Participants' perceptions, experiences and the factors motivating their participation with the informed consent process of a COVID-19 vaccine trial in South Africa.

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KEYWORDS

Informed Consent

Clinical Trial

Research Participants

Ethical Guidelines

COVID-19 Vaccine Trial

ABSTRACT

Background and Objectives: The informed consent process is an important step in conducting ethical clinical trials, as it ensures that research participants are aware of their rights and responsibilities in clinical trials. This study explored participants' perceptions, experiences and the factors motivating their participation with the informed consent process of a COVID-19 vaccine trial in South Africa.

Methods: This descriptive qualitative study was conducted on COVID-19 vaccine study participants between 18 to 65 years, between November 2021 and January 2022. There were 25 participants interviewed for this study. Data was collected using semi-structured interviews and focus group discussions. The data was analysed iteratively using a thematic analysis approach.

Results: Participants who experienced an event (e.g., tested positive for COVID-19) during their participation in the clinical trial talked about the informed consent process more thoroughly compared to the other participants. Participants said they understand the purpose of informed consent better when elements of the informed consent process are repeated throughout the study. Although participants spoke positively about the informed consent process, most of them did not understand or recall the details of the process and came up with their own interpretations of elements covered in the informed consent document. Reimbursement was not the only factor affecting participants' decision to participate in the COVID-19 vaccine trial. Other motivations related to them wanting access to health care and them wanting to protect their families through

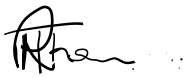
the potential benefits of the vaccine, as well as personal gain, where they could continue to socialize without fear of severe COVID-19.

Conclusion: The informed consent process needs to be ongoing process throughout a clinical trial and not a once-off event at the start of a clinical trial. It is important to understand participants' perspectives, experiences, and motivations for participating in clinical trials, to optimise consent documents and processes.

DECLARATION

I declare that *Participants' perceptions, experiences, and the factors motivating their participation with the informed consent process of a COVID-19 vaccine trial in South Africa* is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full name: Thandeka P Nkosi Date: 29 July 2022

Signed: 

This mini thesis is dedicated to the late

Thandiwe Cynthia Nkosi.

Mom, I did it.

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ACRONYMS AND ABBREVIATIONS

COVID-19	Coronavirus Disease of 2019
FGD	Focus Group Discussions
SA GCP	South African Good Clinical Practice
ICH GCP	International Conference of Harmonization-Good Clinical Practice
NOVAVAX	A PHASE 2A/B, Randomized, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Immunogenicity, and Safety of a SARS-COV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-COV-2 RS) with MATRIX-M1™ Adjuvant in South African Adult Subjects Living Without HIV; and Safety and Immunogenicity in Adults Living with HIV.
HPCSA	Health Professions Council of South Africa

DEFINITION OF KEY TERMS

Consent in research is defined as the process by which a potential research participant voluntarily confirms his or her willingness to participate in a particular research study (e.g., clinical trial), after having been informed of all aspects of the study that are relevant to the participant's decision-making to participate. Informed consent is documented using a written, signed and dated informed consent form (Black Country Partnership, 2018).

Informed Consent is a founding principle of research ethics, and its goal is to ensure that human participants are fully informed before they agree to participate in a research study (University of Oxford, 2019). Informed consent means that sufficient information is provided to the potential participant to make an informed decision and that the potential participant understands the information, including the risks and benefits of participation (SAMA, 2012).

Informed consent process is defined as the process of telling potential research participants about the key elements of a research study and what their participation will involve (University of Michigan, 2018). The informed consent process is central to the conduct of ethical research involving human participants (University of Michigan, 2018).

Ethical pertains to something relating to moral principles or the branch of knowledge dealing with morals (Oxford Languages, 2021).

Good Clinical Practice (GCP) A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides

assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected (ICH Harmonisation for better Health, 2016)

Contents

CHAPTER ONE: INTRODUCTION

Informed consent

Although medical ethicists generally believe that for consent to be effective it needs to be informed, the phrase "informed consent" has raised questions about the procedures involved in obtaining it (Turillazzi & Neri, 2015). Informed consent is a primary principle that sets the framework for protecting participants in research (U.S Department of Health & Human Services, 2018). The concept of informed consent is a fundamental component of modern medical practice, which allows patients (participants) to make their own decisions regarding their health care (Pietrzykowski & Smilowska, 2021). However, it is still not clear whether patients understand the various components of informed consent. This issue undermines the ethical basis of clinical trial practice and raises concerns about patients' participation in the decision-making process (Pietrzykowski & Smilowska, 2021). In addition to being able to sign and read the form, informed consent also involves oral communication, which helps establish a stronger relationship between participant and researcher or patient and physician. Some believe that having a well-defined and objective decision-making process is a prerequisite for good practice (Makoul, 2003; Agozzino et al., 2019). Informed consent is also about the information that is included in the form, such as the risks and benefits associated with the proposed surgical procedure (Agozzino et al., 2019). In most cases, obtaining a patient's signature is a formal act that involves ensuring that they have been informed about the necessary steps to receive a medical intervention. Physicians consider this act to be a necessary part of their patient's care (Turillazzi & Neri, 2015). The goal of informed consent is to allow competent individuals to make an informed decision regarding participating in a study.

This is done by providing the study's potential participants with the necessary information (Wendler & Grady, 2008). In addition to being able to participate in a study, informed consent also allows individuals to decide whether they want to participate. This is done by providing the study's potential participants with the necessary information (Wendler & Grady, 2008). However, informed consent also has other goals and objectives that are not related to the study's objective. These include making sure that the researchers do not violate the participants' rights to privacy and bodily integrity.

Autonomy, beneficence, non-maleficence and justice and the informed consent

There are four principles of biomedical ethics which are autonomy, beneficence, non-maleficence and justice (Beauchamp & Childress, 2019). The concept of autonomy is one of the most important ethical principles that the informed consent considers. Autonomy allows individuals to have for themselves the freedom to make their own decisions regarding their participation as they see fit, and it is permitted by law and ethical evidence. However, autonomy is also possible only as a result of an adequate information (Agozzino et al., 2019). The Belmont report bases the obligation to obtain consent from research participants on the broad ethical principles of Respect for Persons, Beneficence and Justice (Department of Health, Education, and Welfare and National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2014. The concept of respect for persons has at least two ethical principles. One is that individuals should be regarded as autonomous agents, while the other is that those with diminished autonomy should be protected (Anabo et al., 2018). Beneficence is seen as an obligation (U.S Department of Health & Human Services, 2018), acting in such a way to benefit others while promoting their welfare and safety (Beauchamp, 1990). Two general rules are

formulated to guide the actions of beneficence: (1) do not harm and (2) maximize possible benefits and minimize possible harms (Anabo et al., 2018). The ethical principle of non-maleficence also appears within the Belmont Report's section on beneficence (Barrow & Khandhar, 2019). Non-maleficence is the ethical and legal duty to avoid harming others (Beauchamp & Childress, 2008). Lastly, the principle of justice pertains to participants' right to fair treatment and right to privacy (Anabo et al., 2018)

The concept of autonomy should be incorporated into the informed consent process to ensure that patients have the right to make their own decisions regarding their treatment. However, this concept can be very challenging to implement due to patients' limited understanding of the information (Neff, 2008; Durand et al., 2015). The importance of the informed consent process is acknowledged by both the legal and ethical foundations of medicine (Pietrzykowski & Smilowska, 2021). However, Pietrzykowski & Smilowska (2021), say that it is very challenging to obtain adequate consent from patients due to the complexity of the situation. This process involves the discussion of various factors such as the patient's condition, therapeutic options, and the possible side effects of the treatment, as well as the risks and benefits, inconveniences, and uncertainties.

Potential participants' decisions about participating in research studies are usually based on information, comprehension, and voluntariness (Chadwick & Dunn 1999). This means, that providing potential participants with sufficient information is imperative, including information on the study aims and objectives, research procedures, potential risks and anticipated benefits, their rights to ask questions and/or withdraw from the study any time (Nandra et al., 2020). The ability to understand information is a function of various factors such as literacy and language, therefore it is necessary to adapt the presentation of the information to the potential participant's capacities

(Nandra et al., 2020). Participants' understanding of the various components of informed consent is crucial and suggests that participants need to have the necessary knowledge to make informed decisions. This would strengthen the ethical basis of clinical trial practice and lessen concerns about patients' participation in the decision-making process. To ensure that patients have the necessary understanding of the various factors involved in the informed consent process, a form should be made available to them where they are required to read and sign. This should also include oral communication to help them make informed decisions and ensure that they fully understand and are voluntary participants in clinical trials (Manti & Licari, 2018).

Understanding Clinical Trials

A clinical trial is a primary method used by researchers to evaluate a new treatment or procedure (National Institute on Aging, 2020). Clinical trials involve testing the safety and effectiveness of a new drug and are usually conducted to find out if a new treatment is more beneficial than the standard one (National Institute on Aging, 2020). Clinical trials also aim to confirm that the new treatment has less harmful side effects (National Institute on Aging, 2020). Through clinical trials, volunteers are able to participate in studies that are conducted with the help of investigators who are committed to carrying out their studies according to the best ethical and scientific practices (Priyanka and Thomas, 2020). The requirements for the registration of clinical trials were first established by the U.S Food and Drug Administration (FDA) Modernization Act of 1997. The act established a database that allowed for the public to access the details of the clinical trials of investigational drugs being used for treating life-threatening conditions (Priyanka and Thomas, 2020). Clinical trials are controlled by regulatory bodies in various jurisdictions including the U.S.

Food and Drug Administration (US-FDA) for trials being conducted in the US, European Medicines Agency (EMA) for trials being conducted with the European Union, and in South Africa, the South African Health Products Regulatory Authority (SAHPRA). The clinical trial process is conducted over different phases, Phase I-IV, designed to evaluate the safety and effectiveness of a new drug in humans (Ng, 2015).

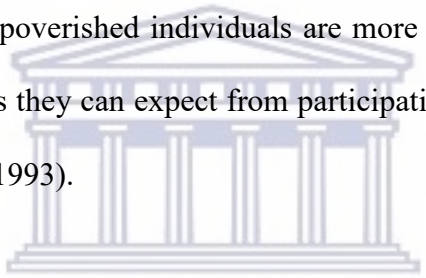
In the first phase, the drug is administered to a small number of participants to find out if the drug can perform as expected (Hughes et al., 2011). If successful, the next step is to carry out further studies to assess the drug's tolerance and safety (Hughes et al., 2011). The goal of phase II is to determine the therapeutic efficacy of an investigational new drug in patients (Hughes et al., 2011). The study's population is defined by the exclusion and inclusion criteria, and the dose or dose range that was determined in the first phase is used to evaluate the drug's safety and effectiveness (Hughes et al., 2011). During phase II, researchers carefully monitor the participants to ensure that they are taking the right dose. They also analyse the data to determine the optimal dose regimen for phase III (Friedman, Furberg, and Demets, 2015). Unlike the first phase, phase III studies are conducted with a larger number of participants. They also have a longer duration, which allows them to identify long-term side effects (Umscheid, Margolis and Grossman, 2011; Friedman, Furberg and Demets, 2015). Phase IV studies are usually conducted after the approval of a new drug by regulatory agencies and are long-term studies that involve thousands of participants (Umscheid, Margolis and Grossman, 2011; Friedman, Furberg and Demets, 2015). Phase IV studies are also designed to gather additional information about the drug's safety and effectiveness and if the results of these studies show that the drug is safe and effective, then it can be used for new indications (Umscheid, Margolis and Grossman, 2011; Friedman, Furberg and Demets, 2015).

Besides the biomedical factors that can be considered when it comes to conducting a clinical trial, other factors such as race, sex, and age can also affect the success of the study (Murthy, Krumholz and Gross, 2004). The success of a clinical trial may also be impacted by knowledge of the risk, attitudes and perceptions towards participation in clinical trials (Asai et al., 2004; Featherstone and Donovan, 2002).

Clinical trials in low- and low-middle-income countries (LMICs)

There has been an increase in the number of clinical trials being conducted in developing countries (Grover et al., 2017). The low cost of conducting a study, the availability of eligible participants, and the country's improving regulatory and operational capacity are some of the factors that have led to the increasing number of clinical trials being conducted in developing countries (Grover et al., 2017; Devasenapathy, Singh and Prabhakaran, 2009).The principles of a clinical trial are generally designed to ensure that the participants have a complete understanding of the study's various aspects and that they have informed consent (Gaul et al., 2006). Besides this, factors such as the motivation of the participants and the type of study that they are participating in can also affect the decision to participate (Gaul et al., 2006). Participants' motivation to participate in a clinical trial can vary depending on the type of study they are participating in. For instance, individuals might be motivated to participate in the study due to their desire to improve their knowledge about medical science or to help others (Gaul et al., 2006). Some people might also be motivated to participate in a clinical trial due to the possibility of getting better quality of care. However, this is not the only reason why people might want to participate in a study (Gaul et al., 2006). There are additionally concerns about the ethical issues involved in conducting a clinical

trial in developing countries (Gaul et al., 2006). Some people might also be motivated to participate in a clinical trial due to the possibility of getting better quality of care (Gaul et al., 2006). Despite the various factors that have contributed to the increasing number of clinical trials being conducted in developing countries, there is still a growing concern about the ethical issues involved in conducting the study (Weigmann, 2015). An inherent bias might develop when it comes to conducting a study in low-resource settings due to the varying characteristics of the population. These include their lack of education, poverty, and health care (Emanuel et al., 2004). Participants in clinical studies may not have the necessary knowledge about the study's procedures and may not participate in the study due to their lack of access to quality medical care (Almeida et al., 2007). Studies have also shown that impoverished individuals are more likely to participate in clinical trials due to the financial benefits they can expect from participating (Almeida et al., 2007; Kass et al., 2007; van Gelderen et al., 1993).



The ethical challenge of conducting clinical research in low- and middle-income countries is to ensure that informed consent is not undermined by potential coercion. Due to the various vulnerabilities that can be encountered in the informed consent process in low- and middle-income countries, there has been a debate about the validity of this process, questioning research participants' competence, comprehension and voluntariness. Literature has been focused on concerns of coercion due to unequal power dynamics and socio-economic disadvantages (St. Fleur and Schwartz, 2019; Fitzgerald and Wasunna, 2005; Shapiro and Meslin, 2001)

Participants' perceptions, experiences and motivations in research studies

There are various issues affecting participants' perceptions, experiences, and motivations when it comes to participating in research studies. Issues influencing participants' choices in research studies may be linked to their literacy levels, financial incentives, gender, race, and socio-economic status (Murthy et al.,2004; Kurt et al., 2016; Giuliano et al., 2000; Huang et al., 2013; George et al., 2014; Farmer et al., 2007; Langford, Resnicow & An, 2010). There are multiple factors influencing potential participants' decision-making, including the clinical staff with whom they interact, the quality of clinical care, and the communication from the research staff (Kurt et al., 2017). According to Pietrzykowski & Smilowska (2021), the most common barriers to obtaining adequate consent from patients are their perception of the quality of the information that they receive. Pietrzykowski & Smilowska (2021) further state that the concept of autonomy is also based on the assumption that the process of obtaining informed consent provides patients with the necessary information to make informed decisions, however, unless this assumption is proven to be true, the current ethical framework for medical experimentation is seriously flawed. Despite the various regulations and codes that have been established to govern the conduct of clinical research, the importance of voluntarism has not been fully practiced (Roberts, 2002). This could help in maintaining the principle of respect for people. Voluntarism is a concept that refers to an individual's ability to judge without independently and freely being coerced and it allows individuals to make their own decisions based on what is best for them and their situation (Roberts, 2002). According to Roberts (2002) and Geppert and Abbott (2007) there are several factors that may affect voluntarism of a participant and these include, "intellectual and emotional maturity to make complex decision; illness-related considerations such as psychological effects of dreaded or

incurable diseases or severe mental disorders; religious and cultural values and beliefs such as catholic beliefs regarding moral action at the beginning and end of life; relationship with caregiver including economic and care burden; and undue influence or coercion for research participation." These factors highlight the need for protection of participants, particularly those that are considered vulnerable, those with limited or no previous experience, and therefore special precautions should be taken to ensure that they are consenting properly.

Valid consent and making an informed decision

To obtain a valid consent, a research participant should be provided with information about their health condition and the proposed study's purpose (Office for Human Research Protections, 1979; Gupta, 2013; ICH Harmonisation for better Health, 2016). This should include, but is not limited to, the type of treatment and intervention that the study will involve, the nature of the illness, the possible outcome of the study, and the availability of alternative treatments, and the right to withdraw at any time (Office for Human Research Protections, 1979; Gupta, 2013; ICH Harmonisation for better Health, 2016). Besides these, other information should also be provided to help the participant make informed decisions (Office for Human Research Protections, 1979; Gupta, 2013; ICH Harmonisation for better Health, 2016). This type of information disclosure is an essential part of a valid consent that should help the participant make an informed decision regarding the study (Gupta, 2013). Although the information disclosure process is generally straightforward, it can be very challenging in real-life situations (Gupta, 2013). For instance, how much information should be provided on certain aspects of the study, such as the risks associated with the intervention and the possible outcome of the study, is not clear. This is because the

approach taken by the investigator is often based on the subjective nature of the study (Gupta, 2013). In addition, if the researcher intentionally presents the information with a biased perspective to get the participant to make a decision, this could invalidate the consent (Manisha, Asmita and H. U., 2018). This type of information disclosure should be conducted in a manner that is free from fraud, coercion, and any biased perspective.

To demonstrate their capacity to make informed decisions, participants should be able to analyze and interpret the information that they have been given (Gupta, 2013). They should also be capable of communicating their voluntary decisions. Although there is a clear definition of what a capable individual should be able to understand, there is still a lot of confusion regarding the level of understanding that is required to be considered adequate (Gupta, 2013). For instance, how much information should be considered enough to make an individual competent? (Gupta, 2013)
Literature demonstrates the importance of participants voluntary and informed decision making. Getting the participant's baseline understanding of the study's goals and procedures is also important to ensure that he or she has the necessary information to make an informed decision. This information should include details about the study's randomization process and treatment.

