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A Case Study to Assess Participants' Perceptions on Voluntariness and Motivations for
Participating in a Clinical Trial in Zimbabwe

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Submitted in partial fulfilment of the requirements for a Masters in Social Sciences- Health
Research Ethics, in the School of Psychology, University of KwaZulu-Natal.

Unless specifically indicated to the contrary, this dissertation is the result of my own work

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STATEMENT OF ORIGINAL AUTHORSHIP

“I, **FARIRAI MUTENHERWA**, declare that the thesis titled: “**A Case Study to Assess Participants’ Perceptions on Voluntariness and Motivations for Participating in a Clinical Trial in Zimbabwe**”, which I hereby submit for the degree of Master of Social Science at the School of Psychology, Faculty of Humanities, Development and Social Science, University of KwaZulu-Natal, is my original work and has not previously been submitted by me for a degree at another university”.

Protocol number and date of the approval from the Faculty of Humanities, Development and Social Science Research Ethics Committee: **11 April 2011**

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Abstract

Introduction: There is little empirical evidence on voluntariness of participation in clinical trials due to absence of acceptable measures and universally accepted conceptual frameworks of voluntariness. *Methods:* A cross-sectional study was conducted in Zimbabwe to examine participants' motivations, levels of voluntariness and perceptions about the effect of offers, pressures and threats on decision making. One hundred participants were recruited from an ongoing diagnostic trial. Questionnaires adapted from published research, the Perceived Coercion Scale and Voluntariness Ladder were used for data collection. *Results:* The need to access diagnostic services and treatment for tuberculosis was the main motivation for enrolment in the trial. Participants were not coerced to participate in the trial but were offered bus fare. The offer had no effect on their decision to enroll in the trial. *Conclusion:* Immediate health benefits have a key impact on participants' decisions to enrol in a clinical trial of a diagnostic technique. A comprehensive conceptual framework together with validated tools for assessing voluntariness in African contexts should be developed.

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Introduction

Informed consent is an essential element of ethical conduct in scientific research. Apart from being an ethical requirement, it is also a legal requirement that has its roots in the Nuremberg Code. Informed consent has five key elements namely: competence, disclosure, understanding, voluntariness and consent (Beauchamp & Childress, 2009; Sugarman, 2002). Competence and voluntariness are regarded as the threshold elements of informed consent (Beauchamp & Childress, 2009; Sugarman, 2002). This implies that before a person gives informed consent, s/he must have adequate decision-making capacity, or competency to do so, and must be in a position to make a voluntary choice about whether or not to participate in a clinical trial (Sugarman, 2002). Only after these two elements have been fulfilled can the other components of consent be considered.

The voluntary participation of subjects in research has been widely debated, especially in clinical trials (Appelbaum, Lidz, & Klitzman, 2009a, 2009b; Litton, 2011; Nelson & Merz, 2002). Ethical and moral questions arise in therapeutic clinical trials, particularly in instances where the drug is not yet widely available or its accessibility in the public health system is limited. In the 1980s, when HIV was first diagnosed, antiretroviral drugs were not widely available and HIV positive individuals could only access these drugs through participation in clinical trials. As such, participants could enrol in clinical trials simply because they were the only sources of the life-saving drugs. Furthermore, participants in clinical trials might receive better health care services during clinical monitoring of the drug compared to the “usual standard of care” that may be available in state hospitals. In settings with limited resources, participation in clinical trials may, therefore, result from inducement, which can be argued to be undue since it might compromise the participants’ ability to make a truly

voluntary decision to participate in the trial. It must be highlighted, however, that although need and limited options are important aspects in considering voluntariness in resource limited settings, these factors do not necessarily imply that voluntariness is compromised. The risks to the research participants should also be given prominence when issues about vulnerability are considered. If the risks are greater than the benefits and the participants are in dire need of the service available in the research project, then undue inducement might pose more of a concern than in the absence of these factors.

Socioeconomic and political factors can also expose individuals and communities to coercion and undue influences, thus complicating the ethical principle of voluntariness. Zimbabwe has been experiencing severe economic challenges which peaked in 2008. The economic downturn resulted in a sharp decrease in funding for social services leading to an unprecedented deterioration of health infrastructure, loss of experienced health professionals, drug shortages and a drastic decline in the quality of health services available for the population (Collaborating Centre for Operational Research and Evaluation, 2010; Ministry of Health and Child Welfare, 2009). There are therefore glaring inadequacies in the six health system building blocks in the country namely human resources, medical products, vaccines and technology, health financing, health information, service delivery and leadership and governance (Ministry of Health and Child Welfare, 2009). These building blocks are prerequisites for a functional health delivery system.

Trends in mortality and morbidity in Zimbabwe show that the population is still affected by common preventable and treatable diseases and conditions including nutritional deficiencies, communicable diseases, diseases associated with pregnancy and childbirth, and newborn-related conditions (Ministry of Health and Child Welfare, 2009). HIV and AIDS, tuberculosis

(TB), diarrhoea, childhood illness, malaria, malnutrition, injuries, selected non-communicable diseases and reproductive health and pregnancy related conditions are amongst the leading causes of morbidity in Zimbabwe. HIV prevalence amongst the 15 – 49 year age group in the country remains at an unacceptably high level of 13.7% (Ministry of Health and Child Welfare, 2009). By 2009, approximately 45 percent (180,000 of an estimated 400,000 persons) of those requiring antiretroviral therapy were actually receiving treatment (Ministry of Health and Child Welfare, 2009).

Tuberculosis is the second leading cause of death in Zimbabwe and is among the top five leading causes of hospital admission and outpatient consultation. Among the 22 high tuberculosis countries in the world, Zimbabwe stands at number 17 (Ministry of Health and Child Welfare, 2010) with an estimated incidence rate of 782 per 100 000 population (Ministry of Health and Child Welfare, 2010). The TB epidemic in the country is largely driven by HIV. It is estimated that of all patients with TB infections, 72% are co-infected with HIV (Ministry of Health and Child Welfare, 2010).

