, particularly marginalized populations [11]. In fact, it is believed that genuine community engagement in community-

based research offers opportunities for enhancing recruitment, safety, security and satisfaction of both research participants and research staff [86]. However, for the Heideveld Community, community leaders were engaged through consultation and involvement in the recruitment process. Community leaders also assured research staff that they would be safe and secure during data collection in the community and the community leaders were present throughout the period of data collection. Nevertheless, the research staff did not feel secure and safe during the conduct of the RHDGen study due to gangsterism. One wonders how best community engagement should have been conducted in such a hostile environment. Could familiarity with the recruitment context as noted by one of the research staff help in understanding individuals involved in the research process? It was of course reassuring to research staff when they were informed that gangs targeted members of rival groups and strangers that might have come to spy on the activities of the gangsters. Apparently, the gangsters were aware that the research staff had come to the Heideveld Community to conduct health related activities and it was very unlikely that they could attack the research staff. Despite all this, research staff did not feel safe and secure because of the gunshots that were heard and the hostility of the environment. Perhaps there is need to find other strategies for engaging community members in such hostile environments as the Heideveld Community. One suggestion is to sensitize community members about such research activities prior to recruitment and request those who are interested to participate to come to the nearest health facility for recruitment instead of conducting the research activities within the community.

The third major finding of this study was about challenges to do with comprehension of research information disclosed to potential research participants by research staff. Some research participants had difficulty in understanding genetics, genomics, DNA and data sharing. Some research participants had difficulty in understanding genetics, genomics, DNA and data sharing. There were various possible reasons that could be attributed to their lack of understanding of the above scientific terms and concepts. One reason could be that they had low levels of education. Educational levels may have played an important role in research participants' understanding of the scientific terms of genetics, genes and DNA as well as the concept of data sharing because it was observed during the consent process that potential research participants who had high levels of literacy were able to

understand the concepts of genetics and DNA from their previous biology studies. Another reason could that the scientific terms and concepts used in genetic and genomic research were quite new to them. In fact, the research staff also acknowledged the difficulty in explaining the scientific terms and concepts to potential research participants because the terms and concepts were new to them as well. In addition, previous studies have reported research staff's difficulties in explaining scientific terms and concepts of genetics, DNA and data sharing to potential research participants [97; 41]. In fact, in the RHDGen study, research staff themselves acknowledged that this genetic study was one of the most difficult studies to explain to research participants. Indeed, genetic and genomic studies present new scientific terms and concepts that are difficult to explain to potential research participants and this calls for research staff to be creative when they are explaining such terms and concepts to potential research participants. The use of pictures and analogies could help in explaining such terms and concepts to potential research participants. Nevertheless, there is need to do further empirical research to understand why research staff find it difficult to explain scientific terms and concepts of genetics, DNA and data sharing to potential research participants despite the fact that these terms and concepts are explained in lay language in study information sheets.

From the findings of this study, some research participants were not willing to share their data and samples with other researchers. Various reasons were given for their unwillingness to share their data and samples. Some research participants expressed fears that other researchers could use their blood samples to do sensitive studies such as HIV/AIDS which they had not consented to. Other research participants refused to share their blood and data with other researchers because they said that blood is life and that it should not be shared with foreign researchers. They also expressed fears that such researchers could not share their blood with South Africans and they could abuse the blood for their own benefit. Of course it is not very clear whether these sentiments were raised by the research participants because of their lack of understanding about data sharing although some research participants who refused to have their data shared appeared to have understood this concept. There were still other research participants who thought that the other researchers might sell their blood samples to *Sangomas* (traditional healers) and Satanists. Though these rumours have not been validated, there

have been raised before by research participants in biomedical research. The other reasons given by the research participants for their refusal to share their blood samples and data were that researchers from developed countries do not share their data and samples with researchers from developing countries.

Related to the finding on comprehension is the issue of research staff's pressure during the recruitment process at the Vanguard Community Health Centre. Based on the observations, research staff were under pressure to recruit prospective research participants especially at the Vanguard Community Health Centre. This was due to the fact that prospective research participants would come in large numbers and queue for recruitment at the site and they were very eager to go through the recruitment process so that they would go back to the clinic to see clinicians for their health care. Due to this pressure, research staff who were involved in the consent process had to do it hurriedly so that they would not miss any of the prospective research participants. This might have impacted on the disclosure of sufficient information to prospective research participants and it might have affected prospective research participants' understanding of the information.