This study therefore looks at participants recruited to a COVID-19 vaccine clinical trial and aims to understand research participants' perceptions of and, experiences with the informed consent process of a COVID-19 vaccine trial in South Africa; including the factors motivating them to participate in the trial. The COVID-19 vaccine trial is A Phase 2 a/b, Randomised, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Immunogenicity, and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-

M1™ Adjuvant in South African adults Living without HIV; and Safety and Immunogenicity in Adults Living With HIV. The abbreviated description is that it is a COVID-19 vaccine (SARS-CoV-2 rS with Matric-M1 adjuvant) trial conducted in South African adults with and without HIV infection. The trial sponsor is NOVAVAX, Inc., and so the study was commonly known as the NOVAVAX study by both staff and participants. For the purpose, this thesis the trial will be referred to as the COVID-19 vaccine trial. The study was conducted in Kwa-Zulu Natal, Durban, Umlazi Town at Prince Mshiyeni Memorial Hospital.

Problem Statement

The COVID-19 pandemic has raised the urgency for the development of a vaccine that can prevent the virus (Excler et al., 2021; Organization for Economic Co-operation and Development, 2021). In recruiting participants into a COVID-19 clinical trial, the informed consent process is a key step in ensuring that potential participants understand the purpose of the trial and their role, rights, and responsibilities in participating in the trial. According to empirical research, the process of providing informed consent often lacks adequate information for people with low health literacy, for example "the expectation of detailed information recall from a document that is often more than 20 pages is not realistic" (Sherlock & Brownie, 2014; Sugarman, 1999). The need for improving the informed consent process has been documented by various studies (Grinnell, 1990; Baker & Taub, 1983; Agre et al., 2003; Hekkenberg et al., 1997; Katz, 2002; Alper & Institute of Medicine (U.S.) Roundtable On Health Literacy, 2015).

There is a need to better understand research participants' perceptions and experiences with the informed consent process, including the factors influencing or motivating them to participate in research in South Africa. There are no studies to our knowledge that have been conducted in South Africa to explore experiences, perceptions and factors that motivate individuals to participate in the COVID 19 clinical trials. This research gap will be explored in the context of a COVID-19 vaccine trial in South Africa called A Phase 2 a/b, Randomised, Observer-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Immunogenicity, and Safety of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine (SARS-CoV-2 rS) With Matrix-M1™ Adjuvant in South African adults Living without HIV; and Safety and Immunogenicity in Adults Living With HIV. Also known as the NOVAVAX study. The NOVAVAX study was conducted in KwaZulu-Natal, Durban, Umlazi at Prince Mshiyeni Memorial Hospital. Recruitment started in September 2020 and was over a period of 12 months.

CHAPTER 2 LITERATURE REVIEW

Introduction

To ensure that the participants are informed about the potential benefits of the treatment, the informed consent should contain information that's designed to help the participants make an informed decision (Joffe et al., 2001). Despite the various methods that have been used to improve the understanding of informed consent in clinical trials, many aspects such as potential discomforts, study risks and benefits and the issue of confidentiality, remain uninformative (Brehaut et al., 2015). Many of the documents that are used to make informed decisions do not meet the standards for promoting good decision-making (Koh et al., 2011).

History of the Informed Consent

Although the concept of informed consent first appeared in 1957, it has only been considered and discussed more seriously since 1972 (Encyclopedia.com, 2019). As it evolved, the concept moved away from a narrow focus on the obligation of a physician to divulge information to a patient; to the quality of a patient's (or participant's) understanding of information and right to authorize or refuse a biomedical intervention (Encyclopedia.com, 2019). There are several international standards and principles that guide the activities of biomedical researchers. These principles and codes aim to protect the rights and welfare of the participants in scientific research, for example, captured in the Nuremberg Code 1947, the Declaration of Helsinki 1964 (amended 2000),

the Belmont Report 1979, the CIOMS Guidelines 1982 (amended 2002), and the Ethical Considerations in Biomedical HIV Prevention Trials: UNAIDS Guidance Document 2007 (Fischer, 2005; Silaigwana, 2017).

Before the Second World War, research ethics were not as influential as they are now. The Nuremberg trials, held for the purpose of bringing Nazi war criminals to justice, were one event that really changed how we think about consent (Military Tribunals & International Military Tribunal, 1949). The Nuremberg Code condemned the Nazi experiments conducted in Germany (Military Tribunals & International Military Tribunal, 1949). The Nuremberg military tribunals unambiguously condemned the sinister political motivation of Nazi experiments in their review of "crimes against humanity." (Military Tribunals & International Military Tribunal, 1949). A list of ten principles constituted the Nuremberg Code. One of the principles of the Code states that the primary consideration when it comes to research is participants' voluntary consent (Military Tribunals & International Military Tribunal, 1949). The Nuremberg Code also emphasizes that the individual who consents must have the necessary knowledge and understanding to make an informed decision, this includes the ability to clearly understand the terms of the research (Katz, 1996). Examples of unethical research have been shown to have violated the rights of individuals and ignore the principle of voluntary participation. A study was conducted in the early 1930s in Tuskegee, Alabama. The objective of the study was to look into the progression of syphilis in black men (Rosner, 1996; Jones & Tuskegee Institute, 1993). Although the study was not financially supported, the participants were still provided with various incentives to participate which were in effect indirect inducement to participate (Rosner, 1996; Jones & Tuskegee Institute, 1993). Participants were enrolled under false pretention of being provided with healthcare services

(Rosner, 1996; Jones & Tuskegee Institute, 1993). This was because they believed they were receiving treatment for a supposedly ill-defined condition. Treatment was not made available, and this information was concealed form the research participants (Rosner, 1996; Jones & Tuskegee Institute, 1993). The study continued despite not adhering to ethical procedures (Emanuel, 2003, States. et al., 1973). It was only later that discussions were held, and the study was halted due to unethical practices (Emanuel, 2003, States. et al., 1973).

Through history, there has been more learnt about the rights of individuals when it comes to participating in clinical trials which has helped address the various challenges that come with conducting studies on participants. Due to the nature of early-phase clinical trials, it is hard for patients to complain about not knowing the full intent of the study, as they have to sign informed consent forms that clearly state the details of the trial (Kimmelman, 2008; Piantadosi, 2008; Fetting et al., 1990; Piantadosi, 1990; Kim, 2006). Despite the legal requirements that require patients to sign consent forms, many studies show that even after learning about the lack of efficacy of the phase I trials, many of them still believe that the trials will benefit them (Kimmelman, 2008; Piantadosi, 2008; Fetting et al., 1990; Piantadosi, 1990; Kim, 2006). Unfortunately, many patients are not always informed about the potential advantages of the various treatment options that are available to them at the same time, or at other research facilities. They are also likely to be subjected to the same kinds of situations and choices that they were previously exposed to during the infamous Tuskegee Syphilis Study (Lowenstein et al., 2009). Despite the various restrictions that were previously placed on patients in the 1930s, participants now have more protections than those enrolled in the Tuskegee Syphilis study. Despite the various advantages of early-phase clinical trials, there are still concerns about their safety and quality. For instance, the situation that

patients experienced in the infamous Tuskegee study is still relevant to the current situation (Frank et al., 2008; Kim et al., 2005).

During the 1980s, a cervical precancer study conducted in New Zealand was also heavily criticized due to its unethical nature. This incident highlighted the failure of professional standards in conducting studies (Campbell, 1989). The National Women's Hospital study, on the other hand, had many similarities to the infamous Tuskegee study. Although the defense of the experiment is not new, the details surrounding the study have been regarded as misleading and ethically questionable. It was reported that the study was conducted on women with carcinoma in situ, but not treated (Jones, 2017; Coney, 1988). Following the revelations about the Tuskegee study, the US Congress enacted the Belmont Report (Department of Health, Education, and Welfare & National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2014). The New Zealand study was also subject to a judicial inquiry, which resulted in the establishment of a code of patients' rights (Coney et al., 1988). The similarities between the two studies are striking. Both followed the natural course of an illness, the adverse effects of the studies were detailed in reports that were published before the studies were stopped (Paul & Brookes, 2015). During this period, the investigators tried to prevent the participants from receiving treatment elsewhere and mostly they both did not seek informed consent (Paul & Brookes, 2015). Aside from the suffering endured by the individuals involved, the ‘subjects’ were not informed about their participation in the studies. They were essentially being used as guinea pigs for medical research. This violation of their rights to be informed about their participation in human studies violated two of the most fundamental principles of informed consent, autonomy and decision-making. The Nuremberg Code in 1948 and the World Medical Association's

Declaration of Helsinki in 1964, were two legal documents already existing at the time and had been accepted at legal documents that had identified ethical restrictions for medical research on humans. The Nuremberg Code stated that an individual's consent should be voluntary, competent, informed, and understandable. It also stated that before an experiment or study can be conducted, a careful review of science or the scientific literature is required to determine if it should be carried out (Annas, 2012).

In 1980, the American College of Obstetricians and Gynecologists (ACOG) issued a policy statement that acknowledged the importance of informed consent. It was then revised in 1992 and 2004 (Young, 2005). The policy statement discussed various ethical considerations related to informed consent. According to the policy statement, the concept of informed consent is about understanding and free consent. It also acknowledges that attaining informed consent can be challenging. Some of the factors that can prevent people from fully understanding and consent include the social imbalance in the relationship between patients and providers, race, class, and gender biases, and the actions and attitudes of institutions and individuals(Young, 2005; Maccullough and Chervenak, 1994) . In terms of medical research, some groups are especially vulnerable: the elderly, the poor, the ignorant, ethnic minorities, the disabled, and women in labor. These groups are often not informed about the procedures and techniques involved in their care.

The actions of the participating physicians in the study, which took place from 1932 to 1980, have raised ethical and moral issues. It was also revealed that they did not inform the participants about the study's possible outcomes. Due to the controversy surrounding the studies, informed consent has been introduced as a means of protecting patients' welfare. In spite of this and the various ethical guidelines that have been established for conducting clinical trials in Africa, they are still

not always followed. This puts the participants at risk of experiencing harm or having their rights violated. WEMOS, an organization founded by a group of Dutch medical students who advocate for the right to health for all; access to health services and protection against threats to health in LMICs; published a summary of four country reports about clinical trials (Egypt, South Africa, Zimbabwe, and Kenya) (WEMOS, 2017). Although the regulations and rules for conducting clinical trials vary significantly in each country, WEMOS found common ground that could lead to systemic problems. For instance, participants were not always informed about the details of their participation in a trial because researchers were not always transparent about this (WEMOS, 2017). Many people agreed to participate in a clinical trial due to the need for treatment, as it was the only way they could get the necessary health care in their country (WEMOS, 2017). This issue highlights the importance of informed consent in the Declaration of Helsinki. It is a crucial aspect of the ethical guidelines that apply to conducting clinical trials. The consent process in these countries was therefore not always voluntary or informed, therefore violating the ethical guidelines of the Declaration of Helsinki. The report also found that financial compensation for those who suffered physical harm due to a trial, was difficult to receive (WEMOS, 2017).

Although the various aspects of legislation and infrastructure in Egypt, Kenya, South Africa, and Zimbabwe differ, the report found common ground when it came to preventing the unethical conduct of clinical trials. Many institutions that are responsible for overseeing clinical trials lack the necessary resources to properly monitor the activities of the trials (WEMOS, 2017).. The involvement of multiple bodies in the approval process also affected the protection of the participants. Another issue that highlighted the unethical conduct of clinical trials is the recruitment of patients by doctors and researchers who are paid a lot of money to join ethics

committees (WEMOS, 2017). Another alarming finding of the report was that many vulnerable trial participants were not given proper justification for participating in placebo-controlled trials. This issue is especially worrying since the effects of these trials on the participants can be severe. In countries with weak oversight and fragile health systems, it is difficult to provide adequate follow-up care for the injured participants (WEMOS, 2017). The CIOMS Guidelines and the Declaration of Helsinki, provide the right to post-treatment access to patients participating in clinical trials. However, accoding to the report, despite these guidelines, many companies still do not provide this facility to their trial participants (WEMOS, 2017).

Although the right to participate in clinical trials is clearly stated in the CIOMS Guidelines and the Declaration of Helsinki, the report has shown that many of the trials were not designed to develop new drugs that could benefit the public health. Instead, they were conducted to protect the market share of the company's existing products (WEMOS, 2017).

Informed Consent -An African Context

Despite the steady increase in the number of clinical trials conducted in Africa over the past five years, the continent's research still remains low in proportion to its population size (Global Data Healthcare, 2022). A review of the 21 studies that were conducted on the topic of informed consent in African research settings revealed that the participants' comprehension of the concept was often poor. This suggests that there is a need to develop a better definition of informed consent in order to help improve the quality of studies conducted in this region (Afolabi et al., 2014). According to researchers, it is important that the international standards of good practice are maintained in order

to address the various local factors that affect the quality of studies being conducted in this region (Bull et al., 2012). For instance, the participants' understanding of the trial's purpose and the risks involved in participating are very important. Therefore, it is important to study how informed consent procedures can be effective in communicating this information to the participants. Researchers often carry out studies in developing countries without considering the various cultural and socioeconomic backgrounds of the individuals they are recruiting. This means that they do not always follow the universal ethical guidelines, for example the informed consent, when it comes to conducting studies with these populations (Appiah, 2021). Despite the universal ethical guidelines, many researchers still do not consider the extent to which the informed consent rests on the cultural and traditional practices of the individuals they are recruiting when it comes to conducting studies (Appiah, 2021). According to Appiah (2020), in Sub-Saharan Africa, cultural norms can have a significant influence on the way people communicate and behave. This makes it important that the process for obtaining informed consent is conducted in a way that is sensitive to the individuals' needs. The reason for this is that the concept of individual autonomy is also reflected in the guidelines' recognition of the autonomy of individuals (Nishimura et al., 2013). This is because the guidelines adopt a consent model that emphasizes the importance of individual autonomy (Nishimura et al., 2013). In settings where literacy and poverty are low, it is possible that participants and researchers may have different views about the informed consent process. This could be due to the varying interpretations or conceptualizations and comprehension of the problem under study (Appiah, 2020). Language barriers can also affect how participants understand the informed consent process (Kruger et al., 2014; Appiah, 2020; Msoroka & Amundsen, 2017). For instance, if the consent forms are not made available in the native language of the participants, their understanding of the process can be affected. Although it is desirable to

have a universal guideline for obtaining informed consent, it is also important to consider the various factors that can affect the way participants understand the process (Kruger et al., 2014; Appiah, 2020; Msoroka & Amundsen, 2017). These include the varying sociocultural perspectives of collectivistic and individualistic societies, as well as the need for more effective communication with the participants (Kruger et al., 2014; Appiah, 2020; Msoroka & Amundsen, 2017). In rural areas in Sub-Saharan Africa, the decision-making process for participating in a research project may involve discussions with family members and other individuals such as community members. This could also affect the participant's decision to participate in the research project (Appiah, 2020).

Understanding Informed Consent in the South African context- SA GCP 2020

In South Africa, the ethical principle of informed consent is enshrined in both the Constitution and the National Health Act 2003, highlighting its importance (Staunton, 2015). The national guidelines (sections 6, 7 and 8) on research ethics require that all participants be informed about the various aspects of the study, including the risks and benefits of participating (Britz &Le Roux-Kemp, 2012). They also need to be made aware of the procedures that will be used to conduct the study and voluntary consent must be based on this information (Staunton, 2015). The guidelines are aware of the fact that many people in South Africa are considered vulnerable due to the varying levels of education and health care in the country and researchers must be aware of this issue (Britz &Le Roux-Kemp, 2012). The guidelines also set out the language and literacy levels that should be used to describe the information (Britz & Le Roux-Kemp, 2012). Language barriers are common in a diverse country like South Africa that has 11 official languages. Aside from these,

the home language of potential participants also differs from that of the researchers, while “the National Health Act demands that informed consent be obtained in a language that users understand and takes into account their literacy level” (Britz & Le Roux-Kemp, 2012). Ethically and legally, it is the participants' choice and preference to use a language that they feel comfortable (Britz & Le Roux-Kemp, 2012).

South African law regulates the rights and responsibilities of individuals involved in medical research (Nienaber, 2010). This law is part of the wider concept of informed consent. The right to informed consent is a fundamental component of the Bill of Rights protected in the South African Constitution, the National Health Act, the Health Professions Act and the HPCSA Ethical Rules and Guidelines (HPCSA, 2015). This right is granted to all South African citizens and health practitioners.

Despite the various guidelines, it is still not easy to obtain informed consent in South Africa for clinical trials. This is also because of the dual purpose of the informed consent form, where the institution or the principal investigator uses the informed consent form as a tool to protect themselves from potential litigation as a result of the culture of litigation in the Western societies (O’Neill, 2003). While the ethical guidelines are focused on providing the participants with the necessary information about the risks associated with conducting research, they have also evolved to become more legalistic. This makes it difficult to read and understand (Lindegger & Richter, 2000). The main objective of the ethical guidelines is to provide legal protection to the participants, but it is also very different from a document that aims to protect them from potential litigation. In South Africa, the guidelines require that the research be explained in a clear and culturally

appropriate manner. This makes it difficult to understand the information provided to the participants (Abdool Karim et al., 1998; Joubert et al., 2003; Moodley, 2005; Groves et al., 2010; Terblanche, 2010). Despite the various guidelines on the subject, it is still not easy to obtain informed consent in South Africa for clinical trials. This is because of the lack of basic understanding of the requirements of the ethical guidelines and the culture of the country (Abdool Karim et al., 1998; Joubert et al., 2003; Moodley, 2005; Groves et al., 2010; Terblanche, 2010).

In June 2021, the South African Health Products Regulatory Authority released the 3rd edition of its Good Clinical Practice guidelines, referred to as South African Good Clinical Practice: Clinical Trial Guidelines (SA GCP 2020). This guideline supersedes the guidelines that were originally published in 2006. The updated guidelines are designed to encourage the implementation of more efficient and effective methods in the design, conduct, and oversight of clinical trials. They also promote the protection of the participants and the validity of the results of the trials. These guidelines are aligned with the International Council of Harmonisation (ICH) Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R2) 2016 (ICH GCP 2016), and the Department of Health Ethics in Health Research Guidelines 2nd edition 2015 (DoH 2015). Understanding these guidelines means that researchers carry out their duties in a manner that is consistent with the ethical principles and values of clinical trials. The updated guidelines contain all the necessary information about conducting clinical trials in South Africa. Some of the guidelines have been consolidated and updated, while others have been reorganized to provide a more user-friendly approach. Where necessary, the guidelines also provide explanations and elaborations on procedures and principles, for the South African context. The SA GCP 2020 guidelines unpack key concepts in clinical trials, with particular reference to the Informed Consent,

Trial Incentives and Participant Reimbursement, Scientific Requirements for Research Protocols, Role of the Investigator, and the Trial Design. The guidelines state that before a clinical trial can be conducted, every participant must be given the necessary informed consent. (See Appendix 1) A serious discrepancy in the SA GCP and ICH GCP compared with the general importance and object of voluntary informed consent in the National Health Act, in section 12 of the Constitution (1996) and in case law, deals with a research participant electing to withdraw from a clinical trial (Britz & Le Roux-Kemp, 2012). The ICH GCP and SA GCP require that although a research participant is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the researcher should attempt to ascertain the reasons while fully respecting the participant's rights (Britz & Le Roux-Kemp, 2012). This requirement is not only contrary to the participant's wishes, but it also undermines the participant's decision to terminate the study (Beauchamp & Childress, 2001).