Efforts to control TB in Zimbabwe are hampered by socioeconomic factors coupled with limited access to diagnostic centres and lack of sensitive and rapid TB tests (Population Services International, 2011). Rapid diagnosis and early treatment are essential for effective control of TB in the community. The most commonly available diagnostic test for TB is smear microscopy. However, its sensitivity is below 50% (Population Services International, 2011) and TB suspects have to make frequent visits for complementary radiography tests before commencing TB treatment. Although the evidence is still emerging, there are growing concerns that some patients might be suffering from drug-resistant TB (DR-TB), which is both difficult and expensive to diagnose and to treat. The Zimbabwean national TB

programme is already stretched. Sensitive and rapid diagnostic tools for drug sensitive and DR-TB are therefore required in order to reduce the burden of TB in Zimbabwe.

The economic decline in the general population is evidenced by the corresponding rise in levels of poverty and unemployment. The majority of the population still lives below the poverty datum line and do not enjoy even the minimum standard of living. By 2008, the economic crisis resulted in an unemployment rate of 80% whilst inflation rates were estimated at over 231 million percent (Ministry of Health and Child Welfare, 2009). Most of the industries were unable to generate employment opportunities as they were operating below capacity.

The soaring inflation rates coupled with the high unemployment rate drastically eroded the purchasing power of the local currency, thus aggravating poverty within the population. Poor people are prone to have more health problems and, furthermore, struggle to access or afford healthcare services. The cost of getting a TB diagnosis can also be a deterrent to the early diagnosis of TB in the country. A study conducted in Harare in 2009, showed that only 20% of the TB suspects could afford to pay for radiography and clinical examination (Population Services International, 2011). In Zimbabwe, patients pay for consultation fees and for diagnosis of TB. However, once diagnosed with TB, treatment is given free of charge.

Access to health resources for both diagnosis and treatment in the developing world can differ significantly from the developed world. In developing countries, regular and quality health care might only be available in a study environment. The perspective of potential participants in the developing world setting on voluntariness might therefore differ from those in developed countries. A research participant in a developing country might arguably be more likely to be influenced to join a trial because of access to health care services offered

in the trial; as such services may not be available or affordable in the public system. It is therefore important to assess the perspectives of participants about voluntariness in a developing world context, bearing in mind that contextual and socioeconomic factors might have a significant impact on participants' decisions.

Appropriate measures of assessing voluntariness to consent to research are poorly developed (Appelbaum et al., 2009b; Mandava, Pace, Campbell, Emanuel, & Grady, 2012; Miller et al., 2011). Additionally, the elements of voluntariness are poorly conceptualized and have been subjected to considerable debate (Appelbaum et al., 2009a, 2009b; Kamuya, Marsh, & Molyneux, 2011; Miller et al., 2011; Nelson et al., 2011). Consequently, empirical studies on voluntariness have been difficult to design and conduct, leaving a very small body of evidence on the subject with little consensus on the findings from these studies (Appelbaum et al., 2009a, 2009b; Nelson et al., 2011). Against this background, it has been argued that the regulation of the consent process could be based on the wrong presumptions about conditions that may impair voluntariness (Appelbaum et al., 2009a).

In this study, the researcher therefore aimed to contribute to the emerging body of literature and debate on voluntariness, using a trial of a new TB diagnostic technique in Zimbabwe as a case study. The study sought to confirm or dispel factors that have traditionally been viewed as threats or constraints to voluntary participation in research in Zimbabwe. Specifically, the study set out to answer the following key questions:

- What motivates research participants to enrol in a clinical trial?
- To what extent do incentives, threats and pressures affect research participants' voluntary decision making?

A cross-sectional exploratory study was carried out to answer the above questions. A semi-structured questionnaire, as well as the Voluntariness Ladder and Perceived Coercion Scale (PCS), which are two global measures used for the assessment of voluntariness in hospital settings, were used during data collection. The questionnaire covered three areas: demographic data, motivations for participating in research, and experience of offers, pressures, or threats.

The research participants were recruited from participants enrolled in a randomized controlled trial assessing the impact of a new TB diagnostic technique in preventing adverse outcomes in smear negative TB suspects in Zimbabwe.

Literature Review

Voluntariness of informed consent has been less explored in the literature of bioethics compared to the other components of consent (Appelbaum et al., 2009a, 2009b; Barsdorf & Wassenaar, 2005; Nelson et al., 2011; Nelson & Merz, 2002). This could be partly due to the complex nature of the concept and difficulties in assessing how voluntariness could be impaired. As Appelbaum aptly puts it: “Getting a conceptual handle on voluntariness is no easy task” (Appelbaum, 2011, p. 18). Consequently, there is little empirical evidence and a lack of acceptable measures of voluntariness to guide policy-makers and ethical and regulatory authorities on how to ensure voluntary participation by research subjects. The lack of acceptable measures and empirical evidence on voluntariness has raised concerns over potential coercion and undue inducement by researchers during recruitment and retention of research participants, particularly in clinical trials in the developing world.

In this section, the concept of voluntariness and its measurement will be discussed together with a summary of studies conducted on this subject. Three main conceptual frameworks will be discussed. The first conceptual framework was developed by Appelbaum and colleagues (Appelbaum et al., 2009a), the second by Nelson and colleagues (Nelson et al., 2011) and the third by Bull and Lindegger (Bull & Lindegger, 2011).

The Concept of Voluntariness

The precise meaning of the term voluntariness is disputed (Appelbaum et al., 2009a; Kamuya et al., 2011; Litton, 2011; Nelson et al., 2011; Nelson & Merz, 2002). In some circles, voluntariness is viewed in terms of the absence or presence of sufficient knowledge, psychological pressure and external control (Feinberg, 1973). This view of voluntariness has

been widely criticised for being broad to the extent of equating voluntariness with autonomous action (Beauchamp & Childress, 2009; Nelson et al., 2011). For an autonomous action to take place the person should be independent from controlling influences and should have the capacity for intentional action (Beauchamp & Childress, 2009; Kukla, 2005).

According to Beauchamp and Childress, a person acts voluntarily “if he or she wills the action without being under the control of another’s influence” (Beauchamp & Childress, 2009, p. 132). External control can result from influences from a second person, accidents or unanticipated events. They also argue that *internal* influences such as debilitating illnesses, psychiatric disorders or drug addiction can also compromise voluntariness (Beauchamp & Childress, 2009) possibly by causing cognitive impairment. Thus, an adequate condition of voluntariness must take into account both internal and external controlling influences.