Another finding based on the observations was that there was a breach of privacy and confidentiality during the consent process in the van at the Vanguard Community Health Centre and the Heideveld Community. This breach of privacy and confidentiality happened because the consent process and collection of personal information from prospective research participants were conducted in the presence of other potential research participants. In fact, the van did not provide the physical space that would respect privacy and confidentiality of potential research participants.

The fifth finding of this study was that the majority of RHD patients decided to join the RHDGen study in order to help future patients suffering from rheumatic heart disease. Most research participants noted that the prevention measures and other drugs that would be developed from the results of the RHDGen study could help other patients suffering from this disease in the future. The hope for development of prophylaxis and better drugs for future patients suffering from a particular disease is a common phenomenon among patients participating in biomedical research and genetic studies in

particular [77, 78, 103]. Patients who participate in research are often influenced by altruistic motives when they agree to join research studies. Most patients do not like seeing others suffering from the same disease they have suffered from and they are always willing to help others who have or are at-risk of developing the disease under study by accepting to participate in studies that may develop better treatment for future patients [79 - 80]. This is due to the compassionate nature of human beings and it is not surprising that some of the RHDGen research participants especially the RHD patients who were recruited in the Cardiac Clinic decided to participate in the study due to altruistic motives. Altruism implies that the research participants were not induced to participate in the RHDGen study but that they made their own voluntary decisions to participate in the study out of compassion for others [101]. Of course, one could observe that the motivations for participation such as diagnostic misconception and therapeutic misconception, which are self-interested benefits, may be incompatible with altruism, which is a collective benefit. However, this study is not unique in reporting these incompatible findings since these may exist and be real to individual research participants as previously reported by Sikweyiya and Jewkes [103].

The final finding of this study was that some research participants were scared of giving blood. There was a strong feeling among some RHDGen research participants that there was too much blood that was being drawn from them and they thought that it might have been done intentionally so that the researchers could sell the left-over blood to traditional healers. However, this was just a misconception about the use of blood that was being drawn from the research participants. Perhaps the research staff did not explain clearly to the research participants the amount of blood that was being collected and why the blood that was collected was to be used for. Some research participants were afraid to give their blood because of the pain that would result from needle injection during blood draws. Indeed, few research participants complained about pain during the blood draws but this was due to failure of the research nurses to find the right vein where they could draw blood at the first attempt and as a result, they injected the needle on several parts of the arm that might have caused some pain to the research participants. Other research participants were afraid of the blood draws because of their perception that excessive blood draws could lead to anaemia. The fear of developing anaemia from excessive blood

draws was more common among RHDGen cases than RHDGen controls because they were required to provide extra blood samples for routine clinical care on the same days they were recruited into the RHDGen study. Perhaps the story would have been different if the RHDGen cases were recruited on separate days from the clinic days in which they had to give extra blood for clinical purposes. Moreover, RHDGen research participants observed that blood is life and it is part of one's body. This finding is about the perceptions of most Africans about blood and bodily integrity. In most African cultures, blood has a symbolic value and strength as highlighted by De Vries and others in their discussion paper [94]. Blood is also considered as a life-giving force by most Africa cultures as reported in the studies conducted by Grietens and others in Gabon [92]. Therefore, it is not surprising that some research participants were afraid of providing their blood to the RHDGen research since they consider blood as life and part of their body. As one of the research participants observed, giving blood was perceived as removing a part of one's body. The fears in giving blood were also evident during the observations. These fears led to some research participants to withdraw from enrolment into the RHDGen study although they had already provided their consent to join the study and had already gone through the other study-related procedures. To counter all these fears about giving blood for research purposes, there is need to provide adequate information to potential research participants about the blood samples that are collected from them. Potential research participants need to be adequately informed about the purposes for collecting blood samples and how the samples are used in research settings.

7 CONCLUSION AND RECOMMENDATIONS

Based on the information which was obtained from participant observations during the recruitment process of both RHD cases and controls as well as in-depth interviews with RHDGen cases, controls and research staff involved in obtaining informed consent from the research participants, the following are conclusions on the ethical challenges in obtaining informed consent from the RHDGen research participants:

●Most RHDGen controls had beliefs related to diagnostic misconception. These research participants joined the RHDGen study in order to be screened for heart conditions and they mistakenly considered the RHDGen study as a free screening program for heart conditions.

●Some RHDGen cases joined the RHDGen study because of therapeutic misconception. Such cases anticipated that drugs would be developed from this study that could help them in improving their own health.