The Declaration of Helsinki states that the efficacy and risks of a new intervention should be evaluated against those of the best-known interventions (World Medical Association 1964). Where there is no proven treatment for a specific condition, the use of a placebo or no intervention is acceptable. However, where there is compelling evidence that the use of a different intervention is not as effective as the best one, or if the use of a placebo is not necessary to determine the safety and efficacy of the intervention, then the use of a different intervention is not considered appropriate. Participants should be aware that this option can lead to additional risks.

The DoH's Article 32 provides that the use of placebos in clinical trials is limited to the investigational use of a new test drug or therapy that is compared with the standard treatment.

Although it is generally not recommended to use a placebo in clinical trials, the use of a placebo can be considered necessary if a new treatment is not feasible or safe. In these circumstances, the use of a placebo can be considered necessary to determine the safety and efficacy of the intervention. Patients who receive a placebo will not be subject to any risk of irreversible harm (World Medical Association, 1964). In addition to following international regulations, South Africa's pharmaceutical companies and clinical trial investigators must also follow the country's Good Clinical Practice guidelines. On the Use of Placebo in Clinical Trials, the SA GCP states that the use of a placebo should only be justified and considered ethical to compare a new treatment with a placebo if there is no known cure for a specific condition (Department of Health, 2020).

The Food and Drug Administration's (FDA)) decision to adopt a less strict set of guidelines could encourage pharmaceutical companies to "take ethical short cuts" (Pretorius & Burgess, 2012 p 87). According to Pretorius and Burgess (2012), this could have negative effects on the ethical practices of research ethics committees in developing countries, as these may not be able to effectively protect the participants. They argue that, in response to the lack of resources for conducting studies in emerging and developing countries, pharmaceutical companies may influence research ethics committees to relax the legislation and guidelines related to the conduct of clinical trials. It would appear that the FDA's decision would not significantly affect South Africa, given the various factors that can be considered when it comes to conducting a clinical trial in the country, and that the use of a placebo is only to be justified if the study is based on scientific evidence and compelling methodology (Pretorius & Burgess, 2012).

Conclusion

The involvement of developing countries in clinical trials is necessary to ensure that the vaccines are tested in the most effective manner. If the development and testing of a vaccine is only conducted in high-income countries, the efficacy of the vaccine may not be the same in developing nations. According to Madhi (2021), who is the trial's National Principal Investigator, it was important for South Africa to participate in such a trail because of the need to study the vaccine (s) in a population with a high density of people. The types of infections that occur under these conditions are different from those in high-income countries. According to Madhi (2021), other factors such as the prevalence of comorbidities such as diabetes and obesity were also considered to determine if the vaccine was effective in this population.

One of the biggest challenges that the clinical trials of vaccines and researchers face during the pandemic is the timing of the study. Since the study is in the middle of a pandemic, it is important that the research is conducted according to the ethical guidelines and principle of the International ICH-GCP E6 (R2) and South African Guidelines for Good Clinical Practice. Therefore, it was important that this study focus on exploring participants' perceptions, experiences and the various factors that affect the motivation and informed consent, of people who participated in a COVID-19 vaccine study.

CHAPTER 3: METHODOLOGY

Introduction

This study aims to explore research participants' perceptions of and experiences with the informed consent process of a COVID-19 vaccine trial in South Africa, as well as the factors motivating them to participate in the trial. The study was conducted within the context of a COVID-19 vaccine trial in Durban, South Africa. A recent paper on participants' understanding of the key components of informed consent showed a low level of understanding overall (Pietrzykowski & Smilowska, 2021). This lack of understanding undermines the ethical pillars of current clinical trial practice and questions the viability of participants' full and genuine involvement in health research (Pietrzykowski & Smilowska, 2021).

The **objectives** of this study are**:**

1. To explore and describe participants' perceptions of the informed consent process
2. To explore and describe participants' experiences with the informed consent process
3. To identify and describe the factors motivating potential participants to consent
4. To identify and describe the factors motivating potential participants to be part of the vaccine study

Study Design

This study used a qualitative descriptive design. Qualitative descriptive studies are typically focused on the presentation of facts in everyday language. They aim to provide a comprehensive analysis of the participants' views (Sandelowski, 2000). A qualitative design is most appropriate when it comes to describing the participants' experiences because it can help explain the findings of the study by describing the various factors that influenced the participants' experiences (Bradshaw, Atkinson and Doody, 2017). The use of a qualitative descriptive approach may not be suitable for studies that do not need a deep theoretical understanding, however for the purpose of this study; the design was used in an effort to provide a straightforward description of the perceptions of, and the experiences of participants with the informed consent process. The study wanted to draw from a variety of naturalistic perspectives when assessing the phenomena of participants' perceptions of and experiences with the informed consent process in its natural state which allowed for a flexible approach when conducting the study (Sandelowski, 2000, 2009).

Study Setting

The COVID-19 vaccine trial enrolled about 4, 404 participants in South Africa and was carried out at four different sites. One of the sites was a Clinical Research Site in Umlazi Township, situated in Prince Mshiyeni Memorial Hospital, Durban. This site enrolled a total of 242 participants.

With a population density of 8530 persons/km2, and population of about 404,811, Umlazi is an urban area located in the southeastern portion of South Africa's KwaZulu-Natal province and is the country's fourth largest township (Britannica, T. Editors of Encyclopaedia, 2017). It lies along the south bank of the Mlazi (Umlazi) River and adjoins the city of Durban on the southwest (Britannica, T. Editors of Encyclopaedia, 2017). There are 104,914 number of households in Umlazi, of which 44,3% are headed by females, 49,9% have piped water inside dwelling and 90,4% use electricity for lighting. Of the population aged 20 years and above, 9,5% have higher education; 3,4 % no schooling and 40% have matric. 22% of the population have no income. Umlazi is 99,4 % black and 91,4 % of the population are isiZulu speaking, 3% isiXhosa and 2,1% English speaking (Statistics South Africa, 2015).

Prince Mshiyeni Hospital offers health services to the community at regional and district in the eThekwini region. It has a capacity of 1075 beds and serves the surrounding area, up to and including part of the Eastern Cape. The hospital has 17 clinics attached and offers various health services to the community. It is also one of the sites for Mother to Child Transmission (MTCT) and has the largest crisis centre. The facility has the largest crisis center that's called the 'Place of Comfort' (Kwa-Zulu Natal Department of Health, 2022).

Consent process of the COVID-19 vaccine trial

Participants who took part in the trial were randomized into one of two groups, namely those that received the COVID-19 vaccine and those that received Placebo. As this was a blinded study, participants, and staff (only the pharmacist was unblinded) did not know who received the vaccine or placebo. All participants received up to two injections of the vaccine or placebo, spaced 21 days apart. Participants were followed up for 1 year after their second vaccination.

At the screening visit, participants were given an information sheet and informed consent form and went through the informed consent process. The informed consent was administered by the researcher working in the capacity of Deputy Study Coordinator and Research Nurse. All clinical staff working in the trial had human subjects' protections (HSP) and Good Clinical Practice (GCP) training, as well as study specific training. If participants agreed to take part in the study, they were asked to sign the consent form. Participants were also given an Information Leaflet and Informed Consent Form for Storage and Future Use of Samples, and Information Leaflet and Informed consent for HIV Testing and Hepatitis B and C Testing. The table below (Table 1) shows the difference between the information in the three consent forms of the trial.

Table 1: Information sheet and informed consent forms used in the COVID-19 vaccine trial

Type of Consent Form	*Summary of Information*
Information Leaflet and Informed Consent form (Main Informed Consent Form)	Contains trial information and information on why the trial is being conducted and what the trial involves. Explains the risks and possible benefits of the trial.
Information Leaflet and Informed Consent Form for Storage and Future Use of Samples;	Permission to store any leftover blood from the main trial for future vaccine research. This excludes genetic testing. Decision to store leftover blood for future use does not affect participation in the trial or the care that participant receives at the research clinic.
Information Leaflet and Informed consent for HIV Testing and Hepatitis B and C Testing.	Human immunodeficiency virus (HIV) testing will be done as part of the trial. Hepatitis B and C virus will also be tested. Before agreeing to be part of the trial participants need to agree to have these tests done. Should participants not agree, they cannot be part of the trial. The HIV test results are being used in the main trail to place participants in the different groups. Group 1- HIV negative and Group 2 for those that test or are HIV positive.

Study Population and Sampling

The study population consists of men (n=8) and women (n=17), aged between 18 to 64 years. The study population is drawn from those participants enrolled in a COVID-19 vaccine trial in Umlazi, Durban, focused on testing the safety and efficacy of a new vaccine against COVID-19. In order to be part of the COVID-19 vaccine trial participants needed to be aged at least 18 years but less than 65 years in group 2 and less than 85 years in group 1.

Purposive sampling was used, which involved identifying and selecting individuals or groups of individuals that are proficient and well-informed about a particular phenomenon of interest, that being the informed consent of the COVID-19 vaccine trial (Creswell & Plano, 2011). A list of participants who had exited the COVID-19 vaccine study was used to sample participants into this study. From that list, participants were sampled for data collection until the required sample was reached and until data saturation (Martínez-Mesa et al., 2016). Data saturation is the situation where no new codes or themes emerge, so redundancy in the data informs the researcher that data collection may come to an end (Guest et al., 2006; Faulkner & Trotter, 2017). The study sampled 15 participants for individual interviews and 10 participants for focus group discussions (with five participants in each of the focus groups). Additionally, to validate some of the themes that were emerging from the discussions, a third focus group was conducted from the sample of participants.

Data Collection

Data collection for this study began in December 2021 and the last interview was completed in January 2022. Two, face-to-face, data collection techniques were used, namely individual interviews(n=15) and focus group discussions (n=3, consisting of 5 in each group). The COVID-19 vaccine trial's information sheet and informed consent form was used to guide the type of questions to ask the participants and to grade their responses based on the information in the trials information sheet. Additionally, the COVID-19 vaccine trial's information sheet and informed consent form was used in the individual interviews and focus group discussions as a form of stimulating discussion about various aspects of the consent process that were administered to the

participants, e.g., their perceptions about the meaning of elements within the consent form and the comprehensiveness of information in the consent form.

Semi- structured interviews

Semi-structured interviews were conducted to collect data on those that had participated in the COVID-19 vaccine trial. This method involves a dialogue between the researcher and the participant, which is followed by a series of follow-up questions and comments (DeJonckheere & Vaughn, 2019). The goal of this type of research is to collect open-ended data and explore the participants' thoughts on a particular topic (DeJonckheere & Vaughn, 2019). This was also a way of gathering information about the participants' personal experiences and beliefs related to the topic (DeJonckheere & Vaughn, 2019). The researcher gained access to participants who were part of the NOVAVAX study, where she worked and as part of the researcher's job, a list of participants who had exited NOVAVAX were used to sample participants into this study. Participants were interviewed using an interview guide developed in English and translated into isiZulu. An interview is a great way to go deeper into the study as it allows the researcher to collect more insights. This method also allows them to gain a deeper understanding of the individuals' perceptions of shared experiences (DeJonckheere & Vaughn, 2019). Researchers can use semi-structured interviews to conduct effective and feasible studies in their settings (DeJonckheere & Vaughn, 2019). Participants will be interviewed using an interview guide developed in English and translated into isiZulu (see Appendices 2 and 3, respectively).

Focus Group Interviews

From the list of participants who had exited the COVID-19 vaccine study, an additional ten participants were sampled, to form part of the focus group discuss. Discussions were held with three focus groups, consisting of 5 members each. The third focus group sampled from the participants that were already part of this study. The focus group discussion was used to gather large amounts of data in one go, and to verify the emerging data amongst different participants (Parker & Tritter, 2006). In addition to gathering additional information, focus group discussions were used to be certain that the participants' individual perspectives were been explored, as well as a group perspective. (Fusch & Ness, 2015). Therefore, a focus group is one way to elicit several perspectives on a given topic to reach data saturation (Fusch & Ness, 2015). A topic guide, developed in English (see Appendix 4) and translated into isiZulu (see Appendix 5) was used to ensure that there was consistency of the issues discussed across all focus groups (Breen, 2006). The focus group discussions were conducted over two consecutive days.

Interview venue and space arrangement

All study related procedures for participants enrolled in the COVID-19 vaccine study were conducted in a marquee-sized tent that was erected in the back of the clinical research site building and was used over the duration of the study. This was marquee would be open to allow for ventilation. The marquee was further segmented by screens to allow for privacy during participant consultation with the clinical research staff. There were two further marquess that were used for the informed consent process and the other used for collection of specimens such as nasal swabs

and blood draws. The semi-structured interviews were conducted in the smaller marquees, while the focus group discussions were conducted in the larger marquee. In semi-structured interviews the ideal location should be private, as it should allow the researcher to speak privately without being interrupted (DeJonckheere & Vaughn, 2019), therefore participants were given a scheduled time for their interviews and the research sites security was available to triage any other participant that may have come in early. The research site's security was also there to prevent any disruptions during the interviews. It's also important that the room has a quiet area so that the audio recording can be conducted in a secure manner (DeJonckheere & Vaughn, 2019). Similarly, the focus group discussions were conducted in the larger marquee. Semi-structured interviews and focus group discussions were scheduled and conducted after all COVID-19 vaccine study participants had completed their exit visits in the vaccine study.

Data Collection Instruments

Participants were interviewed using an interview guide developed in English and translated into isiZulu, as these are the two commonly spoken languages in Durban, Umlazi. An interview guide is a list of the various topics that the researcher will cover in an interview (Jamshed, 2014). It also helps the interviewer identify the questions that they should be asking under the topic (Jamshed, 2014). The interview guide allowed for "a face-to-face conversation between a researcher and participants with the sole purpose of collecting relevant information to satisfy a research purpose" (Adosi, 2020, p 2). The use of the COVID-19 vaccine study's information sheet and informed consent formed also helped facilitate the conduct of the interview by providing the researcher with the necessary topics to prepare for the interview. A focus group discussion guide was used by the

researcher to gather data from the groups. A focus group discussion guide can help researchers gather information of a specific topic of interest from a group of individuals with similar backgrounds and/or experiences (Guest et al., 2017). The interview guide was used because it allowed for flexibility for the researcher and contained questions that were semi-structured, creating opportunity for participants to express themselves fully (Adosi, 2020). The researcher was able "to make use of probing questions on the guide to make the information gathered more relevant and useful" (Adosi, 2020 p 5).

Participants demographic data (see Appendix 6) was collected before the semi-structured interview and focus group discussions. The data collected for each participant were minimal, such as their age, sex, marital status, and education. These attributes were then used to describe the characteristics of the participants.

The researcher has undergone interviewing training in their role within the COVID-19 vaccine trail and isfamiliar with procedures, and guidelines for conducting ethical research interviews. The interview guide was created by the researcher and therefore was able to, instead of reading word for word, to use their own phrasing for asking each question, use additional probes or prompts where necessary. The researcher had also built rapport with the participants throughout the COVID-19 vaccine study. The researcher informed participants that for the study they wanted to understand the participants' experiences and realities from their perspectives.

Data analysis

A thematic analysis approach was used to analyze the data. Thematic Analysis is a process that can help researchers draw interpretations from the data collected (Clarke & Braun, 2016). This study used Braun & Clarke's (2016) six-phase approach to thematic analysis. In the first phase (Familiarization) semi-structured interviews and focus group discussions were uploaded immediately after interviews were complete. They were saved on a USB and on the researcher's laptop drive. All 15 of the semi-structured interviews were transcribed and translated by a transcriber. The researcher back translated, and notes were read and re-read for what participants said during the interviews and focus group discussions to ensure full familiarization. Focus group discussions were transcribed and translated by the researcher and back translation by the transcriber. Transcripts were loaded onto a software program NVIVO 12 for coding and analysis. The second Phase was Coding, where NVIVO 12, a software program was used to code sections of texts according to specific codes. The codes were further classified and grouped into sections to identify patterns. The codes are stored in the program for reference. The third and fourth phase was for the researcher to identify and define the themes. A set of clustering codes that seem to share a unifying feature were grouped into folders to generate themes and sub-themes. Thereafter the researcher reviewed the folders, insuring that new or revised themes were reflective of the data collected. The researcher then completed phase five and six and began grouping the themes and providing each theme with an all-encompassing name. Themes were then linked to the existing concepts and meaning assigned to the themes, which allowed for the formulation of findings and address of the study objectives.

Rigour

To ensure that the research findings of this study are a depiction of the nature of the phenomenon, the researcher applied the four criteria set forth by Lincoln & Guba (1985): credibility, transferability, dependability, and confirmability.

Credibility, which has to do with the accurate depiction of a participant's voice and experience, was reached through the process of peer debriefing (Cypress, 2017). Peer debriefing is an integral part of the research process (Cypress, 2017). The researcher discussed data collection and analysis process with her supervisor to allow for feedback on research processes (Cypress, 2017). Additionally, triangulation was achieved through the cross-checking of data from individual interviews versus focus group discussions. This involved the research carrying out a preliminary analysis after the interviews in order to verify and confirm any issues during the focus group discussions (Cypress, 2017). From this preliminary analysis the researcher added another focus group discussion.

By using the purposive sampling method, transferability was enhanced and by providing a good description of participants, setting and context as well as their responses to interview or focus group questions.

Dependability was achieved by having a peer qualitative researcher and supervisor review the transcribed (anonymous) material to validate the themes and descriptors identified. The researcher kept a notebook to record all the decisions made throughout the research process.