Beauchamp and Childress further assert that not all influences exerted on a person — whether internal or external — are controlling and that the impact of an influence varies from one person to another and depends on circumstances.

Appelbaum and colleagues present a conceptual framework of voluntariness based on the “legal doctrine of informed consent”(Appelbaum et al., 2009a, p. 37). They argue that choices are voluntary unless they are unduly influenced or coerced. Those influences which render decisions involuntary have four characteristics: they are (i) external, (ii) intentional, (iii) illegitimate, and (iv) causally linked to the choice of the person participating in research (Appelbaum et al., 2009a). These four characteristics should all be present for a decision to be regarded as involuntary (Appelbaum et al., 2009a). Borrowing from Talcott Parsons’ conceptualisation of the mechanisms by which an individual can exert influence on another

person's decisions, offers, pressures and threats were identified as forms of influence that meet these four criteria.

Nelson and colleagues provide a theoretical model of voluntary informed consent, which they claim is most applicable in the field of biomedical research (Nelson et al., 2011).

According to their account, two conditions are necessary for voluntary participation to take place: (i) intentionality and (ii) freedom from controlling influences. Intentionality involves acting according to plans. Accidental actions are not intentional and are therefore involuntary.

In their model, controlling influences can be understood according to two main components of control namely, internal and external influences as well as constraining situations. The category of internal influences comprises of biomedical conditions, for example psychiatric disorders, drug addiction and disease. External influences comprise of offers of payment, threats, education, deceit, manipulative advertising and emotional appeals, among other things. Constraining situations refer to the contextual or background situations of the person targeted for exploitation. Examples of contextual factors include social norms and understanding of research.

The model proposed by Nelson and colleagues has two key features. Firstly, it makes a distinction between *interactions* between two people — the one who is influencing and the other whose decision is to be impacted — on the one hand; and the *context* where the interaction happens on the other hand. Secondly, the model highlights that both the interaction between the two people and the context where the interaction is happening have the potential of exerting moral challenges to the informed consent process (Kamuya *et al.*, 2011).

In their model, Nelson and colleagues (Nelson *et al.*, 2011) illustrate the moral challenges that may arise between a physician and a patient both in terms of interaction and context. They argue that if a doctor or clinician orders a reluctant patient to undergo a diagnostic test or examination by threatening the patient with abandonment if the patient does not comply, the doctor's influence would have controlled the patient's choice through coercion. By contrast, if the physician were to persuade a patient who was initially unwilling to undergo the test, the physician's actions influenced but did not control the patient's decision. Influences can thus be controlling or non-controlling and some might be welcome whereas others might not.

Measurement of Voluntariness

In their model, Nelson and colleagues developed a nine-question Decision Making Control Instrument (DMCI) from the original 28 items. The instrument measures self-perception of voluntariness by measuring two components of voluntariness — intentionality and extent of control. Measurements of the extent of intentionality and control are scored on a 6-point Likert scale that ranges from “Strongly Disagree” (1) to “Strongly Agree” (6) (Miller *et al.*, 2011; Nelson *et al.*, 2011). An example of an item on intentionality is: “I made this decision”. Participants are asked to respond to the following nine statements:

1. I was powerless in the face of this decision
2. Someone took this decision away from me
3. I made this decision
4. I was passive in the face of this decision
5. The decision about the protocol was inappropriately influenced by others
6. I was not in control of this decision
7. Others made this decision against my wishes

8. I was not the one to choose
9. The decision was up to me.

Although this model is well thought through, Nelson *et al* seem to have downplayed the role of contextual factors in influencing decision making. In their model, contextual factors are captured as constraining situations. Based on experience in conducting clinical trials in Africa, it has been argued that contextual factors are the most dominant forms of influence on voluntariness in the informed consent process (Kamuya *et al.*, 2011). The danger in underplaying contextual factors is that researchers may be distracted from considering ways in which such challenges could be addressed in real life situations. Additionally, it has been argued that internal influences such as psychiatric disorders, drug addiction and disease are not threats to voluntariness but challenges to autonomy or competency (Kamuya *et al.*, 2011).

The requirement that a voluntary action must be “substantially” free from “controlling influences” is not clearly enunciated in Nelson and colleagues’ conceptual framework (Blumenthal-Barby (Swindell), 2011; Bull & Lindegger, 2011). Specifically, the distinction between “controlling” and “non-controlling” influences is not clear. Most cases of influences might fall between the lines of controlling and non-controlling and unfortunately, the authors do not offer a framework to classify actions that fall in-between these two categories. Furthermore, there is no guidance on whether/how/when a person is substantially free from these influences. In a way, the authors seem to acknowledge that the requirement for voluntary action is quite problematic as they did not attempt to “determine precisely the degree of control an agent must have over causal influences in order to act voluntarily” (Nelson *et al.*, 2011, p. 10).

Bull and Lindegger agree with Nelson and colleagues' assessment of voluntariness as well as Appelbaum's conceptual framework on the issue of intentionality and freedom from controlling influences (Bull & Lindegger, 2011). However, they argue that in as much as external influences are critical in determining voluntary action, authors should also focus on participants' "subjective experiences of voluntariness in decision making" (Bull & Lindegger, 2011, p. 27). Participants may still feel that their decisions were not voluntary even though they are not causally influenced by intentional, external and legitimate influences. Perceived constraints to voluntary participation also need to be taken into consideration even in the absence of evidence of external control. A comprehensive analysis of voluntariness should therefore factor in both participants' subjective experiences of voluntariness as well as objective external influence.

Evidence from the behavioural and cognitive sciences also challenge the notion that acting intentionally — a measure of voluntariness — requires acting according to plans. Rather, people act according to plans less often than is traditionally thought (Blumenthal-Barby (Swindell), McGuire, & Halpern, 2011). People are heavily influenced by subconscious cues in the environment, mood or affect, in addition to deliberative judgment. Most of our decisions and actions do not, therefore, meet the criteria for having been done according to plan (Blumenthal-Barby (Swindell), 2011). In light of the evidence from the behavioural and cognitive sciences, the reliability of Nelson and colleagues' proposed DMCI is challenged. Our perceptions about the intentionality and control of our own and others' decisions are remarkably skewed and un-insightful (Blumenthal-Barby (Swindell), 2011). Furthermore, the DMCI measures perceived *voluntariness* as opposed to *actual voluntariness* and there is no guidance on the relationship between the two.