●Most RHDGen participants decided to join the RHDGen study because of altruistic motives. Altruism as a motivating factor for joining the RHDGen study was more common among RHDGen cases than RHDGen controls. The research participants described that they joined the RHDGen study in order to help other people in future so that they might not suffer from heart disease.

●Most RHDGen research staff were concerned about the issues of safety and insecurity related to gangsterism at one of the recruitment sites. The research staff felt that they were unsafe and insecure at the Heideveld Community in the Cape Flats where some RHDGen controls were recruited. These concerns might have affected how they obtained consent from research participants in this community in that they administered the consent process in fear. In fact, the environment at the Heideveld Community was so hostile for conducting an ethical study. However, the research staff tried their best to conduct the study ethically.

●Some RHDGen research participants were scared of giving blood for study-related activities. Some research participants were afraid of giving the blood because they felt that the quantity of blood draws was too much while other research participants had concerns about the use of left-over blood samples and the pain associated with needle injection.

●Some RHDGen cases had trust in clinicians who were part of the RHDGen research team because of their familiarity with them in the Cardiac Clinic. Because of their trust,

they did not pay much attention to the disclosure of study information and they willingly consented to participate into the RHDGen study.

●Some RHDGen controls were familiar with the RHDGen field officer who was responsible for providing information to potential research participants and recruiting them into the RHDGen study. Some knew the field officer personally while others used to see him in their community. Because of their familiarity with him, they willingly presented themselves to the Van for recruitment.

●There was a potential breach of privacy and confidentiality for RHDGen controls who were recruited in the van at the Vanguard Community Health Centre and the Heideveld Community. The van which was used for recruitment at the two sites did not provide adequate space that would respect privacy and confidentiality for research participants. This was due to the limited space which was available for conducting study-related activities in the two sites.

●Some RHDGen research participants had difficulty in understanding scientific terms and concepts of genomics, DNA and data sharing.

●Research staff had difficulty to explain the scientific terms and concepts of genetics, genomics, DNA and data sharing to potential research participants. The research staff noted that it was time consuming to explain these terms and concepts to potential research participants because they were very unfamiliar to most research participants.

Recommendations:

Based on the above findings, I would like to recommend the following to researchers who are conducting genomic research in limited resource settings;

●Research Staff who are involved in recruiting potential research participants for genomic studies must be creative during the recruitment process and ensure that the studies are conducted properly without compromising ethics. Consent processes must be flexible enough to allow staff to adjust these to the specific recruitment context. Staff must ensure

that they respect their potential research participants and the decisions they make without being judgemental.

●The design of consent forms for genomic research should not be based on checklists for consent documents but they must be informed by experiences of researchers working in communities where the intended research projects are to be conducted. For instance, consent documents for recruiting potential research participants from communities that are unsafe and insecure for research staff must be informed by inputs from community leaders and researchers who have experience in conducting research in such communities.

●There is need for genomic researchers to involve potential research participants and their communities in sensitization activities where they have to explain scientific terms and concepts used in genomic research and allow them to ask questions before approaching individuals to take part in their genomic research projects. Such community engagement has to involve community leaders as well. And in communities where community advisory boards (CABs) exist, CAB members should be involved in communicating scientific terms and concepts in lay terms to their fellow community members. In communities where CABs do not exist, it is important to establish CABs to assist research staff in sensitization activities and communicating information about genomics, DNA and data sharing to community members prior to approaching individual potential research participants to join genomic studies.

●When researchers intend to conduct their research among members of communities where safety and security issues are a concern, they must ensure that they conduct their research activities at health facilities in which such communities fall.

●Researchers who conduct hospital based studies must ensure that they enrol patients into their studies on separate days from the clinic days in order to ensure that potential research participants have ample time to go through the recruitment and study procedures.

●In research studies which involve embedded ethicists as researchers within the research projects, there is need to clarify the roles of the embedded ethicists in the entire research

process and assure research staff involved in recruiting potential research participants of the necessity to collaborate with the embedded ethicists in ensuring that the research projects are being conducted ethically.

●There is need for provision of adequate information about research objectives and procedures including anticipated benefits and risks to potential research participants before obtaining their consent to participate in genomic studies. There is also need to assess potential research participants' understanding or comprehension about scientific terms and concepts used in genomic research prior to enrolling potential research participants in genomic studies.

●Finally, it is necessary to train research staff responsible for recruiting research participants in the protocol and the informed consent process before initiating genomic research projects. After such protocol and informed consent process training, research staff should conduct pre-testing (piloting) of data collection tools and informed consent documents among lay community members and make appropriate corrections or revisions to the data collection tools and informed consent documents before implementing genomic studies.