The researcher maintained a reflexive journal during the research process to document decisions or thoughts to minimize bias and for confirmability. The researcher has used quotes from participants, where appropriate, in the write-up of the study (Cyprus, 2017).

Ethical Considerations

Ethics approval was granted by the Biomedical Research Ethics Committee of the University of the Western Cape- Ethics Reference Number: BM21/10/22 (see Appendix 7). Permission was also obtained from the COVID-19 vaccine trial sponsors (see Appendix 8).

The researcher and participants adhered to COVID-19 safety protocols, including social distancing and mask wearing. Interviews were conducted in a marquee set aside for participants participating in the COVID-19 vaccine trial. Screens were used to maintain privacy. Participants were informed about the study during their COVID-19 vaccine trial exit visit and invited to participate. Participants were asked to provide their explicit, active, and signed consent to participate in this study (Fleming & Zegwaard, 2018). This study's information sheet and consent forms were available in English and isiZulu (see Appendices 9-12, respectively). As part of the informed consent process, participants were provided with detailed information about the objectives of the study, how they will be involved, what the potential risks and benefits are, how their privacy and confidentiality will be upheld, and their right to withdraw from the study at any time without reason. Participant in the focus group discussions were further provided with a focus group

confidentiality binding form to reinforce confidentiality within the group members (see Appendices 13-14).

The researcher informed all participants during recruitment and participants were reminded throughout this study that they had the right to withdraw from the study at any time, that their participation was voluntary, and that withdrawal from the study would not have any negative consequences on them. Additionally, the researcher ensured that the identities of participants are kept confidential or anonymous to avoid any harm (Fleming & Zegwaard, 2018). This includes the avoidance of using self-identifying statements and information in the thesis or any other outputs (Fleming & Zegwaard, 2018).

The audio-recordings and soft-copies of the transcripts were transferred to a USB flash drive and laptop drive that is password protected. The researcher will safely store all hard copies (i.e., notes) in a locked cabinet. The audio recordings and any hard copies will be stored securely for five years. After five years the hard copies will be shredded and the information on the USB flash drive will be permanently deleted.

The introduction of the South African Protection of Personal Information Act (POPIA) has come into effect from 1st July 2021. The researcher will continue to adhere to the act which outlines eight conditions for the lawful processing of personal information, all of which must be fulfilled in order for such processing to be lawful. Including but not limited to ensuring that the participant is informed of their right to access, correct, and delete their personal information and of the manner in which to do so (Sections 23–25) (Adams et al., 2021).

CHAPTER FOUR: FINDINGS

Introduction

The findings below draw on semi-structured interviews and focus group discussions with selected trial participants. Twenty-five participants were interviewed as planned. The study revealed predominant themes that are described in full and are illustrated with verbatim quotes from the research participants.

Participant Demographic Description

The table below (Table 2) shows the demographic distribution of the participants in the study. Of the 25 participants sampled, 17 were female and 8 were male. Majority of the participants were between the ages of 25 and 34 years. Of the 25 participants 12 participants completed matric and 7 did not complete primary level education. There were 14 unemployed participants and 0 participants had full time employment. Language preference is worth noting as participants reading preference was not always the same as language for discussion preference. Most participants preferred both English and isiZulu when it came to discussion or explanation of points in the informed consent form. The table below shows that 13 participants chose the isiZulu informed consent form and 12 chose the English informed consent form.

Table 2: Participant Demographic Description

Variables	Character	Frequency
Gender	Female	17
	Male	8
Age Distribution of Participants	18-24	6
	24-34	11
	35-44	4
	45-54	2
	55-64	2
Highest Grade completed/level of education	Still in Secondary school	1
	Did not complete primary school	7
	Matriculated	12
	Some tertiaries but not completed	3
	Undergraduate degree	2
	Post graduate degree	0
Language Preference (signed informed consent documents)	isiZulu	13
	English	12
What Participant does for a Living	Employed Full time	0
	Employed Part time	5
	Unemployed	14
	Secondary School student	1
	Tertiary Student	4
	Other	1

EMERGING THEMES AND SUBTHEMES

The following section summarizes the various themes and subthemes that emerged from the study. These are illustrated with verbatim quotes from the study participants. The themes emerged from the analysis of the 15 semi-structured interviews and 3 focus group discussions. The themes that emerged speak to the procedural and fundamental requirements of informed consent. These include the nature of the trial such as the study requirements and what the participant should expect should they take part in the study. The risks and benefits of the investigational COVID-19 vaccine, the option not to take part in the trial, and the participant's understanding of all other elements of

the informed consent form. Below is a table (Table 3) summary of the Main themes and their subthemes from the data collected:

Table 3: Themes and Subthemes

Theme	Subtheme
Theme 1: (Mis)Understanding of the elements of informed consent	Subtheme 1: Recall through repetition of processes and experiencing of a study specific event Subtheme 2: Assigning own meaning and interpretation of the elements of informed consent
Theme 2: Factors affecting participation in the research study	Subtheme 1- Fear Subtheme 2- Reimbursement Subtheme 3: - Health Benefits
Theme 3: Involvement of Community and Family on the Trial	
Theme 4: Participants perceptions of the informed consent process	Subtheme 1: - Perceptions about various aspects of the informed consent

Theme 1: (Mis)Understanding of the elements of the informed consent

Participants were asked questions that were designed to highlight the basic ethical issues that are involved in conducting clinical research; that is the ethical guidelines and principles of the International ICH-GCP E6 (R2) and South African guidelines for Good Clinical Practice. The questions covered various aspects of the study, such as the investigational nature of the research trail, the rights of the participants, the confidentiality of data, and the compensation for

participation in the research trial. Each question was designed to highlight the most critical elements of the study that are required by international guidelines and regulations as well as reflected within the informed consent.

Most participants were able to understand the various elements of the trial. Participants understood what the trial was about and why it was being conducted. Below are two participants' responses when asked what the study was about and why it was being conducted. The responses show that participants had knowledge of other COVID-19 vaccines available, such as Johnson and Johnson. Responses also showed how participants had knowledge of the trial vaccine being under investigation. This is an important quote as later we see how most participants were confused about what vaccine was being tested in the trial.

"The Novavax study was the research program for COVID-19 vaccine, since there are other vaccines like Johnson & Johnson and many others, so this study was to check if Novavax vaccine can work." (Male, 32 years old)

"My own understanding is that NOVAVAX study was a CAPRISA research program to find the vaccine for COVID-19, because scientists wanted ways to reduce COVID-19 cases." (Female, 29 years old)

However, there were elements that caused some confusion among the participants. One element that cause confusion among participants was the ***vaccine being tested***. The vaccine that the trial was testing is called SARS-CoV-2 rS with Matrix-M1 adjuvant, and it is developed by researchers

at NOVAVAX. In response to the question, SARS-CoV-2 rS with Matrix-M1 adjuvant and/or NOVAVAX were the accepted responses. However, a few participants, particularly in the semi-structured interviews would either respond that they did not know what vaccine was being tested or believed that the trial was testing the Johnson and Johnson vaccine.

"I remember that we would get two vaccines, placebo and I don't remember the other one. Placebo I heard was not the real vaccine." (Male, 53 years old)

"Yes, I remember now. its Johnson and Johnson." (Female, 40 years old)

During the focus group discussions, participants were able to assist each other, often times ignoring those that mentioned a name other than NOVAVAX**.** This quote below shows how, in this focus group the group ignores participant 5 when she mentions that the name of the vaccine is Johnson and Johnson. The other participants do not inform this participant that she is incorrect but rather they continue discussing among each other, excluding her from the conversation and then another participant shouts, placebo.

"Uhm so for me what I remember that was in the form, firstly it was explained to us what COVID-19 was, then its symptoms, then you would be told that if you were willing to join the study, you would receive two vaccines. The first one was …konje what was it called? ***[Looks to others, they all try to remember, another participant says Johnson and Johnson, and the group ignores her. One member says Placebo]*** *oh yes, the placena [placebo] of which it is fake which is what I*

remember and then you would receive the second one. Oh, and then the side effects that you might experience, uhm I don't remember the rest." (Female, 57 years old)

What was evident in both the semi-structured interviews and the focus group discussions is that participants remember the *placebo*. However, there was notable confusion. Participants understood that they would receive two injections of either SARS-CoV-2 rS with Matrix-M1 adjuvant (NOVAVAX) or a placebo of salt water (sterile normal saline). Almost all participants were able to explain that the sterile normal saline was a placebo and almost all participants understood that a placebo was a "fake vaccine".

"It's a program about COVID-19 vaccine, whereby two vaccines were shown to us which are placebo and Novavax vaccine. Placebo is made up of fake water and salt." (Male, 23 years old)

Subtheme 1: Recall through repetition of processes and experiencing of a study specific event.

Participants understood the purpose of informed consent better, when elements of the informed consent process were repeated to them throughout the study, such as the key procedures of the trial and the reason why they were being done. At each visit, participants would have a pregnancy test, blood draw and a swab to test for COVID-19. This participant recalls that.

"Uhm yes so like the pregnancy test was being done because the study did not accept anyone who was pregnant because the vaccine could affect the unborn baby. Bloods were drawn to check if

there weren't any other illnesses and swabs to check for Covid before receiving the vaccine." (Male, 58 years old)

Participants who experienced an event; for example, those who tested positive for COVID-19 during their participation in the clinical trial, talked about the IC process more thoroughly. These participants were most likely to mention the Flu Pro, which is a questionnaire, provided to the participant to record the symptoms related to possible COVID-19 and their severity for 10 days.

"If you were not feeling well, you could, if you sick and maybe have the flu, you can call them and let them know that you are unwell and then they would fetch you and bring you to the clinic and give you medication. You again return for them to see if you are getting better and if the medication is working. You also were expected to complete a form to track your symptoms each day in the 10 days." (Female, 53 years old)

Those that did not experience such an event either did not remember what would happen when events like testing for COVID-19 occurred, or they provided responses that were more generic when it came to COVID-19 and information that was not specific to the trial.

"They would take me to hospital, and I would get treated until I was better." (Female, 29 years old)

Similarly, those that did not experience vaccine related side effects were unable to differentiate the side effects from COVID-19 symptoms, and they were less likely to mention the Study Subject

Diary. The Subject Diary was given to participants at each vaccination visit to record any reactions after each vaccination for 7 days. This participant mentions that developing a rash is a side effect of the vaccine, when probed on other side effects, they mention that headache and coughing, where coughing is more a likely to developing with COVID-19.

"*They said you might have rash, but if you do get it, they said we can call you and inquire about it, they will then call you back and tell you to come to the facility to receive the treatment…well, they also mentioned that you could get a headache and have coughing." (Female, 37 years old)*

Participants responded correctly to the question about who can take part in the study. Participants understood the age requirement, the reason why women needed to practice effective contraception during the trial.

"They said females and males but from 18 years and above and HIV positive people qualifies for this program, if you had chronic diseases like BP, sugar diabetic people and pregnant did not qualify for this research program." (Female, 21 years old)

"They said pregnant women cannot qualify because the vaccine might cause complications to the unborn child." (Female, 25 years old)

The study included people living with HIV (PLWHIV), if they were on anti-retroviral treatment for at least 8 weeks, were medically stable and had an HIV-1 viral load of <1,000 copies/m². Either participants that mentioned that PLWHIV could be part of the study were those that had friends or

family members LWHIV or they themselves were LWHIV. This participant is LWHIV, and they remember how they were booked at a later stage because the trial was still enrolling into Group 1, which is for HIV negative participants.

"Because with me I came in the first row (group) where they were still taking HIV negative people. They booked me for a later date. So, I told her [friend] since she was negative, she can go and so I sent her the link and helped her get registered and then you guys called her." (Female, 33 years old)

This participant states that the trial did not take PLWHIV since they were negative and their friend that joined the study was also negative.

"The study did not take HIV positive people. You had to be HIV negative to join and since my friend and I are negative we were allowed to join." (Male, 21 years old)

Subtheme 2: Assigning own meaning and interpretation to elements of the informed consent

Although participants spoke positively about the IC process, where they did not understand or recall the details of the process, they came up with their own interpretations of the elements covered in the IC document. The participants were able to interpret the meaning of the elements covered in the IC process based on what they thought the researchers intended and on what they knew about other study participants. Their ability to use information that they have, such as

knowledge of a friend's HIV status also meant the ability to potentially determine HIV status of other research participants. Through conversations with other participants, discussing side effects or lack of side effects, participants felt that they were able to know whether they received the vaccine or placebo, testing whether or not the study was truly blinded to the participants.

The study had two injection periods, the first injection period and the crossover injection period. In the first injection period, participants may receive up to two injections of the COVID-19 vaccine or up to two injections of the placebo. The crossover injection period is when participants receive the COVID-19 vaccine. Participants may have been able to tell determine whether they received the vaccine, or the placebo based on the side effects that they experienced. They believed that those who received the vaccine experienced side effects and those who received the placebo did not. Participants felt that the vaccine in the crossover period was different because experienced side effects. In this way, participants were able to 'know' what they received during each period.

This participant uses their reaction to the vaccine to determine whether they received the vaccine or the placebo. Based on the side effects they mention that they are able to tell apart the time that they received the vaccine and the time that they received the placebo.

"So, the first one is the placebo and the second one is the one that is more effective. The first one has salt and that's what's I remember. The first one did not have any effect on me but the second one I could feel that it gave strength to my blood (was working), yah." (Male, 58 years old,)

Another participant recalls that when they compared their side effects with other participants, they were able to tell which of them had received the vaccine.

"It is different because the second shot for me was quite heavy I felt it and I heard people saying it causes them dizziness and so on, not like that other first shot" (Male, 31 years old)

The trial had two groups (Group 1 and Group 2). Group one included participants not living with HIV and group two included participants living with HIV. After safety data of group 1 was reviewed then group 2 could be enrolled into the trial and vaccinated. This was in the information leaflet and informed consent form; however, to preserve HIV status of individuals, the study team contacted those participants that were HIV negative first. If there were those that tested positive at screening or informed the study team that they were on ART, they were given a return date that was longer than a participant who was HIV negative, to allow for the period of safety data collection. One participant was able to notice how the study had separated those that were HIV positive and those that were HIV negative because they were aware of their friend's HIV status.

"Yes, according to my understanding I realized that we had been separated. I have my own reasons as to why I say this because there are people that I joined with, but we did not come on the same days of which I know their status." (Female, 33 years old)

When the participant was asked why the study team separate HIV positive participants and HIV negative participants would, they responded:

I think for them to see how the vaccine works on people that are HIV negative because we are the ones that received the vaccine first and then the HIV positive people followed." (Female, 33 years old)

Participant shared the information about grouping according to HIV status in the study as if they had acquired it themselves, however this was information captured in the information sheet and consent form.

Another attempt to blind staff and study participants from the study products involved pharmacists covering the vaccines with blue translucent tape. All syringes were concealed, but when a participant was asked how they know which study product he/she is getting, their response was:

"It was said that Novavax vaccine is blue in colour and the other one is white." (Male, 29 years old)"

The informed consent does not mention colour when referring to the make-up of the vaccine but rather describes the placebo as salt water.

Theme 2: Factors affecting participation in the research study

This theme showed how participants perceive their participation and the various factors that influence their participation in the trial.

Subtheme 1: Fear

Fear is a major theme that came up during the interviews, and although it existed, it did not prevent participation. Participants' fears were related to new vaccines being tested, the fear of the unknown about the vaccine and the possible side effects. One participant summarizes their reason for joining the trial because of the fear of getting COVID-19 and despite the fear of the vaccine being investigational. The participant had also heard that someone had died or gotten ill after receiving the vaccine but says that after the information leaflet was explained to them, they felt at ease to re-consent and continue participation. Participant also mentions that their fear and reservations were also because the vaccine was now being trialled in humans after it being only tested in monkeys.

"Well for me the first time I heard about this research, I really don't want to lie, I was scared but then I was like you know what fine, this disease is already here, and invading let me try and see how this goes. So I also came here…The second time we had to sign the second form, I was scared because it was informing us of someone who had received the vaccine and died or I think got sick, from overseas somewhere, I really was nervous to sign and another thing that was really scary, even before I signed the second form, is that this vaccine had never been tested on any one before only in monkeys. Although monkeys are similar to humans, they still not humans so I was scared to join. I had also gone through the form myself and it was also clearly explained to me so then I understood and then joined." (Female 26 years old)

Rather than choosing not to participate in the study, participants seemed to still have the desire to continue. Another participant, although afraid to receive the vaccine, still continued to participate

in the study knowing they would receive the vaccine. Their fears were from what they had heard from others about how they fell sick after receiving the vaccine.

"Me, haai I really was afraid to receive the vaccine but then after I had received the vaccine, I found that nothing happened because the way I was so scared, I would hear others say they got sick." (*Female, 26 years old)*

Another participant describes how the side effects of the vaccine were over dramatized but despite hearing this they still went ahead with receiving the vaccine.

"They said they had gotten sick and there were scary things resulting from the vaccine coming out of there body. However, after I had been vaccinated, I saw that I did not have anything." (Female, 21 years old)

Although participants feared that the study had its own agenda, and could possibly be injecting people with the virus, one participant, still acknowledged that the study information seemed effective and real.

"I heard everything that was said and what was taught, and I was like oh this thing has sense, and it will help us. It's just that I thought that maybe you guys would inject us with COVID, that you had something planned." (Female, 32 years old)

Then there were those participants whose fears seemed to be eased by the possibility of reimbursement. Participants are reimbursed for their inconvenience and time spent during study visits. When participant was asked why they continued in the study with all the reservations, their response was because of the money (reimbursement). Because of reimbursement, participating in the trail was made easier, despite of the existing fears.

"Yes definitely, ha phela imali." [Laughter] (Male, 37 years old)

Most participants were willing to go through with the fear, without asking any questions but rather by being their own 'guinea pig' to test the effects of the study, without care of the outcome. One participant tells of how they had a question that they did not ask during the informed consent process. The question that the participant did not ask was what would happen if they a had a severe adverse event, resulting in death, due to the vaccine. The participant feels that their reason for not asking the question is two-fold. The first reason is that they felt that it was an irrational fear that would not happen.

"No phela, I knew that that danger was not there, it did not really exist, that is why I did not ask the question." (Male, 24 years old)

And the second reason was that they did not want to dwell on the idea that something 'bad' could happen to them as a result of taking part in the trial with an investigational vaccine.