The DMCI is designed to gather empirical data on perceived voluntariness by assessing whether participants felt they were in control of their decisions or that the decision was made on their behalf. The instrument might be useful in identifying a certain category of potential constraints, for example, social constraints on decision making. However, it might not be possible to identify subtle subjective experiences, for example those coming from the social desirability effect in research settings (Bull & Lindegger, 2011). Participants might also alter their behaviour or decisions as a result of their awareness that they are involved in an experimental study — a phenomenon popularly referred to as the “Hawthorne effect” (Shuttleworth, 2009). Such effects might even be more difficult to deduce from the DMCI.

An Alternative Conceptual Framework

Bull and Lindegger (2011) argue that although intentionality and freedom from control are critical, there is a need to consider the role of relationships and socio-cultural factors in decision making when assessing voluntariness. They propose that voluntariness be viewed as falling on a continuum which ranges from independent voluntariness on one extreme, to controlled decisions on the other extreme. In between the two extremes is cooperative decision making which is based on relational autonomy.

In independent voluntariness, a person makes an independent decision even though there is influence from other people. On the other extreme, a person makes a decision under the control of another without exercising their autonomy or voluntariness. In between is a third position which they regard as “cooperative decision making” which is based on relational autonomy (Bull & Lindegger, 2011, p. 29). In this form of voluntariness there is joint and collaborative decision making with regard to participation in research.

Independent voluntariness is believed to be common in individualistic societies, whilst collaborative decision making and controlled decision making might be found in communalistic societies where respect for persons is not understood in terms of individual autonomy and privacy but rather in terms of cohesion and wellbeing of the entire community. This is common in traditional African societies and East Asian societies where decisions about research participation and medical care may be made by family members or traditional leaders (Engelhardt, 1980; Mills, Nixon, Singh, Dolma, & Nayyar, 2006; Tan, Angeles, & Lumitao, 2001). For example, to access a prospective female participant in an African community, a researcher might need to get approval from a community leader, then the woman's husband, and in some cases approval from in-laws is also expected (Mills *et al.*, 2006; Nyika, Wassenaar, & Mamotte, 2009). This is because of the relational nature of personhood in the African context and the emphasis on consensus and community, which makes individual consent and voluntariness, as defined in Western cultures, virtually impossible in some cultural contexts.

A Comparison of the Three Frameworks: Appelbaum et al, Nelson et al and Bull and Lindegger's Conceptual Frameworks

Two notable differences exist in the frameworks discussed. Firstly, in Appelbaum's account, internal influences, for example psychiatric conditions, do not negate voluntariness. A person can only be deprived of voluntariness through external influences resulting from the deliberate actions of another person (Appelbaum *et al.*, 2009a). On the contrary, Nelson and colleagues suggest that, in addition to external influences like threats, internal influences such as mental illness can indeed render an action non-voluntary.

Secondly, whilst Appelbaum asserts that an illegitimate influence is a requirement for involuntariness, this notion is excluded from Nelson *et al*'s analysis. Instead, Nelson and colleagues argue that it is not the *illegitimacy of an influence* that renders an action involuntary but rather the *controlling effect of that influence*. In Nelson *et al*'s account there is a distinction between the legitimacy of an influence and whether or not it causes a voluntary or involuntary decision (Nelson *et al.*, 2011).

The main distinction between Bull and Lindegger's model and the other two models (Nelson *et al* and Appelbaum *et al*'s conceptual frameworks) is that Bull and Lindegger view voluntariness as falling on a continuum from independent voluntariness to total control. Bull and Lindegger also highlight that social-cultural factors play a significant role in influencing participants' decisions. They also give room for collaborative decision making which they argue could still be considered as voluntary. Bull and Lindegger's model has a lot of appeal in African settings where cohesion and communal stability take precedence over individual autonomy.

The differences notwithstanding, there seems to be consensus in the three accounts that voluntary decisions should reflect the will of the decision-maker rather than of another person. Additionally, influences exerted on a person by another are not always controlling and may or may not render decisions involuntary.

Forms of Influence

Influences range from acts of love, threats, education, lies, manipulation and emotional appeals. For the purposes of this study, three categories of influence will be discussed: coercion, persuasion and manipulation (Beauchamp & Childress, 2009; Nelson *et al.*, 2011).

Coercion is the intentional use of a credible and severe threat of harm or force to control another person (Beauchamp & Childress, 2009) or compel him or her to do something. Coercion, therefore, requires the presence of three main aspects: (a) an unfavourably narrowed set of options; (b) that some human agents be limiting a person's options in an attempt to manipulate him or her; and (c) a threat (Hawkins & Emanuel, 2005). A classic case of coercion is as follows: A wants B to do X. If B does not do X, A will make B worse off than B was before the interaction. If B either accepts or refuses, B will be worse off than if A had never approached him (Wertheimer, 1987). A practical example of a coercive action would be withholding treatment from participants enrolled in a therapeutic study in order for them to continue with the study up to its end. Withholding treatment is a threat that will narrow the participants' options thereby forcing them to comply. It will also make the participants worse off than they were before if they do not comply. Like undue inducement, coercion can be understood as a threat to voluntary informed consent as it renders the actions of the coerced person non-autonomous.

Whether or not coercion occurs is a function of the subjective responses of the person targeted for coercion (Beauchamp & Childress, 2009). Coercion does not occur in circumstances where a person complies because they feel threatened but in actual fact no threat has been issued. Similarly, persons may feel pressured to enrol in a study because they are desperately in need of money or other goods from the study or simply have no option because of severe illness, lack of food or shelter. Although they might feel constrained by these influences to enrol in the study, their decision to enrol cannot be attributed to coercion. For coercion to occur, the self-directed course of action of the target of the coercive action should be displaced by a credible and intended threat (Beauchamp & Childress, 2009). In the

constraining situations such as illness and poverty, there is no coercion because no one has issued a threat in order to gain their compliance or enrolment in the study.