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9 APPENDICES

Appendix I: Information Sheet and Consent Form for RHDGen Adult Cases and Controls Participating in IDIs

Title of the study: **Ethical Challenges in Obtaining Informed Consent in the RHDGen Study**

Student Investigator: Mr. Francis Masiye

Supervisors: Prof Bongani Mayosi and Dr. Jantina de Vries

Introduction

We invite you to participate in a study. This consent form explains the research study you are being asked to join. Please, read it carefully and ask any questions about the study before you agree to join. You may also ask questions at any time after joining the study. If you agree to participate, our interview will be recorded and written down. The interview will be anonymised and nobody except the researchers will know what you said. If we report on this study, we may use one of your sentences but even if we do that we will not put your name; nobody will know that it was you who said it.

Purpose of the study

The purpose of this study is to understand ethical challenges in obtaining informed consent for the study on rheumatic heart disease that you joined. We hope to use the findings of this study to explore possible interventions for improving ethical challenges in obtaining informed consent in genomic research

Participants

For this study, we hope to talk to patients with rheumatic heart disease and people who do not have the disease who were recruited into the RHDGen research project. We will

also talk to research staff who are involved in the recruitment of study participants in the RHDGen research project at the Groote Schuur Hospital and in communities within Cape Town. We are asking you to participate in an interview of the study on rheumatic heart disease that you participated in.

If you agree to participate, we would like to hear your views about the informed consent process: what you understood during the consent process, what you think about the consent process, and how best you would like it to be done. We would also like to know your understanding of genetics. The interview will last about 60 minutes. It will be conducted either in English by Mr. Francis Masiye or in your local language by a Research Assistant. It will be recorded as this will help us to focus on what you say to us. The recordings will be written down after which they will be destroyed. At the end of this study, we would like to keep the transcript of the interview with you. The transcript will be anonymous and nobody will know that it was you who was in the interview.

Risks/Discomforts

There are no physical risks in this study. However, you might feel upset or worried to reveal your personal information when answering some of the questions. To minimize this, please, feel free to choose not to answer any questions you do not want to answer. The interview will take about 60 minutes of your time.

Anticipated Benefits

If you decide to participate in this study, you will receive no direct benefits from answering our questions. However, your contribution may help researchers better understand the challenges in obtaining informed consent in the RHDGen study. We hope that this study will help us to improve the current consent process for genomic and genetic studies.

Confidentiality

We will keep what you say to us in the interview strictly confidential. You will be assigned a unique identification number. We will only refer to the number in future and not to your

name. The information collected will be kept in restricted access offices and on password-secured computers. The recording of the interview and transcript will be kept until the end of the study. When we report on our findings, we may use some of the sentences that you said. If we use one of your sentences, it will appear together with your unique identification number for the interview (**for instance, IDI#18).** We also ask you to keep what we discuss in the interview private.

Voluntariness and the right to withdraw

Your participation in this study is entirely voluntary, and there are no consequences if you decide not to participate. If a question makes you uncomfortable and you don't want to answer it, then you don't have to. If during the interview or at a later date you have second thoughts, then please feel free to withdraw from the study and if you do we will not consider what you said during the interview. Please, feel free to ask me any questions you may have about this research study.

Compensation

In order to thank you for your time, and to compensate you for any expenses, we will give you R150.

Contact Information

If you would like more information about this research project before deciding to participate, and if you have questions or comments, please contact Mr. Francis Masiye, at any time on the following telephone number; 021 650 1902 and he will answer your questions. You can also contact Jantina de Vries at 021 650 5716 or Bongani Mayosi at 021 406 6200.If you have concerns about your rights because you think you have not been treated fairly or think you have been hurt by joining the study, you can contact the Human Research Ethics Committee in the Faculty of Health Sciences at the University of Cape Town on 021 406 6338 or write to Shuretta Thomas, Human Research Ethics Committee, Room E52-24, Old Main Building, Groote Schuur Hospital, OBSERVATORY 7925.

Signature

Have you been provided with sufficient information about the study? ☐ Yes ☐ No

Have you had an opportunity to ask questions and discuss this study? ☐ Yes ☐ No

Have you received satisfactory answers to all your questions? ☐ Yes ☐ No

Do you understand that your participation is voluntary, and that you are free to withdraw from the study at any time? ☐ Yes ☐ No

Do you agree to take part in this study? ☐ Yes ☐ No

Do you agree to be audio-recorded during the interview? ☐ Yes ☐ No

Signature……..Date…….

Name of Study Participant……..