"Really did not want to entertain this idea or place this thought in my head." (Male, 24 years old)

The participant also felt that if the outcome was death, then there is nothing that they could do about it at that point and therefore adopts a Que sera, sera attitude (whatever will be, will be).

Kuyobonakala khona. We will see when we get there [laughs] when it happens… at that point I would not be alive then will I?" (Male, 24 years old)

Other participants were consoled by the knowledge that the research staff had gone and received the vaccine, albeit it being a different vaccine to the one which was being tested in the trial.

"I was scared cause I did not know if the vaccine will work or not but because you [referring to study team] had vaccinated then I went." (Female 34, years old)

Similarly, others found that seeing members of the community go through the process and come out fine, was enough for them to get the vaccine:

"People from my area had already taken their shots, so I said to myself let me try it out." (Female, 34 years old)

The study team also played a role in assuring participants that should there be any issues or concerns, or if participants needed immediate medical treatment, the study staff would assist them:

"I liked that if I had any issues I could still come to this clinic and that I would be helped and not sent away." (Female, 33 years old)

Subtheme 2: Reimbursement

The study reimbursed participants for their time and travel expenses, including taking blood tests and administering procedures. The minimum amount paid per visit was R300 in cash. All participants had an overall clear understanding as to what was in the in informed consent and why the study was reimbursing them per visit. A few participants saw attending study visits and undergoing all the trial procedures as a job, which they needed to be compensated for. The R300 was seen as reasonable amount for the work that they had done, resulting in a mutual exchange where researcher gets the bloods and swabs, and the participant gets compensation. Many participants did not have jobs and sought alternative income. Participants felt that study reimbursement provided the financial relief that many of them needed.

"Eyi for me if the money was not there, I don't think it would have been that interesting and it would not have had that pull to attract someone because firstly there is no one who just wants to be drawn bloods; certainly there are a few people who take these things seriously. So, I think the money had a huge impact and drew us to the study. Because you would be like oh you got paid [pay day] and when you come back with that money…also the time that we were in, in the initial stages of covid many of us had limited means of getting money and so this study would help because you could budget. You would come for your visit and come back with money to do 1,2 and 3." (Female, 36 years old)

A few participants expressed no other reasons to participate in the study except for the monetary compensation, which facilitated their decision and interest to participate:

"Ok so for me what was interesting or what made me decide to come here was the money nje first of all. So, when people told me that they were getting paid, bayahola, [laughs] that made me interested." (Female, 22 years old)

Reimbursement and fear seemed to also overlap with some of the participant responses. Reimbursement was seen by participants as a necessary addition because it helped with fears around study uncertainty, study procedures and helped with the recruiting of their friends or family. One participant, although uncertain of the reason for reimbursement still felt that the money helped with their fear and that it was the least that could be done by the research team.

"Ha-ha, oh yes, I think it's for transport maybe but in fact I don't know why they gave us money…Maybe for participating, they had to compensate us with something, I was scared hahaha." (Male, 20 years old)

Participants would also use money to recruit other participants. It was used as an enticement as participants felt that certain study procedures were a deterrent and caused fear amongst some people and so by mentioning that there is reimbursement, more people would be interested in joining. The below response shows that participants feared not only the procedures but also that

they may get COVID-19 and so in mentioning the reimbursement as a conversation starter, it makes it more palatable

"Well, I would start with the money…because when I mention the swabs they would run away and say eyi this thing might touch my brain ***[man 1 in the group says they are afraid of ukuhlokolozwa- the probing by the swab]*** *they were scared and that one might get COVID." (Female, 57 years old)*

There were also those participants who recruited family members because they understood that the family members would benefit from the money, and it could be used to help with their daily needs. And although money was a huge factor, they also emphasized other study requirements to the family members such as:

"Look with me when I got home, I told my cousin and said at Mshiyeni go and get your COVID vaccine and get more information on COVID because sometimes you come back with money and that money can help you with things that you need. But I did say to them that if they have BP or sugar (diabetes) or HIV, no they don't take you and that's what I said." (*Female, 29 years old)*

One participant shared how they showed their reimbursement as proof to their friend. This participant also shared that there was a form that needed to be signed to get that money. The form was seen as something that provided information on the study and a guarantee that you would receive money.

"Ok so for me after I came back from my visit, I told my friend that there is a study at Mshiyeni and there is a link to join and I told them haai here is the money, I really did get it. You get money but before you get the money, there are forms that you get, and the study is explained to you and these forms will allow you to continue in the study and also once you have signed them you get the money." (Female 22 years old)

Another participant shares how within a group of friend's money opportunities are always discussed. When they joined the trial, they shared with their friends because friends always shared when 'opportunities' to make money presented themselves. What is also mentioned is that there were those participants who would not return after signing the informed consent form, after they received their reimbursement.

"So, me I said there is something that I have joined. Sis Thandeka, you know that as friends we always discuss with each other that if there is anything that has connection, that involves money we should always plug each other. So, I told them that there is something that I joined in Mshiyeni, it's about corona, you use a link to join. And they rush with their phones [snap fingers] …actually no if I remember correctly, they all used my phone because I remember that others were called before me. Oh, ok and another thing was that you would tell someone and then they would say they will come for one visit and not come back because once you explain that you will be getting a vaccine because it is research. So, they would come the first time [screening] and not come back after that, and ignore your calls, having received the first money." (Female, 26 years old)

The money was also used by the participants to 'replenish' what had been taken through the blood draws and were able to buy themselves food that would help them restore what had been taken during study procedures.

"Mina I would buy ama 100% because I need to boost my blood and eat healthy things to prepare for the next time bloods are taken." (Female, 33 years old)

Subtheme 3: Health Benefits

Although money was initially the main motivator, participants found that after going through the informed consent process there were many benefits that they identified with to participating in the study. These benefits facilitated continued participation in the study. Participants said that access to care that is facilitated by being part of the study, was a benefit and the availability of resources without having to stand in long queues.

"I got here, and it was explained to me, I realized ok, besides the money there are other things that would benefit me that aren't associated with the money." (Female, 21 years old)

There was additional benefit to participating in the study. Participants recognized that being part of the trial, they were able to have access to free healthcare and medication.

"And also, another thing that helped, the fact that we were here under research, once you saw you had an issue, they would be able to take care of you here (at the clinic). Because should you feel

sick, you would call, and they would come to you to check on how you were doing" I will get care that is free and right. In addition, when we were sick, we would get the medication, care, and expertise that showed us you cared for us." (Female, 21 years old)

While most participants did not desire other study procedures, there were those that were welcomed, particularly by the female trial participants. Routine pregnancy tests and family planning was part of the study procedures. This participant viewed these procedures as beneficial as they also did not come with any prejudice or reprimand and as an added benefit, there were no long queues to navigate.

Secondly, like the family planning like I said it meant not going to the clinic and standing long queues… Like you will find you missed a period and now you scared and not sure if you pregnant I could get a pregnancy test here." (Female, 26 years old)

Participants were also able to check their HIV status. This participant speaks of how people are afraid of checking and knowing their HIV status and being able to test as part of the trials procedures was another reason, they felt that being part of the trial benefited them.

Another thing was the ability to check my status. A lot of people are afraid to check and know of which these were all things that were beneficial for me that allowed me to continue in the study." (Female, 29 years old)

The study also provided a way for participants to check in on their COVID-19 status and participants felt that even though the vaccine was still being tested, there was some protection from severe COVID-19 illness.

"The benefit of this program is that you know your status all the time and that when we first came here corona cases were high and people were panicking so for me it helped me to know that I am not infected with COVID-19." (male 20 years old)

"Although they did mention that vaccinating does not guarantees us that we will not be affected with COVID-19, but it won't be severe as it would to someone who did not vaccinate, they said we will still have signs of COVID-19 but not as severe." (Female, 33 years old)

Participants also explained how the research environment allowed them to be free with their visit schedules and that they did not always feel like there were going to be repercussions for missing study visits. The study environment and team always provided individualised care, making participants feel like they were a priority when they attended their visits, and the research staff were always professional. Participants also felt like they could discuss anything with the research staff

"Nami, I agree that the way we were treated was right and you could discuss whatever that was on your mind even if it's you date and you can't make it, it was easy to reschedule without fear of being exited from the study." (Male, 20 years old)

One participant mentions that they appreciated how they were also made to feel like they were a priority and that whatever they reported to the research team, they always had immediate feedback, with desired professionalism.

"Eh what I like about the study everyone here, as you guys as colleagues, you would make a person feel like a priority you see when someone reported something you would get back to them same time. And the way you treated us shem, haai it was right it was professional." (Female, 57 years)

Participants made note that since the pandemic there were issues with going to the clinics and getting contraception and being part of the study helped them access contraception. They noted that study staff in comparison to local clinic staff did not shout at them and they felt like being part of the study was the same as having private medical aid.

"*So, for me it's all that has been mentioned and also there was that care, no shouting at you, for example if you arrived late. It was like we had our own medical aid. Another thing that was a bonus is that family planning at the local clinics was scarce so we could still continue with family planning here in the study. It was easy and you avoided the long queues at the clinic." (Female, 29 years old)*

In addition to the individualised care, participants appreciated the telephonic follow-up after they have come in for their visits.

"…and when you came in for a visit, they pass a few days and then call you to check up on you…you see that on its own… they would ask you are you ok and about your health." (Female, 33 years old)

The study seemed to benefit participants whether they were screened and enrolled into the study or whether they were screened and failed due to not meeting the eligibility requirements. Participants felt that the study fast tracked the way participants received care in the local health facilities. One participant recount how her friend benefited by finding out that "they had an issue with their blood", and she was able to get a letter referring her to the hospital.

"So, for me the girl I refereed she came and wanted to join the study and she was told she has an issue with her blood. She does not have enough, and this is something that she knew but had stopped taking her treatment. She went back to the hospital with her referral letter and restarted on treatment. You see she got help." (Female, 33 years old)

Most participants did not enjoy certain study procedures such as swabs and blood draws at each visit, but there were those participants that did not complain. They joined the trial because they wanted to continue with their social life and the study inevitably allowed them that opportunity to do so. Participants felt that since they were now vaccinated against COVID-19 and they were routinely getting tested for COVID-19, they could continue with their social life.

"What made me sign, I saw that this this has sense for example nje it checks covid a lot. See with me I love going out, covid or no covid I still would go out. So, it helped me joining this research

because I knew where I stood. If I felt like something was off, I would always call and get tested. The testing for covid was what I loved." (Female, 21 years old)

Including the need for a social life, other participants saw that they were losing many people in the community, and they wanted to protect themselves and their immediate family.

"Me, what made me sign is that a lot of people that I was close with passed on due to covid and I saw that I needed to protect myself and my children because I also go out a lot." (Male, 58 years old,)

Participants also joined because of fears of being infected with COVID-19 outside of the research study. One participant mentions that they were attending the social services department, and they felt that they were at risk of getting COVID-19 because of waiting in long queues with individuals may or may not be COVID-19 positive.

"I joined because of my friend and because I use the 'Office' (Social services department) a lot and you can never be sure who you meet does not have COVID especially in the long queues." (Female, 40 years old)

Theme 3: Community and Family Involvement on the Trial

Participants spoke about their experiences during the trial and how the community and their family responded to their participation. There were several dynamics that emerged, namely related to conspiracy theories and misinformation about the COVID-19 vaccine, study procedures and continued study participation.

The community feared the trial and did not trust the vaccine. There was belief that participants would not be receiving a vaccine, but they were being injected with the virus itself or 'something' that cause harm to the body and would result in death.

"The risk was that we did not know how everything would turn out, especially starting something and people saying that this is not the vaccine this is something that could cause us to maybe demise." (Female, 26 years old)

Fears within the community were also around the study procedures, such as nasal swab and blood draws, and that by joining the study and undergoing tests one could potentially receive news about a newly diagnosed health condition and as one participant mentioned, people do not like knowing what health issues they have, particularly when it comes to HIV status.

"Another thing that I would say, you see many people do not like checking their health and especially their HIV status, so the study helped you to be in the know about your status and people don't like that." (Male, 58 years old)

While there were those participants feared receiving unexpected news regarding their health, other participants sought to learn more about their health condition, and seeing their neighbours join the study influenced them to do so.

"Ok so some of my neighbours were already on this program here in Philasande so they told me to come check it out, you know as a sick person you always want to try everything that can help me get better." (Male, 31 years old)

Other participants mentioned how their family had concerns with them joining the study due to lack of study understanding and that they were concerned that participant would 'bring the virus back to them'. One participant had decided to initially not disclose to her family that she had joined the study, she secretly attend study visits and when she did feel comfortable to inform them, they wanted her to leave the study.

"…at home they felt that I would come back with COVID and that I should leave the study, because I would now come here [to the research clinic] without them knowing. So then, I explained to them that this thing is for them to help us with this disease. They are teaching us about ways to avoid this disease and in the end there will be a vaccine…Haai they couldn't understand at home and wouldn't hear of it..." (Female 25 years old)

There were many other participants who felt that now that they were part of the study, onus was on them to go back to their families and the community and show them that they were doing well

and dismiss the rumours. Participants noted the importance of using what was in the informed consent and what was discussed with them by the study team when going back to the community.

"What can I say, I think like with all of us when we have joined. We shouldn't go back now and frighten others. Like let me go back and explain the study like it was explained to me and not add extras things that were not mentioned that will scare us that oh we will now do 1, 2 and 3. We will get injected, like others were now scared that once you receive the vaccine you would die. Let's talk what's in the study and direct and not make up things. I think that it's important that we as participants do that and where we cannot answer refer people" (Male, 58 years old)

On the other hand, participants had a different experience when it came to interactions with friends. Friends took little convincing or motivation. Participants did not always go to great detail about the study but were able to influence their friends because they were already part of the study. This participant speaks on how as friends whenever there is an 'opportunity' that brings money, they share it amongst each other.

"So, me I said there is something that I have joined. Sis Thandeka, you know that as friends we always discuss with each other that if there is anything that has connection, that involves money we should always plug each other…" (Female, 25 years old)

There was not much convincing needed when it came to friends and joining the COVID-19 vaccine study. Friends did not need to explain the COVID-19 vaccine study in great detail, all that was needed was confirmation that the friend who was also part of the study.,

"You know shame with me, she did not explain much to me. She was like friend there is thing at Mshiyeni you get money go to it. And I was like oh ok. And she told me how to register. You see this is why I did not want to answer this part. So, she told me how to register and I did, and I came. So, for me I came here with no knowledge at all." *(Female, 29 years old)*

There were many other participants that joined the study because their loved ones had died, likely due to COVID-19, particularly the elderly, and therefore wanted to participate in the study because of the loss as well as prevent another loss of a family member.

"So, like I explained how I decided to join was because of the passing of my gran and my sister then told me that there was a study that did such and such so let us try and get on this study so that we can also help the old man (grandfather) that he doesn't find himself in trouble. And that's what made me join." (Male, 32 years old)

Participants were also used by their family to test 'theories' that were circulating within the communities such as the coin test. There were videos on social media platforms such as Instagram and TikTok where individuals who claimed to have been vaccinated would stick a coin where they had received the vaccine. These people believed that the COVID-19 vaccine contained something that was magnetic, while others claim that it was proof of a microchip used by the government to track people.

One participant had family members stick a coin on their vaccinated arm. They confirm how the coin did not stick. Although the coin did not stick the participant still sought confirmation from the interviewer that indeed the coin theory was not true.

"They say that after vaccinating, if you put money on the vaccinated arm it will stick? ...yes, at home, they tested it with me, and the money did not stick (*Male, 31 years old)*

Participants did look to the study staff to validate their concerns and also had more trust towards the study because of the appearance of the research organisation's Director and South African clinical infectious diseases epidemiologiston the news, explaining the vaccine studies as well as COVID-19 and its effect on healthcare.

"I heard yesterday on the news because I like watching news, I saw Prof Slim… He said people do not want to vaccinate, ay people like to risk their life." (Male, 31 years old)

When asked whether seeing the organisations Director had any impact on their participation in the trial, the participant felt that it helped them understand the need for the trial and that for them they joined the study for two reasons, access to the vaccine and the reimbursement benefit.

"I see now Ha-ha the need for the study, really some people on this program only wanted money, me I wanted both money and the vaccine." (Male, 31 years old)

Theme 4: Participants perceptions of the informed consent process

The goal of this study was to determine the extent to which participants remembered and understood the information they received during the study. During the trial the participants were reconsented three times. The reasons for reconsenting were:

1. There was a change to the eligibility and this change affected age and sample size. Initially the trial looked to enroll a total of 2, 904 participants in South Africa between the ages of 18 and 65 years. The change was 4,404 participants in South Africa and be an adult aged at least 18 years but less than 65 years in group 2 and less than 85 years in group 1.
2. As part of the trial participants would be tested for HIV at the screening and enrolment visit only and based on their results would be assigned to either group 1 (HIV negative) or group 2 (HIV positive). The change included a repeat HIV test that would be done at Day 201, which is 6 months post the initial vaccination period.
3. Safety information was distributed to participants via a memo (SEP 2021 and update Jan 2022) informing participants of a safety update of the trial's vaccine. The results of the trial's interim analysis noted an imbalance of acute cholecystitis (which is inflammation of the gallbladder) in vaccine recipients. The participants were not required to sign the memo, only once addendum to Version 4 of the Information Leaflet and Informed Consent Form were approved and received, were participants required to sign. This affected only a few participants who remained on the study.

Subtheme 1: Perceptions about various aspects of the informed consent

Of the 25 participants interviewed only one participant was able to recall the information around the reconsenting, such as the increase in age for eligibility and change in visit scheduling.

"If I remember correctly the first few months, we use to do visits every week, but it changed as time goes and then I think i-age more old people allowed…" (Male, 21 years old)

Other participants did not recall signing any other informed consent throughout the trial. One participant mentions that the only other documents that they were required to sign in the trial were the Flu Pro and the Subject Diary.

"The first time I came here I did sign a form, but I don't remember signing any new forms afterwards, except for those forms that were meant for self-examination, things like temperature or any signs of corona" (Male, 53 years old)

While most participants recalled signing another Information leaflet and informed consent form, they did not remember why. One participant says there were changes to the vaccine and therefore because they were receiving another vaccine, they had to sign a new form.