In *persuasion*, a person is encouraged to believe in something through the merit of the reasons proposed by another person (Beauchamp & Childress, 2009; Nelson *et al.*, 2011).

Manipulation is a generic term which encompasses several forms of influence that can neither be regarded as coercive nor persuasive. In manipulation, a person is swayed to do what the manipulator desires through other means besides coercion or persuasion. In clinical trials, manipulation might occur through manipulation of information or manipulation of options. Information can be manipulated through the ways a researcher presents information — tone of voice, forceful gestures, and the way information is framed. Researchers may also lie, withhold or exaggerate critical information required by prospective participants to make informed decisions. For example, instead of presenting to potential participants the failure rate of an investigational drug as 25%, a researcher might choose to say: “The success rate of the drug is 75%”.

Options can be manipulated through offers of rewards or benefits promised to prospective subjects (Beauchamp & Childress, 2009; Nelson *et al.*, 2011). Compensation for participation, provision of financial incentives, access to drugs or medical care or presentation of limited choices during the enrolment process can also affect a person’s perception of the study, thereby affecting understanding and voluntariness. Investigators may also manipulate trust (Brown *et al.*, 1989) or create a sense of false security for those enrolling in the study in order to increase enrolment.

Studies on Voluntary Participation in Clinical Trials

Voluntariness of research participation has been poorly conceptualised in the literature, making it difficult to design and conduct empirical studies on the subject (Appelbaum *et al.*, 2009a; Barsdorf & Wassenaar, 2005; Beauchamp & Childress, 2009; Nelson *et al.*, 2011). A few studies have been conducted, mostly in the developed world, but there is no evidence suggesting that studies to assess participants' voluntariness in clinical trials have been conducted in Zimbabwe.

Studies on voluntariness can be classified into two broad categories: (i) those that focus on participants' perceptions on pressures and (ii) those that ask participants about their knowledge about their right to refuse to participate or to withdraw as and when they wish to do so without suffering any adverse consequences. With regard to the first category, studies conducted in the United States of America, Canada and the United Kingdom across a range of clinical trials revealed that between 90% and 99% of the participants were not pressured to participate in the clinical trials they enrolled in (Franck, Winter, & Oulton, 2007; Knifed, Lipsman, & Mason, 2008; Marshall & Rotimi, 2001) or that their participation was voluntary (Montgomery & Sneyd, 1998).

In the context of developing countries, studies in Africa show similar patterns of voluntariness among clinical trial participants. For example, 95% of women whose children were enrolled in a paediatric trial conducted in Ghana (Sarkar, Grandin, & Gladstone, 2009) and 99% of participants in an influenza vaccine trial in South Africa (Moodley, Pather, & Myer, 2005) reported that their participation in the respective trials was voluntary. Similar results were obtained in an Indian paediatric trial where 98% of the women enrolled reported

that they did so without any pressures or compulsion (Minnies, Hawkrigde, & Hanekom, 2008).

In the few cases where participants felt pressured to participate in clinical trials, the source of pressure was mainly their health condition or other constraining situations (Mandava et al., 2012). In the developed countries, pressure from another person was rarely reported and, when reported, the source of the pressure was the treating physician (Agrawal, Grady, & Fairclough, 2006; Lyno'e, Sandlund, & Dahlqvist, 1991; Penman, Holland, & Bahna, 1984; Riecken & Ravich, 1982). Similarly, in the developing countries, pressure from other people was reported by few respondents ranging from six percent to 26%, depending on the type of trial (Mandava et al., 2012). Spouses, family members or friends, members of the research team and village elders were cited as the sources of pressure (Krosin, Klitzman, & Levin, 2006; Pace et al., 2005).

The majority of participants (87%) in a clinical trial in Bangladesh reported that they felt pressured by the fear of the negative consequences that could arise if they withdrew from the study (Lyno'e, Hyder, & Chowdhury, 2001). They reported that the trial offered so many advantages making it difficult to refuse enrolling. Similarly, in a perinatal HIV transmission trial conducted in South Africa, 32% and 23% of participants in the evaluation study group and sensitization group respectively thought that care would be compromised if they refused to participate in the study (Karim, Karim, Coovadia, & Susser, 1998). Furthermore, 44% of parents enrolled in a paediatric malaria vaccine clinical trial in Mali, thought that they would be deprived of healthcare services should they refuse to participate in the study (Krosin et al., 2006).

Studies that investigated whether participants knew that they could refuse or withdraw to participate in the trial demonstrate the clearest differences in perceptions of participants in developing and developed countries. Out of the 18 countries that measured voluntariness in terms of whether or not participants knew they could withdraw or refuse to participate, in 15 studies at least 75 percent of the participants in developed countries were aware that they could withdraw or refuse. Furthermore, in 10 of these studies 90% or more reported that they were not only aware but believed that they could actually withdraw from research if they wished. In contrast, less than 50% of the participants in five of the 15 studies conducted in developing countries that measured knowledge of withdrawal or refusal, knew they could withdraw from research (Mandava et al., 2012).

It is pertinent to highlight that there are also differences between and within developing countries. For instance, in some developing countries, high proportions of participants knew that they could withdraw or refuse to participate in the trial. In a malaria vaccine trial conducted in Mali, more than 90% of adults and parents of children enrolled in the trial were aware that they could withdraw from the trial (Ellis, Sagara, & Durbin, 2010). Similarly, 88% of participants enrolled in a vaccine trial in Thailand knew that they had a right to refuse participation as they wished (Pitisuttithum, Migasena, & Laothai, 1997) whilst 93% of the women in a South African HIV trial reported that they had the right to quit (Verheggen & van Wijmen, 1996). However, 10% of mothers in a malaria vaccine trial conducted in Mali knew that they could withdraw their child from the trial any time (Krosin et al., 2006). Knowledge to refuse or withdraw in a clinical trial was also recorded in a study in an HIV vaccine trial conducted in Côte d'Ivoire, in which 27% of the participants knew they could withdraw any time (Ekouevi, Becquet, & Viho, 2004).