Student Investigator/Research Assistant Statement

I confirm that I have carefully explained the proposed study to the participant.

Signature…….…. Date…….

Name of Person Obtaining Consent……

Appendix II: Information Sheet and Consent Form for RHDGen Research Staff Participating in IDIs

Title of the study: **Ethical Challenges in Obtaining Informed Consent in the RHDGen Study**

Student Investigator: Mr. Francis Masiye

Supervisors: Prof Bongani Mayosi and Dr. Jantina de Vries

Introduction

We invite you to participate in a study. This consent form explains the research study you are being asked to join. Please, read it carefully and ask any questions about the study before you agree to join. You may also ask questions at any time after joining the study. If you agree to participate, our discussion will be recorded and written down. The interview will be anonymised and nobody except the researchers will know what you said. If we report on this study, we may use one of your sentences but even if we do that we will not put your name; nobody will know that it was you who said it.

Purpose of the study

The purpose of this study is to understand ethical challenges in obtaining informed consent for the genomic epidemiological study on rheumatic heart disease you are involved in as a Research Staff. We hope to use the findings of this study to explore possible interventions for improving ethical challenges in obtaining valid informed consent in genomic research

Participants

For this study, we hope to talk to adult cases and healthy population controls who have been recruited into the RHDGen research project and research staff who are involved in

the recruitment of study participants in the RHDGen research project at the Groote Schuur Hospital and in communities within Cape Town.

We will interview 4 of you who are involved in the recruitment of research participants into the RHDGen research project. If you agree to participate, we would like to hear your views about the informed consent process: the challenges you encounter during the consent process, what you think should be done in order to improve the consent process. The interview will last about 60 minutes. The interview will be conducted in English by Francis Masiye, who is the Student Investigator. It will be recorded as this will help us to focus on what you say. The recordings will be transcribed verbatim. At the end of this study, we would like to keep the transcript of the interview with you. The transcript will be anonymous and nobody will know that it was you who was in the interview.

Risks/Discomforts

There are no physical risks in this study. However, you might feel upset or worried to reveal your personal information when answering some of the questions. To minimize this, please, feel free to choose not to answer any questions you do not want to. The interview will take about 60 minutes of your time.

Anticipated Benefits

If you decide to participate in this study, you will receive no direct benefits from answering our questions. However, your contribution may help researchers better understand challenges you encounter in obtaining informed consent in the RHDGen study. We hope that this study will help us to improve the current informed consent process in genomic and genetic studies.

Confidentiality

We will keep what you have said to us private. You will be assigned a unique identification number. We will only refer to the numbers in future and not to your name. The information collected will be kept in restricted access offices and on password-secured computers. The information will be available to the Student Investigator and Dr Jantina De Vries only. The Principal Investigator of the RHDGen study will not have access to your transcript. In

addition, we will get your permission to use quotes from you in the thesis and publication. The recordings of the interview and transcript will be kept until the end of the study. When we report on our findings, we may use some of the sentences that you said. If we use one of your sentences, it will appear together with your unique identification number for the interview (**for instance, IDI #02).** We also ask you to keep what we discuss in the interview private.

Voluntariness and the right to withdraw

Your participation in this study is entirely voluntary, and there are no consequences if you decide not to participate. If a question makes you uncomfortable and you don't want to answer it, then feel free to skip it. If during the interview or at a later date you have second thoughts, then please feel free to withdraw from the study and if you do we will not consider what you said during the interview. Please, feel free to ask the Student Investigator any questions you may have about this research study.

Compensation

You will not receive any compensation for your participation in this study.

Contact Information

If you would like more information about this research study before deciding to participate, and if you have questions or comments, please contact Mr. Francis Masiye, at any time on the following telephone number; 021 650 1902 and he will answer your questions. You can also contact Dr. Jantina de Vries at 021 650 5716 or Prof Bongani Mayosi at 021 406 6200.If you have concerns about your rights because you think you have not been treated fairly or think you have been hurt by joining the study, you can contact the Human Research Ethics Committee in the Faculty of Health Sciences at the University of Cape Town on 021 406 6338 or write to Shuretta Thomas, Human Research Ethics Committee, Room E52 - 24, Old Main Building, Groote Schuur Hospital, OBSERVATORY 7925.

Signature Page of Consent Form

Have you been provided with sufficient information about the study? Yes ☐ No ☐

	Yes	No
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Have you received satisfactory answers to all your questions?	☐	☐
Do you understand that your participation is voluntary, and that you are free to withdraw from the study at any time?	☐	☐
Do you agree to take part in this study?	☐	☐
Do you agree to be audio-recorded during the interview?	☐	☐

Signature……..Date…….