"That time we were changing the vaccine because the first time we vaccinated we did sign the forms, but I don't remember what the first vaccine was called but the second vaccine we got was called Novavax" (Female, 29 years old)

Another participant mentions the vaccines that they are Pfizer and the placebo and not all participants in the trial would receive both vaccines at the same time but would be scheduled to receive either Pfizer or Placebo.

"It was about the two vaccines that we would receive and their names and that the ones that would receive …gosh I don't remember their name, but I think there was Pfizer and placebo. That there would those that receive Pfizer and those that receive placebo. the ones that receive Pfizer first will not receive…eeesh, how can I explain this?! What I'm trying to say is that participants won't get both vaccines and the same time. They will receive…they will be booked for a separate day to receive the other vaccine." (Female, 33 years old)

Other participants did not recall the content but remember being reconsented by the Researcher.

"I don't remember well but there was a second one we signed. I think either last year or this year. I honestly don't remember what we were signing for" (Female, 25 years old)

"There were changes it's just that I do not remember, If I do remember I'll tell you but it's you Thandeka who explained it to us." (Male, 21 years old)

What was evident is that majority of participants who answered yes to the question, of whether there was a second or third Information leaflet and informed consent form, recalled the most recent contents of the notification around cholecystitis (inflammation of the gallbladder) that was found in a small number of male participants in the USA.

"It was that there are now some people that were found to have…when you have received your vaccine there is a disease you get, I don't know whether it's in your gall bladder or something, but we had to sign to confirm that we have been informed of that." (Male, 53 years old)

Participants remembered the Information Leaflet and Informed consent form for Storage and future Use, however there was a disconnect when it came to understanding the contents and reason for storage and future use of the samples. Participants understood that their samples would be stored and used for future use and that there was a choice on whether you wanted your samples to be stored for future use.

"Ehm with the bloods, I think I was asked whether or not I wanted the bloods to be used after the study for other things and I said yes and then the swabs I'm not sure hey." (Female, 40 years old)

"The swabs I think they get destroyed because you cannot keep such a specimen. The blood, well I do have knowledge on that, you sign to say whether you agree for it to be destroyed or can be used." (Female, 21 years old)

When asked to provide examples of how samples would be used for the future use, participants believed that the bloods would be used for donating to other patients that may need blood in hospitals.

"Eh they are sent to hospital for people who need blood, to assist them." (Female, 21 years old)

"They were stored to help others maybe who had a shortage of blood. But only those that matched my blood type that is healthy and does not have any illnesses." (Female, 33 years old)

With further probing participant responded:

"Can I explain according to my understanding. Ok so there's this thing called blood type, correct? So, I think that people that are HIV negative first get tested according to those things, which blood type. Because when you are in hospital, they first check your blood type before they donate to you. I think. This is according to my understanding ukuthi how do they check. They divide according to blood type." (Female, 33 years old)

CONCLUSION

Although participants expressed an overall good understanding of the purpose of the clinical trial they were enrolled in, there was a lack in conceptual understanding. There were participants who did not understand the process and came up with their own interpretations of elements covered in the informed consent document. Participants who experienced an event such as, testing positive for COVID-19 during their participation in the clinical trial, talked about the informed consent process more thoroughly. Participants understood the purpose of informed consent better when elements of the informed consent process were repeated throughout the study. Recall of the reconsenting showed that participants were most likely to recall most recent events and changes in the study. Participants were moved by several factors related to the clinical trial besides reimbursement. Other motivations related to them wanting to know about the vaccine and what

participation entailed, them wanting to learn about COVID-19 and vaccines, them wanting access to healthcare and them wanting to protect their families through the potential benefits of the vaccine. The community, family, and friends, although vocal about participants participation and about the trial, did not deter participants from participating.

CHAPTER 5: DISCUSSION

Introduction

This chapter will discuss the study findings under three broad themes (i) Participants' perceptions of the informed consent process (ii) Participants' experiences with the informed consent and lastly (iii) Factors motivating potential participation.

Participants' perceptions of the informed consent process

The results of this study revealed that most participants understood the trial's goals, however there were misunderstandings and knowledge gaps to some aspects of the trial's informed consent. The trial had two vaccination or injection periods. These injection periods seemed to be major cause of confusion for participants. Most participants understood that in the two injections periods they were receiving different COVID-19 vaccines. While other participants would confuse placebo for a vaccine, and believed that at the second injection period, they were receiving Johnson and Johnson or Pfizer. This confusion is supported by systematic reviews (Mandava et al., 2012 and Tam et al., 2015) conducted on consent assessment studies which show that certain elements of informed consent, such as randomization, the experimental nature of a study, availability of alternative treatments, distinguishing study and non-study procedures and compensation for trial-related injuries are universally difficult to grasp for participants. Similar to the systematic reviews the study showed that participants understood the investigational nature of the vaccine however

there were difficulties with understanding of placebo and the different injection periods in the COVID-19 vaccine trial.

In another systematic review which aimed at identifying participants' comprehension of specific informed consent components, it was reported that most people's comprehension of fundamental informed consent components was low (Pietrzykowski & Smilowska, 2021). Pietrzykowski and Smilowska (2021) found that there are various discrepancies in the knowledge of participants about the multiple components of informed consent, such as freedom to withdraw, voluntary participation, and blinding. Only a few percent of them were able to correctly respond to questionnaire items (Pietrzykowski & Smilowska, 2021). Results also suggest that a small number of participants have a clear understanding of all of these components. They additionally had a hard time understanding safety and risks, side effects and grasping the concept of placebo (Schumacher et al., 2017; Chu et al., 2012; Chaisson et al., 2011; Ellis et al., 2010). In this study there was an overall good understanding of most components of the informed consent, in contrast to the studies in the review (Schumacher et al., 2017; Chu et al., 2012; Chaisson et al., 2011; Ellis et al., 2010). In contrast to this study, the review included statistical data where 69.6% of participants understood the purpose of the study and only 54.9% could name at least one risk (Pietrzykowski & Smilowska, 2021). In this study almost all participants understood the purpose of the study and there were a few participants who confused vaccine risk and risk of getting COVID-19. The findings by Schumacher et al., 2017; Chu et al., 2012; Chaisson et al., 2011; Ellis et al., 2010 reported that approximately half of the participants understood placebo and randomization concept, whereas in this study we found that almost all participants could define placebo and its

contents, however this study did find that only a few participants were able to grasp the concept of what a placebo is without confusing the placebo as a form of vaccine.

Most participants in the COVID-19 vaccine trial gave their consent to the use of their samples for future research. The results of the study suggest that although participants consented in a simple choice to either allow or decline their participation in future research, participants had limited understanding of the conditions and complexities involved in the use of their samples for future COVID-19 research. Participants attitudes, beliefs, and level of knowledge were that the samples would be donated to patients that needed it. Contextual factors are reported to influence understanding (Eisenhauer et al., 2017). Although the contextual factors found in the review were also in this study, such as demographic characteristics, they were not used to measure understanding of informed consents. The contextual factors found by Eisenhauer et al (2017) include circumstances of recruitment; education, literacy, and reading; consent modalities; locality; other demographics (e.g., age, gender, and income), consenters; and the amount of time spent explaining consent information. The findings by Eisenhauser et al (2017) suggest that the use of biobanking in clinical trials should be conducted with caution. In addition, the participants' understanding of the benefits of the procedure was also not clear. For instance, even though they were told that it was intended to help others, many of them still held expectations of their own benefits. In this study, participants that were HIV positive reinforced this as they believed that their samples would be sent to different doctors or specialist that would review their blood and if there was anything of concern found, the research site and the participant would be contacted and participant would receive necessary attention. These participants believed that the bloods would be tested not only for viral load or CD4 count but drug levels and efficacy.

The incongruences found by Eisenhauer et al (2017) suggest that the participants' expectations of their own personal benefit may be influenced by the study's goal or purpose. This suggests that the lack of awareness of these knowledge gaps of the trial's consent form is an important implication for the design and implementation of future clinical trials. The capacity of the researcher to intentionally explain and the ability of the participant to grasp the information are both factors that influence how well participants are informed about these elements of the trial.

This finding is contrary to that of this study as participants in this study believed that the samples would be "donated" to those that need blood in hospitals and in that way, they were helping others. Participants that were HIV positive believed that their samples were going to be "analysed" by specialists and that if they found any discrepancy in the blood such as high viral load they would be contacted immediately. Others believed that their samples would be donated to an HIV positive individual who needed blood. In this study, we found that most participants understood that the concept of their 'samples being stored', however participants had their own understanding of what 'for future use', despite being prompted by the interviewer on the logistics of their understanding. Participants in this study all consented to their samples being stored and used for future use with no objectives. The lack of understanding of storage and future use informed consent is similar to previous studies by Munung et al. (2015) and Rutakumwa et al. (2019)) that have shown that participants had a hard time comprehending certain concepts.

According to studies (Appelbaum et al., 2004; Falagas et al., 2009; Tam et al., 2015), 50% of participants do not understand all the components of informed consent when it comes to participating in clinical trials and surgical procedures. Factors that contribute to this issue include

the lack of awareness of the various components of informed consent, the complexity of the language used, and the length of the consent documents, often making it difficult for people to navigate and understand them (Bickmore et al., 2009, Sieber & Levine, 2006). What is worth noting is that in this study the third reconsent was in a form of an information leaflet and related only to the information that participants needed to know. The first two reconsents participants were reconsented on the entire study, even though the changes were minimal and affected just illegibility and visit scheduling and HIV testing.

Participants' experiences with the informed consent

Language was one of the key emerging issues when it comes to participants' experience with the informed consent. The current study found that participants later changed their information leaflet from initially collecting the isiZulu leaflet to then asking for an English information leaflet. The reason behind this was that they found the isiZulu version of the leaflet more difficult to understand. This study found that this could be due to the nature in which isiZulu informed consent forms are translated, where some Zulu words may be lost in translation. One English word when translated into isiZulu often is wordier. Another reason is that the consent forms do not conform to contextual relevant terminology to ensure that participants are able to understand the terms used in the study, and that these terms are terms that are familiar and relevant within the community. Muzanyi et al. (2020) revealed that the choice of the consent language used during their study was associated with the participant's level of education. However, it did not find a similar study that analyzed the same question in other literature. The results of their study showed that the participants' consent language preference for English gradually increased as the literacy level rose.

The study did not find a link between gender and the level of education. The participants' preference for English was also associated with their age (18-25 years old) (Muzanyi et al., 2020). Interestingly with this study, age, gender, and level of education were not a factor. The request for an English informed consent form was across all demographics.

The only word participants were able to elaborate on, without any prompts, was *reimburse* or *ukukhokhelwa*. What is worth noting is that participants were able to elaborate on *side effects* and *evaluate safety and immunogenicity* once it was translated into English, only then did it prompt a response. The translated text seemed highly technical in isiZulu compared to when it is said or explained in English. A study conducted by Jack et al. (2014) had similar findings, almost all of the participants did not know or understand the term 'telemedicine', or the term 'video conference' the term 'electronic records. Words such as 'consent' and 'autonomy' were understood by less than a third of the participants and only 35% understood the word 'consent', with only 7% understanding both the words 'consent' and 'telemedicine'. Jack et al. (2014) attribute language barriers to the lack of help from interpreters, who at times may further cause confusion due to their lack of understanding of the words and terminology in the consent form. A limitation of this study was not able to assess the researcher's and the interpreter's knowledge of the terms used in the consultation. Language barriers in South Africa hospitals have been studied in order to understand their effects on the quality of care (Schlemmer and Mash, 2006). In a debate about the ethical issues surrounding the use of vaccines in clinical trials, Lindegger and Richter (2000) looked into similar problems that occurred when it came to the handling of informed consent. Although the legal requirements were met, the processes did not address the ethical considerations involved in making decisions that are in one's best interests.

A finding in this study that perhaps need to be researched further is that protection of confidentiality particularly when a study will randomize participants according to HIV status. Although the findings of this study do no suggest that stigmatization occurred, but rather participants were concerned about being part of the study, it does seem that the way and the period of randomization left room for participants to know HIV status of other participants. What is interesting is that participants were able to understand that the study needed HIV negative people first and after safety had been collected, then PLWHIV could participate, however participants were not able to tell from the number of tubes of bloods collected during the COVID-19 vaccine study. This information was also available in the informed consent form, as well as information of taking extra tubes of blood if you were HIV positive.

Although we did not observe differences in the responses of HIV-positive individuals to questions about their participation in research studies, there is still a lack of research on what factors influence the value of PLWH participation in such studies and the value of confidentiality or lack thereof because of clinical procedures or study design. One review found that various factors such as distrust of researchers, societal discrimination, and pragmatic obstacles are barriers to participation in HIV clinical trials (Mills et al., 2006). The review found that confidentiality is an important factor that PWH consider when it comes to participating in clinical trials (Mills et al., 2006). Although there is a wide body of research on the various factors that affect the decisions of people living with HIV, only one study by Tindell et al. (1994) examined the thoughts of PLWH about the informed consent process. This study was conducted to assess the process of providing consent for a drug trial. It found that about 56% of the participants understood all of the information on the forms, while 21% thought that too much information was included (Tindall et al., 1994).

The authors of the study failed to analyze the thoughts of PLWH about the information that they were provided with, how the study design unintentionally disclose status, which could help improve the informed consent process. This lack of research highlights the need for further studies on how PLWH perceive the process of providing consent.

The study highlights the importance of protecting the privacy of participants while also addressing the evolving informational risk that is presented by online platforms.

Factors motivating potential participation

Reimbursement was not the only factor affecting participants' decision to participate in the COVID-19 vaccine trial, but also the possibility that participants could protect their family members from COVID-19. The younger respondents were still going out to see friends, despite the lockdown restrictions and they did not want to bring the virus home to their family members, especially those that had children and those that lived with an elderly person. Other participants had lost family members and/or witness loss of neighbours or friends due to COVID-19.

Participants' fear of some of the study procedures, their perceived intention of the trial, and the investigational vaccine, did not seem to affect their ability to participate in the study. Participants in the trial experienced community and family hesitancy, which may have been largely contingent on the misinformation circulating in social media and fear of study procedures, and their inconsistent understanding of the trial and the vaccine. Participants felt that by being part of the study they were helping dispel the misinformation and show the community and their family that

they were not harmed through their participation. Participants felts that their participation would either prove to the community that they were correct to be fearful or that the vaccine was safe and that the community and family can and should also receive a COVID-19 vaccine.

In a study conducted by Abdelhafiz et al. (2021) the factors that influence the likelihood of people participating in COVID-19 clinical trials were analysed. According to the respondents of the study, altruism is a factor that influences their willingness to participate in clinical trials. These people said that they would like to protect their families and communities from diseases (Abdelhafiz et al., 2021). Similarly, this study found that participants not only wanted to protect their families from COVID-19 but through their participation, participants felt that they were helping dispel the misinformation and fear within the community and their families, and their 'successful' participation would increase the chances of trust in the COVID-19 vaccine, therefore increasing uptake amongst members. Tohid et al. (2017) and Abdelhafiz et al. (2021) both found that aside from financial rewards, receiving additional healthcare was also associated with a higher likelihood of patients [participants] participating in clinical trials. In Abdelhafiz et al. (2021), for instance, people were more likely to participate in medical research if they received additional medical care. Similarly, in this study, participants found that the trial was more like their personal medical aid. Women found that they benefited more from participating in the trail as they were still able to continue with their family planning as there was a shortage in the local clinics.

The findings for the reasons for participants to participate in the COVID-19 vaccine trial were also supported by a survey conducted among a population of healthcare workers in Uganda, looking at the healthcare workers willingness to participate in COVID-19 vaccine trials (Kitonsa et al., 2021).

Both studies found that motivators for willingness to participate included hope of being protected against COVID-19, altruism, the opportunity to get health care, and the hope of receiving monetary benefits (Kitonsa et al., 2021).

Overall, participants expressed willingness to participate in the COVID-19 vaccine trials due to motivators such as reimbursement, hope of being protected against COVID-19, the opportunity to get health benefits, personal gain, and family protection.

Limitations/Assumptions

One limitation is that the researcher was involved in the recruitment and consent process of participants into the COVID-19 vaccine trial. The researcher ensured that participants sampled into this study understood that this is a new and different study from the COVID-19 Vaccine trial. Participants were continuously reminded that the purpose of this study is to learn more about their perceptions of, experiences with and motivations in the consent process, merely using COVID-19 vaccine trial as an example. As such, they were encouraged to provide criticism and point out areas of improvement.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

Conclusion

The study was conducted on participants who were part of COVID-19 vaccine study. It revealed that many of the participants understood the purpose of the study, however there were also issues with certain elements of the informed consent. Some participants did not have a clear understanding of the various aspects of their consent. Their level of formal education was not assessed or associated with their poor understanding of the process.

The study was conducted on an array of participants varying in age and level of education however lack of understanding of certain components of the informed consent was across the age group and the level of education. Those participants that experienced an event such as testing positive for COVID-19, or having extra blood tubes taken because of HIV status, were more likely to understand the procedures and remember what was in the informed consent. Also, participants were more likely to sign an isiZulu informed consent form but ask to take home a copy of the English informed consent form as participants found it easier to read in English. Participants also were like to ask for definition of terms in the informed consent in English, that isiZulu.

Recommendations

This study suggests the need for a greater focus on not only determining understanding of the study and study procedures but also focusing on how participants perceive and interpret information received. Therefore, these are some recommendations:

- Explorations of participant understanding of the Investigational Product (IP) (COVID-19 vaccines) and the placebo be done in larger populations and in other clinical trials involving an IP and Placebo.
- Informed consent needs to be ongoing and recall needs to be assessed at specific time points of the trial focusing on fundamental elements of the informed consent, particularly those found to cause confusion, such as which vaccine is being tested. To facilitate this, more studies need to be done exploring tools or measures that assess participants understanding of in clinical trials.
- The informed consent should include information on other vaccines. The difference between the study product and the other vaccines should be clearly stated.
- There is a need to do similar studies to determine how best to approach storage and future use informed consent in all clinical studies.
- During translation of the informed consent form, translations should be clear and mindful of the local language. The recommendation would be that translators of informed consent forms for clinical trials should be familiar with local language and acknowledge the changing dialect of Nguni languages.