In a study, conducted in South Africa, the results showed that there were racial differences in the public's perceptions of voluntariness in medical research. Specifically, Black participants had the lowest scores on voluntariness compared to both Indians and Whites (Barsdorf & Wassenaar, 2005). This could partly be explained by the systematic human rights abuses and violations perpetrated on the Black community during the apartheid era, resulting in Black people being apprehensive of any medical research targeting them.

A preliminary empirical investigation conducted by Appelbaum *et al* among clinical trial participants at a university medical centre in the United States of America on voluntariness and motivations for participating in different clinical trials, revealed that participants have diverse reasons for wanting to participate in a clinical trial (Appelbaum *et al.*, 2009b). The study also showed that participants' decisions to enrol are affected by more than one consideration. Participants cited the possibility of better care, trust in the researchers and the reputation of the host institutions as important motivations for their participation. However, participants placed different values on their motivations for participation depending on the nature of the clinical trial they were enrolled in and their health condition. For example, respondents who were enrolled in substance abuse trials placed less emphasis on altruism as a motivation for participation and placed more emphasis on the availability of free treatment and the seriousness of their need for treatment. On the other hand, those faced with life-threatening conditions, for example participants enrolled in oncology trials, placed the greatest weight on advice from their medical caregivers.

With regards to constraints to voluntary participation, the study revealed little evidence of constraints to voluntary participation. Where constraints to voluntary participation were reported, they were perceived as rarely playing a significant role in influencing the decisions

of the participants on whether to participate or not. However, participants who cited that they received advice from a physician or nurse had a high score on the Perceived Coercion Scale suggesting that participants might have been constrained to say no.

It is pertinent to highlight that the findings from studies on voluntariness have been criticized on methodological and conceptual grounds (Appelbaum *et al.*, 2009a, 2009b; Mandava *et al.*, 2012; Pace, Grady, & Emanuel, 2003). Specifically, there is presently neither an agreed conceptual framework to guide research on voluntariness nor standard and reliable techniques for its assessment (Appelbaum *et al.*, 2009a; Pace *et al.*, 2003). Different studies were thus using different measurement techniques for assessing voluntariness and, consequently, the body of data collected on the subject are hardly comparable and to a greater extent inconclusive.

Efforts to establish participants' motivations and possible constraints of voluntariness in clinical trials are essential if one acknowledges the fact that informed consent is a process of shared decision making between the researcher and the participant (Lindegger *et al.*, 2006; Lindegger & Richter, 2000; Sastry *et al.*, 2004). This entails a two way process in which the researcher should first understand the needs, values and motivation of the participants, and how best to inform them and optimize their involvement in the research study (Lindegger & Richter, 2000). Consistent with this conception of informed consent, Mkhize (2006) argues that informed consent should in fact be viewed as a semiotic process whereby all concerned parties negotiate the processes and procedures to be followed. Although this might be the ideal situation, it might not be possible to achieve in real life situations.

Against this background, a new agenda has been set for health researchers to come up with reliable assessment techniques for assessing constraints to voluntariness and to study the epidemiology of these constraints. The ultimate objective of this research agenda is to develop ways of preventing constraints to voluntariness with a view to enhancing the voluntary participation of research subjects in research (Appelbaum *et al.*, 2009a).

Calls have also been made to understand the perceptions of potential research participants about health research (Barsdorf & Wassenaar, 2005; Benatar, 2002). It has been argued that health research in developing countries should in fact be preceded by social science research in order for health researchers to understand the culture, customs, attitudes and perceptions of local communities (Barsdorf & Wassenaar, 2005; Mills *et al.*, 2006). Such information would be critical in providing insights into the presence or absence of constraints to voluntariness within a given society and inform remedies to deal with these constraints.

As with participants in other developing countries, and in particular post colonial African countries, research participants in Zimbabwe are vulnerable to unethical research due to deprivation of educational opportunities, lack of political power, poverty, unfamiliarity with medical interventions and dire need for medical care (Teays & Purdy, 2001). Consequently, they may view health research participation as mandatory and non-voluntary. Their vulnerability might potentially make them more susceptible to coercion, threats, deception and manipulation. It is against this background that an exploratory descriptive study was conducted to understand in detail the prevailing situation with regards to voluntariness of participation in clinical trials in Zimbabwe.

Of the three conceptual frameworks described in this paper, Bull and Lindegger's account is arguably the best. However, there were neither previous studies nor validated data collection tools tied to their model, which could be adapted for the current study. In order to overcome the conceptual and methodological shortcomings of previous studies on voluntariness and to enhance comparability of research results, this study adopted the conceptual framework and tools developed by Appelbaum *et al* (2009a).

Aims and Objectives

The overall objective of this study was to ascertain research participants' views regarding the presence and importance of offers, pressures, and threats to their decisions about enrolling in a diagnostic trial.

Specifically, the study set out to answer the following key questions:

- i. What are the key factors that influence research subjects' decisions to participate in a clinical trial of a new TB screening and diagnostic technique?
- ii. What is the role of offers, pressures and threats on research subjects' decisions to enrol in a clinical trial?
- iii. What proportion of research subjects perceive themselves as having volunteered to participate in the clinical trial?
- iv. Is there an association between the factors that influence participants' decisions to enrol in a clinical trial and levels of voluntariness? If so, what is the level of association?
- v. What are the predictors of diminished voluntariness?

Method

In this section, the materials and methods used to collect the data are presented. For clarity, the source of research subjects for the current study will be referred to as the *primary study*. The current study will be referred to as the *sub-study*.

Study design

A cross-sectional descriptive study design was used.

Subjects

Respondents for this study were recruited from participants enrolled in a randomized controlled trial of the impact of a new diagnostic test for TB in Zimbabwe, referred to as the primary study.

The Primary Study

Background of the primary study

The aims of the primary study were to prevent adverse outcomes in primary health clinic smear negative tuberculosis suspects. The sample size for the primary study was 766 participants aged 16 years and above. The study design was a randomised controlled trial with two arms. In the first arm (routine arm) participants were offered the standard of care and in the intervention arm GeneXpert (GXP) testing was offered to smear negative TB suspects. GeneXpert is a new molecular diagnostic test used to detect *Mycobacterium tuberculosis* (MTB) and resistance to rifampicin. It is easy to use, has minimal requirements

and produces results within minutes (Helb, Jones, Story, & Boehme, 2010). The study was conducted in Zimbabwe at a TB referral centre.