Name of Study Participant……..

Student Investigator Statement

I confirm that the study participant has understood the information and voluntarily agreed to participate in the study.

Signature…….….Date…….

Name of Student Investigator…….

Appendix III: Information Sheet and Consent Form for RHDGen Research Staff Participating in Participant Observations

Title of the study: **Ethical Challenges in Obtaining Informed Consent in the RHDGen Study**

Student Investigator: Mr. Francis Masiye

Supervisors: Prof Bongani Mayosi and Dr. Jantina de Vries

Introduction

We invite you to participate in a study. This consent form explains the research study you are being asked to join. Please, read it carefully and ask any questions about the study before you agree to join. You may also ask questions at any time after joining the study. If you agree to participate, the Student Investigator will observe your administration of the consent procedures of potential research participant in the RHDGen Study and take notes during the observation. The observation will be anonymised and nobody except the Student Investigator will have access to the notes taken during the consent process except in cases when you give your permission to have them used in the thesis and publications.

Purpose of the study

The purpose of this study is to understand ethical challenges in obtaining informed consent for the genomic epidemiological study on rheumatic heart disease you are involved in as a Research Staff. We hope to use the findings of this study to explore possible interventions for improving ethical challenges in obtaining informed consent in genomic research.

Participants

For this study, the Student Investigator hopes to observe administration of the consent procedures of adult cases and healthy population controls who will be recruited into the RHDGen research project at the Groote Schuur Hospital and in communities within Cape Town.

He will be present at as many consent procedures as possible for both adult cases and population controls until he feels that he has developed a clear understanding of the dynamics of issues in the consent process. If you agree to participate, he will obtain your written consent once before the first participant observation and continue observing the rest of the consent procedures of both adult cases and healthy population controls recruited into the RHDGen study. During each observation, he will take notes and type the notes immediately after the observation. The observation will last at the end of the consent procedures. At the end of this study, we would like to keep the typed notes of the observation. The notes will be anonymous and nobody will know that it was you who administered the consent procedures.

Risks/Discomforts

There are no physical risks in this study. However, you might feel disturbed or tensed with the presence of the Student Investigator during the consent procedures. To minimize this, please, feel free to ask the Student Investigator not to observe and take notes during any of the consent procedures.

Anticipated Benefits

If you decide to participate in this study, you will receive no direct benefits. However, observations of the consent procedures may help researchers better understand challenges you encounter in obtaining informed consent in the RHDGen study. We hope that this study will help us to improve the current informed consent process in genomic and genetic studies.

Confidentiality

We will keep the notes taken during the consent procedures private. Each observation will be assigned a unique identification number. We will only refer to the observation numbers in future. The information collected will be kept in restricted access offices and on password-secured computers. The information will be available to the Student Investigator. The Principal Investigator of the RHDGen study will not have access to the notes. In addition, we will get your permission to the typed notes in the thesis and publications. The typed notes of the observations will be kept until the end of the study. When we report on our findings, we may highlight some of the issues noted during the observations and if we highlight the issues, they will appear together with the observation unique identification number (**for instance, PO #05).**

Voluntariness and the right to withdraw

Your participation in this study is entirely voluntary, and there are no consequences if you decide not to let the Student Investigator observe any of the consent procedures. If during the observation or at a later date you have second thoughts, then please feel free to ask the Student Investigator not to use the notes from the observation and if you do he will not consider the notes taken during the consent process. Please, feel free to ask the Student Investigator any questions you may have about this research study.

Compensation

You will not receive any compensation for your participation in this study.

Contact Information

If you would like more information about this research project before deciding to participate, and if you have questions or comments, please contact Mr Francis Masiye at any time and he will answer your questions. You can contact Mr Francis Masiye at the following number; 021 650 1902. You can also contact Jantina de Vries at 021 650 5716 or Bongani Mayosi at 021 406 6200.If you have concerns about your rights because you think you have not been treated fairly or think you have been hurt by joining the study, you can contact the Human Research Ethics Committee on 021 406 6338 or go to their Office in Room E52 - 24

Signature Page of Consent Form

Have you been provided with sufficient information about the study? ☐ Yes ☐ No

Have you had an opportunity to ask questions and discuss this study? ☐ Yes ☐ No

Have you received satisfactory answers to all your questions? ☐ Yes ☐ No

Do you understand that your participation is voluntary, and that you are free to withdraw from the study at any time? ☐ Yes ☐ No

Do you agree to take part in this study? ☐ Yes ☐ No

Signature……..Date…….