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Appendix 1: The SA GCP 2020 guidelines key concepts in clinical trials

- The procedures and documentation for multi-site and multi-country trials must be sensitive to the requirements of each country and each site. The site's Principal Investigator should also ensure that the procedures and informed consent content are tailored accordingly.
- The informed consent documents must be approved by the Regulatory Ethics Committee (REC). They should be signed and witnessed by the participating participants.
- Incentives should not be used to encourage or undervalue the risks associated with a clinical trial. This should be done in a way that does not cause the participant to ignore or undervalue the trial's risks.
- The informed consent process should also help participants understand the various risks associated with a clinical trial. It should additionally not be focused on incentives when making a decision to participate.
- It is important to avoid paternalism. "If a clinical trial has been approved on the basis that it is ethical including having a reasonable risk/benefit ratio, then no principled objection to persons choosing to participate should exist"
- Reimbursement or payment of the participants' expenses is not an incentive. The trial should also provide refreshments and transport for the participants.
- The reimbursement rate should be determined using the Time, Inconvenience and Expenses (TIE) method, which takes into account the time, inconvenience, and expenses associated with participating in the study. This method costs expenses at the prevailing market rate for unskilled labour, regardless of participant's employment status

- The clinical trials that are conducted should be scientifically sound and should be based on the latest scientific information.
- "The available pre-clinical and clinical information on an investigational product (IP) should be adequate to support the proposed clinical trial"
- Clinical trials should be described in a clear, detailed protocol.
- The language used in an informed consent document should not be too technical or misleading.
- The informed consent document should be provided in a participant's preferred written language.
- Before a participant can be asked to participate in a clinical trial, they should have sufficient time to consider the trial and to ask questions. All questions should be answered in a way that is appropriate to the participant's satisfaction.
- The consent document should be signed by both the participant and the person who conducted the discussion.
- The investigator should also have the necessary information to obtain the participant's consent. This should be done in accordance with the principles of the Declaration of Helsinki and other guidelines
- After the participant has been informed about the trial, the signed consent document should be kept with the records of the study. A copy of this document should also be provided to the participant. The source documents or medical records of the participant should additionally be included with the signed consent document.

- Before a clinical trial is conducted, the sponsor should ensure that the data collected from pre-clinical studies and clinical trials are sufficient to support the study's safety and efficacy.
- If a proposed use of a placebo is made, this should be justified in accordance with the Declaration of Helsinki and contextualised for local circumstances.
- In principle, the use of a placebo in a clinical trial should only be justified if it is scientifically justified. This can be done if there is no evidence supporting the effectiveness of an existing treatment or if the placebo does not pose a risk of irreversible harm to the participants.
- When there is no established treatment for a condition under study, a placebo may be used as a comparison. It can also be used as a replacement for an existing treatment if the results of the study show that the new one is effective.

Appendix 2: English semi-structure interview guide

SEMI-STRUCTURED INTERVIEW
INTERVIEW GUIDE

Participant Identifier:	
Date of Interview:	

□	1. Please tell me what you understand about the NOVAVAX study and why it is being done?
□	2. What is the vaccine that is being tested?
□	3. Who can take part in the NOVAVAX study?
□	4. What were you told would happen if you participated in the NOVAVAX study?
□	5. How long is/was the NOVAVAX study?
□	6. What are the main procedures that were done in the NOVAVAX study?
□	7. What were you told to avoid during the NOVAVAX study?
□	8. What are/were the possible risks to participating in the NOVAVAX study?
□	9. What are/were the possible benefits to participating in the NOVAVAX study?
□	10. What were you told would happen if you test positive for COVID-19 while in the NOVAVAX study?
□	11. Where there any changes to the informed consent form? Do you remember them?
□	12. If you have questions or concerns about the NOVAVAX study, who do you contact and how?
□	13. What happens to all the information that is collected, and the specimens collected during the duration of the NOVAVAX study?
□	14. The money that you receive in the NOVAVAX study, what is it for?
□	15. Did you have any questions at the end of the informed consent process of the NOVAVX study and what were they?

Appendix 3: isiZulu semi-structured interview guide

SEMI-STRUCTURED INTERVIEW
INTERVIEW GUIDE

Participant Identifier:	
Date of Interview:	

□	1. Ngicela ungitshele ukuthi uqonde ini ngocwaningo luka-NOVAVAX nokuthi kungani lwenziwa?
□	2. Uyini umuthi wokugoma ohlolwayo?
□	3. Ngubani ongabamba iqhaza ocwaningweni luka-NOVAVAX?
□	4. Yini owatshelwa ukuthi izokwenzeka uma ubambe iqhaza ocwaningweni luka-NOVAVAX?
□	5. Saside kangakanani / side kangakanani ugwaningo luka-NOVAVAX?
□	6. Yiziphi izinqubo eziyinhloko ezenziwe ocwaningweni luka-NOVAVAX?
□	7. Yini owatshelwa ukuthi uyigweme ngesikhathi socwangino luka-NOVAVAX?
□	8. Buyini / bebuyini ubungozi kokubamba iqhaza ocwaningweni luka-NOVAVAX?
□	9. Yiziphi / zaziyini izinzuzo zokubamba iqhaza ocwaningweni luka-NOVAVAX?
□	10. Yini owatshelwa ukuthi izokwenzeka uma uhlola ukuthi une-COVID-19 ngenkathi ukucwaningo luka-NOVAVAX?
□	11. Zike zabakhona izinguquko kwifomu lokuvuma? Uyazikhumbula?
□	12. Uma unemibuzo noma okukhathazayo ngocwaningo luka-NOVAVAX, uthinta bani futhi kanjani?
□	13. Kwenzekani kulo lonke ulwazi oluqoqiwe, kanye nama-sampula aqoqwe kulesikhathi ukucwaningo luka-NOVAVAX?
□	14. Imali oyithola ocwaningweni luka-NOVAVAX, eyani?
□	15. Ikhona imibuzo owawunayo ngemva kukuchazelwa ngocwaningo luka-NOVAVAX, yayithini?

Appendix 4: English focus group guide

FOCUS GROUP

TOPIC GUIDE

✓	QUESTIONS
	1. What was your first reaction when you heard about the NOVAVAX study?
	2. How would you describe the NOVAVAX study to someone else? Did you invite friends or family members to be part of the NOVAVAX study?
	3. What made you decide to take part in the NOVAVAX study?
	4. What are your thoughts on how the NOVAVAX study was conducted? What are you happy about? What are you least happy about?
	5. The informed consent is 23 pages in English and 25 pages in isiZulu, what is it that you remember from the form? What do you think is important to remember and what do you think is not as important to remember?
	6. What words or feelings come to mind when I say the following from the informed consent? ***a) Placebos*** ***b) Evaluate safety and immunogenicity*** ***c) Reimburse*** ***d) Side effects***
	7. If you could add or improve anything about the 1) study and 2) the informed consent, what would it be?
	8. Some people have said that there are those that join the NOVAVAX study because of the money. What is your take on this?
	9. Is there anything you wish to add that I have not touched on before we end this discussion?

Appendix 5: isiZulu focus group guide

FOCUS GROUP
TOPIC GUIDE

✓	IMIBUZO
	10. Yaba yini imicabango yakho yokuqala lapho uzwa ngocwaningo luka-NOVAVAX?
	11. Ungaluchaza kanjani ucwaningo luka-NOVAVAX komunye umuntu? Ngabe wamema abangani noma amalungu omndeni ukuthi abe yingxenye yocwaningo luka-NOVAVAX?
	12. Yini ekwenze wanquma ukubamba iqhaza ocwaningweni luka-NOVAVAX?
	13. Ithini imibono yakho ngendlela olwenziwe ngayo ucwaningo luka-NOVAVAX? Ujabule ngani? Yini ongajabuli ngayo?
	14. Ifomu yemvume yesingisi ingamakhasi awu-23 eyesizulu yona awu-25, yini oyikhumbulayo ngalefomu? Ucabanga ukuthi yini ebalulekile okufanele uyikhumbule futhi ucabanga ukuthi yini engabalulekile kangako ukuyikhumbula?
	15. Yimaphi amagama noma imizwa efika engqondweni uma ngisho lokhu okulandelayo kusuka kwifomu yemvume? *a) Placebo* *b) Evaluate safety and immunogenicity (*Ukuhlola ukusebenza kahle kokuphepha kokuzivikela komzimba) *c) Reimburse (Ukukhokhelwa)* *d) Side effects (*Imiphumela emibi yomugomo)
	16. Uma ungangeza noma uthuthukise noma yini mayelana 1) nocwaningo noma-2) ngefomu yemvume, kungaba yini?
	17. Kuthiwa abanye bangenela lolucwaningo ngoba kutholakala imali. Wena uthini?
	18. Ngabe kukhona ofisa ukukungeza engingakakuthinti ngaphambi kokuqeda le ngxoxo?

Appendix 6: Demographic Data

Participant Demographic Data:

1. How old are you? ☐☐
2. What is your gender? Male ☐ Female ☐ Other ☐
3. What is your language preference? IsiZulu ☐ English ☐
4. What do you do for a living? Employed full time ☐ Employed Part-time ☐ Unemployed ☐

   Secondary school student ☐
   Tertiary School student ☐ Other
   (specify) _____
5. What is the highest grade or level of education that you have completed?
   - Still in secondary school (specify grade)
   - Did not complete primary or secondary school (specify grade)
   - Matriculated
   - Some tertiaries but no degree
   - Undergraduate degree
   - Postgraduate degree

Appendix 7 –BMREC Approval

UNIVERSITY of the WESTERN CAPE

60 YEARS of hope, action & knowledge

29 November 2021

Ms T Nkosi
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number:	BM21/10/22
Project Title:	Participants' perceptions, experiences and the factors motivating their participation with the informed consent process of a COVID-19 vaccine trial in South Africa.
Approval Period:	**29 November 2021 – 29 November 2024**

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project and the requested amendment to the project.

Any further amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report annually by 30 November for the duration of the project.

For permission to conduct research using student and/or staff data or to distribute research surveys/questionnaires please apply via:
https://sites.google.com/uwc.ac.za/permissionresearch/home

The permission letter must then be submitted to BMREC for record keeping purposes.

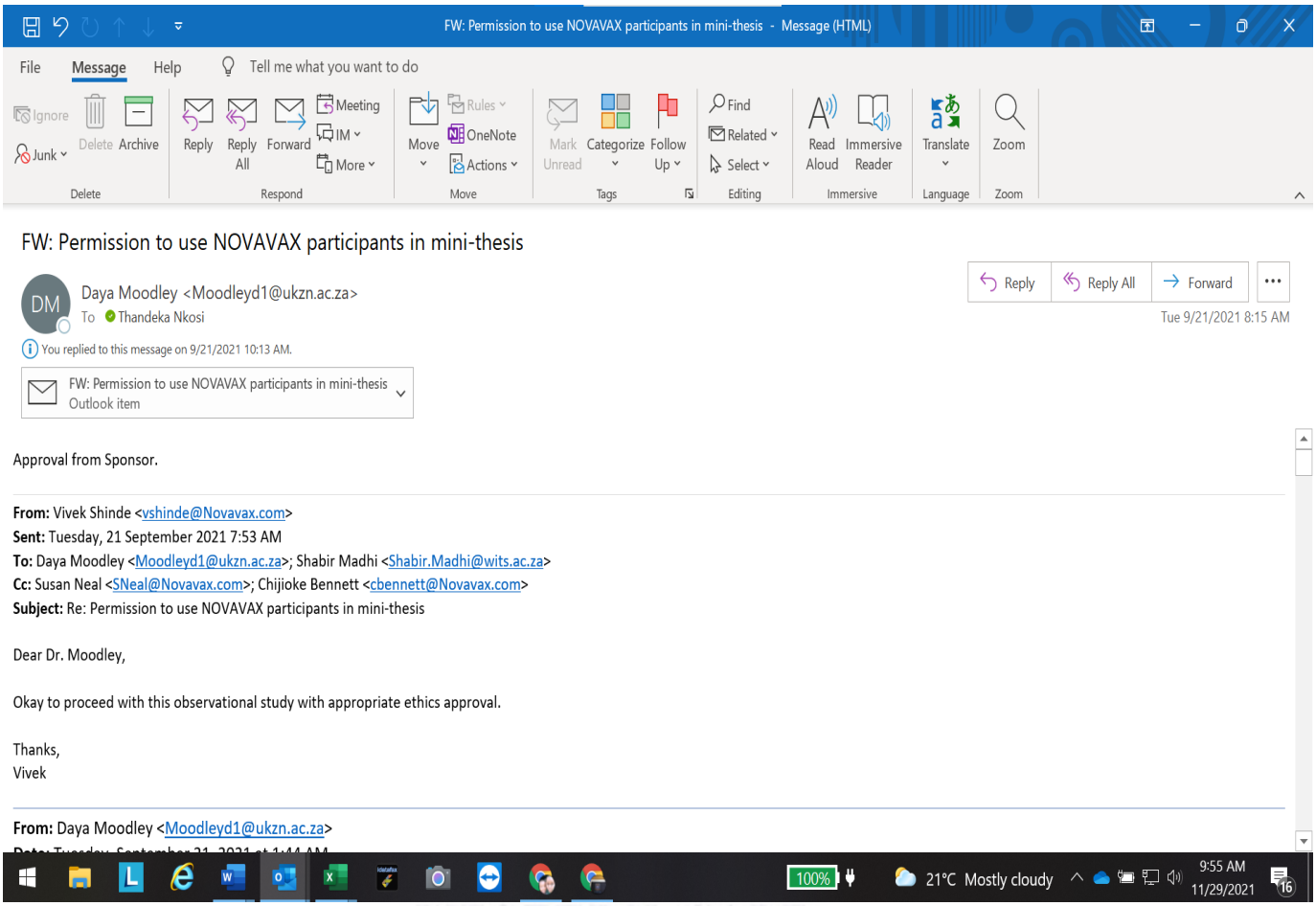
The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

NHREC Registration Number: BMREC-130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE.

Appendix 8: Permission from Sponsor



FW: Permission to use NOVAVAX participants in mini-thesis - Message (HTML)

File Message Help Tell me what you want to do

Ignore Junk Delete Archive Reply Reply All Forward Meeting IM More Move Rules OneNote Actions Mark Unread Categorize Follow Up Find Related Select Read Aloud Immersive Reader Translate Zoom

Delete Respond Move Tags Editing Immersive Language Zoom

FW: Permission to use NOVAVAX participants in mini-thesis

DM Daya Moodley <Moodleyd1@ukzn.ac.za>
To Thandeka Nkosi

Reply Reply All Forward

Tue 9/21/2021 8:15 AM

You replied to this message on 9/21/2021 10:13 AM.

FW: Permission to use NOVAVAX participants in mini-thesis
Outlook item

Approval from Sponsor.

From: Vivek Shinde <vshinde@Novavax.com>
Sent: Tuesday, 21 September 2021 7:53 AM
To: Daya Moodley <Moodleyd1@ukzn.ac.za>; Shabir Madhi <Shabir.Madhi@wits.ac.za>
Cc: Susan Neal <SNeal@Novavax.com>; Chijioke Bennett <cbennett@Novavax.com>
Subject: Re: Permission to use NOVAVAX participants in mini-thesis

Dear Dr. Moodley,

Okay to proceed with this observational study with appropriate ethics approval.

Thanks,
Vivek

From: Daya Moodley <Moodleyd1@ukzn.ac.za>

100% 21°C Mostly cloudy 9:55 AM 11/29/2021

Appendix 9: English Information sheet

INFORMATION SHEET

Project Title: Participants' perceptions, experiences and the factors motivating their participation with the informed consent process of a COVID-19 vaccine trial in South Africa.

What is this study about?
This is a research project being conducted by Thandeka P. Nkosi at the University of the Western Cape for the fulfilment of her mini thesis. We are inviting you to participate in this research project because you have undergone informed consent for the NOVAVAX study.

The purpose of this research project is to gather information on research participants' perceptions, experiences and the factors motivating their participation with the informed consent process of a COVID-19 vaccine trial in South Africa. Information from this study would help identify what things to make better in the informed consent process (including how information is given) for future research studies or clinical trials. We hope to collect information on which things work well or not in the informed consent process if you agree to participate in this study.

What will I be asked to do if I agree to participate?
Participation is fully voluntary. To decide if you want to take part in this study, this form explains your role as a research participant. It will also explain any risks and possible benefits of the study. In addition to me explaining this study, please read this form carefully. Please ask any questions that might help you decide if you would like to take part in this study. If you decide to take part in this study, you will be asked to sign this consent form. A copy of this signed form will be given to you to keep.

You will be asked to be interviewed individually or you will be asked to be part of a focus group discussion. In the individual interviews, I will ask you some questions about your views or thoughts with the with informed consent process of the NOVAVAX study. You will also be asked about what motivated you to take part in the NOVAVAX study. I would like you to discuss your views, thoughts of motivations in a private and confidential interview. This will take about 45-60 minutes of your time. This interview will be audio recorded, should you provide permission. The interview will take place at Umlazi Clinical Research site, in Prince Mshiyeni Memorial Hospital.

Below are examples of the topics that I will discuss with you, and I will also have the NOVAVAX study's information sheet and consent form to help guide our discussion during the interview process:

- Your perceptions of and experiences with the informed consent process of the NOVAVAX study
- Your motivations for participating in the NOVAVAX study

The focus group discussion will consist of other research participants who also participated in the NOVAVAX study and have agreed to take part in this study. The focus group discussion will take 45-60 minutes of your time. The focus group discussion will be audio recorded, should you provide permission. The focus group discussion will take place at Umlazi Clinical Research site, in Prince Mshiyeni Memorial Hospital. Below are examples of the topics that will be discussed, and I will also have the NOVAVAX study's information sheet and consent form to help guide our discussion during the discussion:

- Your perceptions of and experiences with the informed consent process of the NOVAVAX study
- Your motivations for participating in the NOVAVAX study

Would my participation in this study be kept confidential?

The researcher undertakes to protect your identity and the nature of your contribution. To ensure your anonymity, only my supervisor and I will have access to the information collected from you, no one else. My supervisor will only have access to the information once I have replaced your real name with a fake name or code to ensure your privacy. This means confidentiality of your information (interview responses and information sheet) will be maintained. Your identity and contact details (name, address, etc.,) will remain private. They will only be known by me.