Procedure

The TB suspects presenting for investigation at the primary health clinics in Harare were offered to join the study. Specimens were collected from suspects after obtaining their written informed consent. On the first day, participants were requested to provide two spot sputum specimens, a urine specimen and whole blood for HIV, CD4 cell count and interferon gamma assays. On the second day, patients were asked to come back to the clinic to provide one morning sputum and one additional spot sputum. One spot sputum specimen from the smear negative participants was subsequently randomised to GXP (Intervention arm) or fluorescence smear microscopy testing (control arm).

GeneXpert Intervention

Specimens randomised to this arm were tested for TB with the GeneXpert. Participants with positive GeneXpert results were referred for TB treatment whilst those with negative GeneXpert results would continue with their standard of care provided through the routine clinical care from clinics. The study also provided transport costs for these patients to visit the Infectious Diseases Hospital and get a chest X-ray, at no cost, for routine investigations.

Fluorescence Microscopy Arm

Specimens randomised to the fluorescence microscopy arm were tested with fluorescence smear microscopy. Participants with positive fluorescence screen were referred for TB

treatment and those with negative fluorescence screening continued with their routine standard of care as provided by the clinics.

Smear Negative TB Suspects

All smear negative TB suspects who tested positive on GXP or fluorescence microscopy were followed-up and referred for treatment. Smear negative TB suspects who failed to return to collect their results at their local clinic and were negative on all TB tests were followed up to establish the reason for not collecting results and reinvestigated for TB if they were still symptomatic.

HIV Testing and Counselling

Diagnostic HIV testing and counseling were offered to participants in both the GeneXpert intervention and Fluorescence microscopy arms. Participants not wishing to know their results were asked to consent to anonymised testing for study purposes. All trial participants found to be HIV-positive were started on cotrimoxazole (if WHO stage 2 to 4) and referred to the HIV clinic.

The Sub-Study

Sample Size

Assuming a prevalence of involuntariness of 8 percent, a sample size of 100 was calculated. The prevalence of involuntariness was based on studies conducted in developing countries which showed that levels of involuntariness ranged from five to 10% (Ellis et al., 2010; Sarkar et al., 2009; Verheggen & van Wijmen, 1996). The inclusion criterion was that the participant needed to be 18 years of age and be a current study participant in the primary

study. Participants were approached when they came for their research visits for the primary study.

Data Collection Instrument

A set of three data collection tools were used. These instruments were first used by Appelbaum and colleagues in a study conducted at a major university medical centre in the United States of America (Appelbaum *et al.*, 2009b). Their study sought to generate preliminary data on the extent and correlates of limitations on voluntariness across different clinical trials, which included trials on substance abuse, cancer, HIV, interventional cardiology, or depression.

The first instrument (Appendix 1) is a structured questionnaire that addresses three areas: socio-demographic data, motivations for participating in research, and experience of offers, pressures, or threats. The structured questionnaire was adopted with some modifications to suit the Zimbabwean context and for relevance to the current study. For example, questions from the original instrument that was developed by Appelbaum *et al* (2009b), which were deemed irrelevant to the Zimbabwean context, were excluded in the current tool. These included, Question 6 on the background section (What study are you currently involved in?) together with questions 5a (Do you have any pending legal cases or criminal charges?), 5b (Are you currently on parole or probation?) and 5c (Did your legal case/criminal charges/being on parole or probation influence your decision to participate in the study?) under Part II of the same tool.

Additional questions were also included in the questionnaire to capture information on the socioeconomic status of the research subjects, in particular, their income and level of education. The specific questions that were added are the following:

- What is your current marital status?
- What is the highest level of formal school that you have completed?
- What is your occupation?
- On average, what is your monthly salary?

These questions were added with a view to explore any associations between the socioeconomic factors, motivations to participate in a trial and the levels of voluntariness.

The other two instruments that were used were the Perceived Coercion Scale (PCS) (Appendix 2) and the Voluntariness Ladder (Appendix 3), which are global measures of voluntariness in hospital settings. The PCS was a modified version of the MacArthur Perceived Coercion Scale (MPCS) (Gardner, Hoge, & Bennett, 1993). The original MacArthur Perceived Coercion Scale was used to measure patients' perceptions of coercion during admission in a hospital. The original questions in the (MPCS) were as follows:

1. I felt free to do what I wanted about coming into the hospital.
2. I chose to come into the hospital.
3. It was my idea to come into the hospital.
4. I had a lot of control over whether I went into the hospital.
5. I had more influence than anyone else on whether I came into the hospital.

In the current and modified version of the PCS the five questions were phrased as above except that, instead of making reference to hospital admission, the questions were referring to the participant's involvement in research. Respondents were asked whether the five

statements were true or false with regards to their decisions to participate in the trial. The five questions used in the current study were phrased as follows:

1. I felt free to do what I wanted about signing up for the research project.
2. I chose to sign up for the research project
3. It was my idea to sign up for the research project.
4. I had a lot of control over whether I signed up for the research
5. I had more influence than anyone else on whether I signed up for the research project

A true statement was given a score of zero (0) whilst a false statement received a score of one (1).

The Voluntariness Ladder is a modified version of the Coercion Ladder (Hoyer, Kjellin, & Engberg, 2002). The Coercion Ladder is a visual analogue scale shown to patients so as to assess the degree of coercion prior to hospital admission. Each step on the ladder corresponds to the degree of pressure that a patient might have been subjected to. Patients are asked to put a mark on any one of the ladder steps that corresponds to their degree of perceived coercion. The steps range from 1 to 10. A score of 10 represents maximum perception of coercion whilst a score of 1 shows minimum perception of coercion.

The difference between the original Coercion Ladder and its modified version that was used in the current study is that instead of asking participants about perceptions of coercion with regards to hospital admission, participants were asked about their perceptions of voluntariness with regards to participation in a trial. Thus the Voluntariness Ladder was used to measure how voluntary a participant's decision was by asking each participant to circle a number on a ladder that best matched their decision. A score of 10 represented a completely voluntary decision whilst a score of 1 showed that a decision was not at all voluntary.