Name of Study Participant……..

Student Investigator Statement

I confirm that the study participant has understood the information and voluntarily agreed to participate in the study.

Signature…….….Date…….

Name of Student Investigator……

Appendix IV: Information Sheet for RHDGen Adult Cases and Controls Participating in Observations

Title of the study: **Ethical Challenges in Obtaining Informed Consent in the RHDGen Study**

Student Investigator: Mr. Francis Masiye

Supervisors: Prof Bongani Mayosi and Dr. Jantina de Vries

Introduction

We invite you to participate in a study. This information sheet explains the research study you are being asked to join. Please, read it carefully and ask any questions about the study before you agree to join. You may also ask questions at any time after joining the study. If you agree to participate, the Student Investigator will observe your consent process into the RHDGen study. The observation will be anonymised and nobody except the researchers will know it was you who was being consented into the RHDGen study.

Purpose of the study

The purpose of this study is to understand ethical challenges in obtaining informed consent for the study on rheumatic heart disease that you are being asked to join. We hope to use the findings of this study to explore possible interventions for improving ethical challenges in obtaining informed consent in genomic research

Participants

For this study, we hope to observe the consent procedures of patients with rheumatic heart disease and people who do not have the disease who are being recruited into the RHDGen research project at the Groote Schuur Hospital and in communities within Cape Town. If you agree to participate, the Student Investigator will be present during the consent process and he will write down notes that are relevant for the observation. The

notes will be typed immediately after the observation. At the end of this study, we would like to keep the typed notes. The notes will be anonymous and nobody will know that it was you who was being consented into the RHDGen study. The observation will last at the end of the consent process.

Risks/Discomforts

There are no physical risks in this study. However, you might feel uncomfortable with the presence of the Student Investigator during the consent process. To minimize this, please, feel free to choose not to have the Student Investigator observe the consent process.

Anticipated Benefits

If you decide to participate in this study, you will receive no direct benefits. However, the notes taken during the observation may help researchers better understand the challenges in obtaining informed consent in the RHDGen study. We hope that this study will help us to improve the current consent process for genomic and genetic studies.

Confidentiality

We will keep the notes taken during the observation strictly confidential. Each observation will be assigned a unique identification number. We will only refer to the observation number in our reports. The typed notes will be kept in restricted access offices and on password-secured computers. The notes will be kept until the end of the study. When we report on our findings, we may highlight some of the issues noted during the observation and if we use them they will appear together with the unique identification number for the observation (**for instance, PO#10).**

Voluntariness and the right to withdraw

Your participation in this study is entirely voluntary, and there are no consequences if you decide not to participate. If you allow the Student Investigator to observe the consent process and during the observation or at a later date you have second thoughts, then feel free to ask the Student Investigator not to use the notes taken during the consent

procedures. And if you do we will not consider the notes. Please, feel free to ask me any questions you may have about this research study.

Compensation

You will not receive any compensation for participating in the observation.

Contact Information

If you would like more information about this research project before deciding to participate, please ask the Student Investigator before the beginning of the consent process at the following number; 021 650 1902. You can also contact Jantina de Vries at 021 650 5716 or Bongani Mayosi at 021 406 6200. If you have concerns about your rights because you think you have not been treated fairly or think you have been hurt by joining the study, you can contact the Human Research Ethics Committee in the Faculty of Health Sciences at the University of Cape Town on 021 406 6338 or write to Shuretta Thomas, Human Research Ethics Committee, Room E52 - 24, Old Main Building, Groote Schuur Hospital, OBSERVATORY 7925.

Participant Observation Number: _____

Verbal Consent for the Observation

Do you agree to take part in this study? ☐ Yes ☐ No

Appendix V: In-Depth Interview Guide for RHDGen Adult Cases and Controls

Title of the study: **Ethical Challenges in Obtaining Informed Consent in the RHDGen Study**

Student Investigator: Mr. Francis Masiye

Supervisors: Prof Bongani Mayosi and Dr. Jantina De Vries

1. **Knowledge about genetics**

    a. What do you understand by the term “genetics”? (Probe: what she/he knows about genes, DNA and genetic mutation)
    b. Why are genetic studies conducted?

2. **Knowledge about the RHDGen Study**

    a. Please, tell me about the study you joined (Probe: what was the purpose of the study or why the study is being conducted)
    b. Can you tell me a little bit about your disease? (Prompt: are participants familiar with the term Rheumatic Heart Disease/ Valve Disease)
    c. Please, explain to me the procedures that were followed during your recruitment and participation in the study (Probe about the consent procedures and study procedures)
    d. How did you feel about being in the study and why?