I will ask you at the beginning of the interview and/or the focus group discussion if you are fine with me audio-recording. Audio-recording will help make sure that we have your words exactly how you said them. Neither your name nor any other identifying information will be associated with the audio recording or the interview and/or focus group discussion transcripts. Only the researcher will be able to listen to the recordings. The audio-recordings and soft-copies of the transcripts will not contain your name or other identifying information. The audio-recordings and soft-copies of the transcripts will be transferred to a USB flash drive and stored with any hard-copies (i.e., notes) in a locked cabinet at the researcher's workplace.

The audio will be transcribed and translated by the researcher and the transcriptions will be checked for accuracy. Transcripts of your interview may be reproduced in part for use in written products that result from this study. Neither your name nor any other identifying information (such as your voice) will be used in papers, presentations or in other products resulting from the study. After five years the hard copies will be shredded and the information on the USB flash drive will be permanently deleted.

This study will use focus groups therefore the extent to which your identity will remain confidential is dependent on the participants in the focus group with you, however, all participants will be asked to maintain confidentiality and sign a focus group confidentiality binding agreement.

What are the risks of this research?
There may be some risks from participating in this research study. Some of the interview questions on your experiences may make you uncomfortable. If you feel uncomfortable you can skip the question, take a break, or stop the interview completely. Every effort will be taken to protect your identity. No name or identifying information will be matched with your interview responses. Interviews will be conducted in private, and every effort will be made to protect your privacy and confidentiality to the extent where possible.

All human interactions and talking about self or others carry some number of risks. We will nevertheless minimise such risks and act promptly to assist you if you experience any discomfort, psychological or otherwise during the process of your participation in this study. Where necessary, an appropriate referral will be made to a suitable professional for further assistance or intervention.

What are the benefits of this research?

This research is not designed to help you personally, but the results may help the investigator learn more about research participants experiences of, and perceptions of the informed consent and the reason for taking part in research studies. We hope that, in the future, other people might benefit from this study through improved understanding of the informed consent, its process and understanding.

Do I have to be in this research, and may I stop participating at any time?
Your participation in this research is completely voluntary. You may choose not to take part at all. If you decide to participate in this research, you may stop participating at any time. If you decide not to participate in this study or if you stop participating at any time, you will not be penalized or lose any benefits to which you otherwise qualify.

What if I have questions?
This research is being conducted by ***Thandeka P Nkosi with the School of Public Health*** at the University of the Western Cape.

If you have any questions about the research study itself, please contact:

Thandeka P Nkosi
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Umlazi Clinical research Site
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Prof Uta Lehmann
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This research has been approved by the University of the Western Cape's Biomedical Research Ethics Committee.

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Appendix 10: isiZulu information sheet

ISHIDI LOKWAZISWA

Isihloko sohlelo: Imibono yababambiqhaza, okuhlangenwe nakho kanye nezinto ezikhuthaza ukubamba kwabo iqhaza enqubweni yemvume enolwazi yocwaningo lokugoma lwe-COVID-19 eNingizimu Afrika.

Ngabe lolu cwaningo lumayelana nani?

Lolu wuhlelo lokucwaninga olwenziwa **nguThandeka P. Nkosi** eNyuvesi yaseWestern Cape ukuze kufezeke umbhalo onobuhlakani wokuthola iziqu enyuvesi. Sikumema ukuthi ubambe iqhaza kulo luhlelo locwaningo ngoba kwenziwa inqubo yokuthola imvume yocwaningo lwe-NOVAVAX kuwe.

Inhloso yalo lucwaningo ukuqoqa imibono yababambiqhaza, okuhlangenwe nakho kanye nezinto ezikhuthaza ukubamba kwabo iqhaza enqubweni yemvume enolwazi yocwaningo lokugoma lwe-COVID-19 eNingizimu Afrika. Imininingwane evela kulolu cwaningo izosiza ukukhomba ukuthi yiziphi izinto ezizokwenza ngcono kunqubo yemvume enolwazi (kufaka phakathi nokuthi imininingwane inikezwa kanjani) ezifundweni zocwaningo ezizayo noma ezivivinyweni zokwelashwa. Siyethemba ukuqoqa ulwazi lokuthi yiziphi izinto ezisebenza kahle noma ezingasebenzi kahle kwinqubo yemvume enolwazi, uma uvuma ukubamba iqhaza kulolu cwaningo.

Yini engizocelwa ukuba ngiyenze uma ngivuma ukubamba iqhaza?

Ukubamba iqhaza kwenziwa ngokuzithandela ngokuphelele. Ukunquma ukuthi uyafuna yini ukubamba iqhaza kulolu cwaningo, leli fomu lichaza iqhaza lakho njengomhlanganyeli ocwaningweni. Izophinde ichaze noma yiziphi izingozi nezinzuzo ezingaba khona zocwaningo. Ngaphezu kokuchaza kwami lolu cwaningo, ngicela ufunde leli fomu ngokucophelela. Sicela ubuze noma yimiphi imibuzo engakusiza unqume ukuthi ungathanda yini ukubamba iqhaza kulolu cwaningo. Uma uthatha isinqumo sokubamba iqhaza kulolu cwaningo, uzocelwa ukuthi usayine leli fomu lokuvuma. Ikhophi yaleli fomu elisayiniwe uzonikezwa ukuthi uligcine.

Uzocelwa ukuthi kuxoxwe nawe ngamunye noma uzocelwa ukuthi ube yingxenye yengxoxo yeqembu. Ezingxoxweni zomuntu ngamunye ngizobe sengikubuza imibuzo ethile mayelana nemibono noma imicabango yakho ngenqubo yemvume enolwazi yocwaningo lwe-NOVAVAX. Uzobuzwa futhi nokuthi yini ekugqugquzele ukuthi ubambe iqhaza ocwaningweni lwe-NOVAVAX. Ngingathanda ukuthi we uxoxe ngemibono yakho, imicabango yokugqugquzelwa,

enkulumweni yangasese neyimfihlo. Lokhu kuzothatha cishe imizuzu engama-45-60 yesikhathi sakho. Le ngxoxo izorekhodwa, uma unganikeza imvume. Inhlolokhono izoba seMlazi Clinical Research site, esibedlela iPrince Mshiyeni Memorial. Ngezansi kunezibonelo zezihloko engizoxoxa ngazo nawe, futhi ngizoba nephepha lolwazi locwaningo lwe-NOVAVAX kanye nefomu lemvume ukuze lisize ukuqondisa ingxoxo yethu ngesikhathi senhlolokhono:

- Imibono yakho kanye nolwazi lwakho ngenqubo yemvume enolwazi yocwaningo lwe-NOVAVAX
- Izizathu zakho zokubamba iqhaza ocwaningweni lwe-NOVAVAX

Ingxoxo yeqembu lokugxila izokwenzeka ngosuku ozonikezwa lona ngaphambi kwesikhathi. Ingxoxo yeqembu okugxilwe kuyo izobandakanya abanye ababambiqhaza bocwaningo nabo ababambe iqhaza ocwaningweni lwe-NOVAVAX futhi bavumile ukubamba iqhaza kulolu cwaningo. Ingxoxo yeqembu okugxilwe kuyo izorekhodwa, uma unikeza imvume. Inhlolokhono izoba seMlazi Clinical Research site, esibedlela iPrince Mshiyeni Memorial. Ngezansi kunezibonelo zezihloko okuzoxoxwa ngazo, futhi ngizoba nephepha lolwazi locwaningo lwe-NOVAVAX kanye nefomu lemvume ukusiza ukuqondisa ingxoxo yethu ngesikhathi sengxoxo:

- Imibono yakho kanye nolwazi lwakho ngenqubo yemvume enolwazi yocwaningo lwe-NOVAVAX
- Izizathu zakho zokubamba iqhaza ocwaningweni lwe-NOVAVAX

Ngabe ukuzibandakanya kwami kulolu cwaningo kungagcinwa kuyimfihlo?

Umcwaningi uzibophezela ukuvikela ubunikazi bakho kanye nohlobo lomnikelo wakho. Ukuqinisekisa ukungaziwa kwakho, mina nomphathi wami kuphela esizokwazi ukufinyelela kulwazi oluqoqwe kuwe, hhayi omunye umuntu. Umphathi wami uzokwazi ukufinyelela kulwazi uma sengisuse igama lakho langempela ngafaka igama noma ikhodi yamanga ukuqinisekisa ubumfihlo bakho. Lokhu kusho ukuthi imininingwane yakho iyimfihlo (izimpendulo zenhlolokhono kanye nephepha lemininingwane) kuzogcinwa. Ubunikazi bakho nemininingwane yokuxhumana (igama, ikheli, njll.,) Kuzohlala kuyimfihlo. Bazokwaziwa yimi kuphela.
Ngizokubuza ekuqaleni kwengxoxo kanye / noma engxoxweni yeqembu okugxilwe kulo uma ngabe ulungile nami ngokuqoshwa kwengxoxo. Ukuqoshwa kwengxoxo kuzosiza ekuqinisekiseni ukuthi sinawo amagama akho ngendlela owasho ngayo. Alikho igama lakho noma eminye imininingwane ekhomba ezohlotshaniswa nokiqosha kwengxoxo noma inhlolokhono kanye / noma imibhalo yengxoxo yeqembu lokugxila. Umcwaningi kuphela ozokwazi ukulalela okuqoshiwe. Ukurekhodwa komsindo namakhophi athambile wemibhalo ngeke kube negama lakho noma eminye imininingwane ekhomba. Ukuqoshwa kwengxoxo

namakhophi wemibhalo kuzodluliselwa kwi-USB bese kugcinwa nanoma yimaphi amakhophi (okungukuthi, amanothi) kwikhabethe elikhiyiwe emsebenzini womcwaningi.
Ingxoxo izobhalwa futhi ihunyushwe ngumcwaningi bese okubhaliwe kuzohlolwa ukuthi kunembile yini. Okubhaliwe kwengxoxo yakho kungaphinde kukhiqizwe ngokwengxenye ukuze kusetshenziswe kwimikhiqizo ebhaliwe okuvela kulolu cwaningo. Igama lakho noma olunye ulwazi olukhombayo (njengephimbo lakho) ngeke lusetshenziswe emaphepheni, ezethulweni noma kweminye imikhiqizo evela ocwaningweni. Ngemuva kweminyaka emihlanu amakhophi aqinile azosikwa bese imininingwane kwi-USB izosuswa unomphela.

Lolu cwaningo luzosebenzisa amaqembu okugxila ngakho-ke ukuthi ubunikazi bakho buzohlala buyimfihlo kangakanani buxhomeke kubahlanganyeli abaseqenjini okugxilwe kulo nawe, noma kunjalo, bonke ababambiqhaza bazocelwa ukuthi bagcine imfihlo futhi basayine isivumelwano esibophezela imfihlo seqembu lokugxila.

Buyini ubungozi balo lolucwaningo?

Kungaba nezingozi ezithile ngokubamba iqhaza kulolu cwaningo. Eminye yemibuzo yengxoxo kokuhlangenwe nakho kwakho ingakwenza ungakhululeki. Uma uzizwa ungakhululekile ungeqa umbuzo, uthathe ikhefu, noma umise ingxoxo ngokuphelele. Yonke imizamo izothathwa ukuvikela ubuwena. Alikho igama noma imininingwane ekhomba ezofaniswa nezimpendulo zakho zenhlolokhono. Izingxoxo zizoqhutshwa ngasese, futhi kuzokwenziwa yonke imizamo ukuvikela ubumfihlo bakho kanye nokugcinwa kwakho kuyimfihlo kuze kube sezingeni lapho kungenzeka khona.

Konke ukuxhumana kwabantu nokukhuluma ngawe noma abanye kuthwala ubungozi obuthile. Noma kunjalo sizobunciphisa ubungozi obunjalo futhi sithathe isinyathelo ngokushesha ukukusiza uma uhlangabezana nokungaphatheki kahle, kwengqondo noma ngenye indlela ngesikhathi sokubamba iqhaza kwakho kulolu cwaningo. Uma kunesidingo, kuzodluliselwa uchwepheshe ofanele ukuze athole olunye usizo noma ukungenelela.

Ziyini izinzuzo zalolu cwaningo?

Lolu cwaningo alwenzelwe ukukusiza uqobo, kepha imiphumela ingasiza umphenyi ukuthi afunde kabanzi ngalo imibono yababambiqhaza kanye nokuhlangenwe nakho kwabo, ngenqubo yemvume yocwaningo, nezinto ezigqugquzela ukubamba kwabo iqhaza. Siyethemba ukuthi, ngokuzayo, abanye abantu bangazuza kulolu cwaningo ngokuqonda okuthuthukile kwemvume enolwazi, inqubo nokuqonda kwayo.

Ngabe kufanele ngibe kulolu cwaningo, futhi ngingayeka ukubamba iqhaza nganoma yisiphi isikhathi? Ukubamba iqhaza kwakho kulolu cwaningo kungokuzithandela ngokuphelele. Ungakhetha ukungabambi iqhaza nhlobo. Uma uthatha isinqumo sokubamba iqhaza kulolu cwaningo, ungayeka ukubamba iqhaza nganoma yisiphi isikhathi. Uma uthatha isinqumo

sokungabambi iqhaza kulolu cwaningo noma uma uyeka ukubamba iqhaza nganoma yisiphi isikhathi, ngeke ujeziswe noma ulahlekelwe yiminye imihlomulo ofanele ukuyithola.

Kuthiwani uma nginemibuzo?
This research is being conducted by ***Thandeka P Nkosi with the School of Public Health*** at the University of the Western Cape. Lolu cwaningo lwenziwa **nguThandeka P Nkosi neSikole Sempilo Yomphakathi** eNyuvesi yaseWestern Cape.

Uma unemibuzo mayelana nocwaningo uqobo, sicela uthinte:
Thandeka P Nkosi
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Umlazi Clinical research Site
076 196 1923 or 031 260 1985 (during office hours)
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Lolu cwaningo luvunyiwe yiKomidi Lezimilo Zokuziphatha Ngezocwaningo Ngezomnotho eNyuvesi yaseWestern Cape

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Appendix 11: English consent form

CONSENT FORM

Title of Research Project: Participants' perceptions, experiences and the factors motivating their participation with the informed consent process of a COVID-19 vaccine trial in South Africa.

The study has been described to me in language that I understand. My questions about the study have been answered. I understand what my participation will involve, and I agree to participate of my own choice and free will. I understand that my identity will not be disclosed to anyone. I understand that I may withdraw from the study at any time without giving a reason and without fear of negative consequences or loss of benefits.

___ I agree to be **[**videotaped/audiotaped/photographed**]** during my participation in this study.
___ I do not agree to be **[**videotaped/audiotaped/photographed**]** during my participation in this study.

Participant's name…….
Participant's signature…….
Date……

Appendix 12: isiZulu Consent Form

IFOMU YEMVUME

Isihloko sohlelo: Imibono yababambiqhaza, okuhlangenwe nakho kanye nezinto ezikhuthaza ukubamba kwabo iqhaza enqubweni yemvume enolwazi yocwaningo lokugoma lwe-COVID-19 eNingizimu Afrika.

Ucwaningo luchazwe kimi ngolimi engiluqondayo. Imibuzo yami mayelana nocwaningo iphenduliwe. Ngiyakuqonda ukuthi ukubamba iqhaza kwami kuzobandakanya ini futhi ngiyavuma ukubamba iqhaza ngokuzikhethela nenkululeko yami. Ngiyakuqonda ukuthi ubunikazi bami abuzukudalulwa kunoma ngubani. Ngiyaqonda ukuthi ngingahoxa ocwaningweni nganoma yisiphi isikhathi ngaphandle kokubeka isizathu futhi ngaphandle kokwesaba imiphumela emibi noma ukulahleka kwezinzuzo.

___ Ngiyavuma ukuthi [ngiqoshwe ngevidiyo / ngiqoshwe inkulumo / ngithwetshulwe izithombe] ngesikhathi ngibambe iqhaza kulolu cwaningo.

___ Angivumi ukuthi [ngiqoshwe ngevidiyo / ngiqoshwe inkulumo noma ngithwetshulwe izithombe] ngesikhathi ngibambe iqhaza kulolu cwaningo.

Igama lombambiqhaza…….

Isiginesha yombambiqhaza……...

Usuku……

Appendix 13: English Focus group confidentiality binding form

FOCUS GROUP CONFIDENTIALITY BINDING FORM

Title of Research Project: Participants' perceptions, experiences and the factors motivating their participation with the informed consent process of a COVID-19 vaccine trial in South Africa.

The study has been described to me in language that I understand. My questions about the study have been answered. I understand what my participation will involve, and I agree to participate of my own choice and free will. I understand that my identity will not be disclosed to anyone by the researchers. I understand that I may withdraw from the study at any time without giving a reason and without fear of negative consequences or loss of benefits. I understand that confidentiality is dependent on participants in the Focus Group maintaining confidentiality.

I hereby agree to uphold the confidentiality of the discussions in the focus group by not disclosing the identity of other participants or any aspects of their contributions to members outside of the group.

Participant's name…….
Participant's signature…….
Date……

Appendix 14: isiZulu focus group confidentiality binding form

IFOMU LOKUBOPHELA IMFIHLO YOKUGCINA INGXOXO YEQEMBU

Isihloko sohlelo locwaningo: Imibono yababambiqhaza, okuhlangenwe nakho kanye nezinto ezikhuthaza ukubamba kwabo iqhaza enqubweni yemvume enolwazi yocwaningo lokugoma lwe-COVID-19 eNingizimu Afrika.

Ucwaningo luchazwe kimi ngolimi engiluqondayo. Imibuzo yami mayelana nocwaningo iphenduliwe. Ngiyakuqonda ukuthi ukubamba iqhaza kwami kuzobandakanya ini futhi ngiyavuma ukubamba iqhaza ngokuzikhethela nenkululeko yami. Ngiyakuqonda ukuthi ubunikazi bami abuzukudalulwa kunoma ngubani. Ngiyaqonda ukuthi ngingahoxa ocwaningweni nganoma yisiphi isikhathi ngaphandle kokubeka isizathu futhi ngaphandle kokwesaba imiphumela emibi noma ukulahleka kwezinzuzo. Ngiyaqonda ukuthi imfihlo incike kubabambiqhaza beQembu ekugcineni imfihlo.

Ngiyavuma ukugcina izimfihlo zezingxoxo eziseqenjini lokugxila ngokungadaluli ubunikazi babanye ababambiqhaza noma ezinye izici zeminikelo yabo kumalungu angaphandle kweqembu.

Igama lombambiqhaza…….

Isiginesha yombambiqhaza……...

Usuku……