3. **Understanding of information disclosed during the consent process**

    a. Can you remember what the nurse told you about the study? (Probe about the types of sample that were being collected and why they were being collected)
    b. Did she say anything about risks or benefits involved? (If yes, what were the risks of the study and what were the benefits of the study?
    c. Did she tell you about the study procedures? What did the nurse tell you about genetics?

d. What did the sharing of your samples and data with other researchers mean to you?

e. What do you think about giving permission for the use of your samples and data in future research?

f. Were you satisfied with the information which was given to you about the study? (Probe why or why not?

g. What things helped you to understand the study? (Probe: Ask her/him to explain what could be done to ensure understanding of the information)

4. <u>Voluntariness of decision to participate in the study</u>

a. Why did you choose to participate in the study? Or what motivated you to join the study?

b. Did you feel any pressure, from any source, to participate in the study (If so, from whom and can you elaborate)?

c. Did you inform your family about your participation in the study? If yes or no, why?

d. What problems (if any) did you face during your participation in the study and what do you think can be done to minimize such problems?

5. <u>Suggestions for improving the consent process</u>

a. What can be done to improve the consent process and the recruitment in this study?

b. Is there anything that we didn't discuss that you would like to mention or talk about?

<u>THANK YOU VERY MUCH FOR YOUR PARTICIPATION!</u>

Appendix VI: In-depth Interview Guide for RHDGen Research Staff

Title of the study: **Ethical Challenges in Obtaining Informed Consent in the RHDGen Study**

Student Investigator: Mr. Francis Masiye

Supervisors: Prof Bongani Mayosi and Dr. Jantina de Vries

1. What do you know of the RHDGen study, can you briefly describe it to me?
2. What are your experiences with seeking IC for this study? (Prompt: particular challenges? What do you find difficult?)
3. How do you explain the concepts of genes, genetics, DNA and data release to potential research participants?
4. Do you link these explanations specifically to participants' disease?
5. Do you think potential participants understand the concepts of sample sharing and data sharing?
6. Do people ask you questions about the study? If so, what questions do you get?
7. Do people refuse and why?
8. Do you think your role as a Research Nurse affects the decision potential participants make to join the RHDGen study or not and why do you think so?
9. Do you try to ensure that potential participants understand the RHDGen study?
10. In your opinion, what factors hinder potential participants' understanding of the study?
11. What information do potential participants find difficult to understand and why do you think so?
12. What aspects of the study do you find difficult to explain to potential study participants?
13. How do you ensure that their decision to participate in the study is voluntary?
14. Do you face any challenges when you are recruiting patients from the clinic versus the Clinical Research Centre? If so, what are the challenges?

15. In your opinion, are there any differences between recruiting patients in the hospital and recruiting healthy volunteers in the communities? If so, what are the differences and where is it easy to recruit potential participants and why?
16. How best should the consenting process be obtained from potential research participants in the RHDGen study?

THANK YOU VERY MUCH FOR YOUR PARTICIPATION!

Appendix VII: IDI DEMOGRAPHIC DATA FORM FOR RHDGEN RESEARCH STAFF

TITLE OF STUDY: Ethical Challenges for Obtaining Informed Consent in the RHDGen Study

NAME OF INTERVIEWER: _____

VENUE/SITE OF INTERVIEW: _____

NAME OF RESPONDENT: _____

TYPE OF RESPONDENT: _____

DATE OF INTERVIEW: _____

TIME START: _____ TIME FINISH: _____

Subject ID No.	Specific roles in RHDGen Study

Appendix VIII: IDI RESPONDENT DEMOGRAPHIC DATA FORM FOR CONTROLS AND CASES

TITLE OF STUDY: Ethical Challenges in Obtaining Informed Consent in the RHDGen Study

NAME OF INTERVIEWER: _____

RHDGEN PARTICIPANT NUMBER: _____

VENUE/SITE OF INTERVIEW: _____

TYPE OF RESPONDENT: ☐ **Control** ☐ **Case**

TIME SINCE RECRUITMENT INTO RHDGEN STUDY: Same Day ☐ **Later** ☐

No. of months_____

DATE OF INTERVIEW: _____

TIME START: _____ TIME FINISH: _____

Subject ID No.	Sex	Age	Highest education achieved	1st Language	Occupation	Religion	Location/Community