It is worth mentioning that there is no evidence that the questionnaire, the PCS and Voluntariness Ladder have been formally validated or used in a different cultural context apart from their use in the United States of America.

Measures

Participants completed a questionnaire which captured socio-demographic information (age, sex, education, marital status, income) as well as their experiences with offers, threats and pressures.

Voluntariness was assessed using the PCS as well as the Voluntariness Ladder. The Voluntariness Ladder is a simple measure that asks subjects to rate how voluntary their decision was on a “Ladder” ranging from 1 to 10. A score of 1 indicates a choice that is not at all voluntary and a score of 10 reflects a completely voluntary choice.

Scores on the PCS ranged from zero (0) to five (5) and were based on true or false responses to five questions. A score of 5 on the PCS indicates a high perception of coercion whilst a score of zero reflects perceptions of non-coercion.

Procedure

Recruitment took place when participants came for their routine clinic visits in the primary study. Participants were only referred to the sub-study after finishing the business of their visit in the primary study. A research nurse in the primary study introduced participants to the sub-study and requested the participants’ permission to be accessed by research assistants from our research team. Those interested in participating in the sub-study were asked to make arrangements with a research assistant at a convenient time. They were then taken through

the consent process and only after they had consented to participate in this study, were interviews conducted by the researcher and one trained research assistant.

A question that often arises on studies on voluntariness in research is the voluntariness of the research participants taking part in such studies. Although no specific measures were done to assess the levels of voluntariness of the respondents in the current study, efforts were made by the researcher to enhance voluntary participation. For example, during the consent process, participants were informed that they did not have to take part in the sub-study if they did not want to. If they decided not to participate in the sub-study that decision would not in any way affect their regular benefits and medical care from the primary study. They were also told that they could withdraw from the study at any time if they so wished. It must be highlighted, however, that even though prospective participants were provided with the relevant information to improve their voluntariness, there is no guarantee that such efforts resulted in voluntary participation.

After expressing their willingness to participate in the sub-study and signing the consent form (Appendix 4b), participants were asked to choose from among 14 possible motivations for enrolling in research. If they identified a motivation as having played a role in their decision to participate, they were asked to indicate the degree of influence associated with that motivation on a scale ranging from 1 to 10. Respondents were also asked whether they had been subjected to offers, pressures and threats in the clinical trial. If they indicated that they had been subjected to these influences, they were asked to describe (i) what happened, (ii) the extent to which it influenced their decisions, and (iii) the degree to which they considered the offer, pressure, or threat to have been unfair. Influence was again indicated on a scale ranging from 1 to 10.

Respondents were also asked about the risks they perceived to be associated with the primary study and the role of offers, pressures, or threats in making the risks worth accepting. Finally, respondents completed a modified version of the MacArthur Perceived Coercion Scale (Appelbaum *et al.*, 2009b; Gardner *et al.*, 1993) and a Voluntariness Ladder, which is a modification of the Coercion Ladder (Hoyer *et al.*, 2002). These two instruments are published measures of voluntariness of decisions in treatment contexts.

All the three instruments were pilot-tested on ten respondents to ensure understanding of the questions by participants and relevance to the study and cultural context. This is particularly important in view of the fact that the same tools were first used in a developed country set up and have neither been formally validated nor used in a different cultural context. The instruments were also translated into Shona, the language spoken by most people in the town where the primary study was conducted.

Ethical approval was obtained from the University of KwaZulu-Natal Faculty of Development and Social Sciences (Appendix 5), Medical Research Council of Zimbabwe, which serves as the National Ethics Committee (Appendix 6) as well as the Biomedical Research and Training Institute Institutional Review Board (Appendix 7). Written permission to access patients was obtained from the City Health Department (Appendix 8) as well as from the Principal Investigator of the primary study (Appendix 9). In the letter written to the PI of the primary study requesting permission to access study participants (see Appendix 9), the researcher indicated that information generated from the current study would only be used for academic purposes. Additionally, the letter also stated that the study as well as the participants to be interviewed would not be identified in the research report or in any

publications that might come out of the study. Instead of specifying the exact name or title of the primary study, it shall be reported that data came from participants in a diagnostic trial in Zimbabwe.

Challenges

It must be highlighted that getting permission to access clinical trial participants was a major challenge. During research proposal development, the researcher was given assurance by the Clinical Trial Manager in Zimbabwe that he could access participants of an international randomised clinical trial in Zimbabwe. The only condition given for accessing clinical trial participants in this study was that the student gets approval from the local Principal Investigator of the trial. The proposal was thus finalised with this study in mind. The proposal was developed and finalised whilst the student was still in South Africa.

The main reason why the study was chosen was that the trial had two sites in Zimbabwe, one in an urban area, and the other in a small farming town. As such it was hoped that comparisons would be made between participants in the two groups in terms of their motivations and opinions on voluntariness. Furthermore, the study was conveniently chosen because it was administered by the institution where the student was employed at that time. Previous attempts to access clinical trials conducted under the auspices of other organisations that the researcher was not affiliated with had not been successful and it was hoped that this clinical trial would be the best option.

Upon return to Zimbabwe, an application for permission was made to the local PI of the international clinical trial as per agreement and conditional approval was granted on 11

January 2011. The approval was given on the condition that the Chief Principal Investigator approves the study, hence an application was also sent to the Chief PI, who was based in the United Kingdom, on 17 January 2011. In response, the chief PI indicated that the sub-study needed to be approved by the Technical Steering Committee (TSC) and hence the researcher had to wait until he received feedback. The Chief PI had also hinted that there could be concerns about confidentiality.

Against that background, the researcher had to write a letter to assure the TSC and Chief PI that confidentiality and anonymity would be guaranteed and that the study would only be used for academic purposes. In response the Chief PI indicated that she was going to organise a meeting between the Project Manager of the clinical trial and the researcher in order to get more insight into the proposed study. That meeting never took place. In a sudden turn of events, the Chief PI sent an email advising the researcher to consider doing the research “on other trials of which there must be several in South Africa and Zimbabwe” (Chief Principal Investigator, personal communication, March 15, 2011). Following the resolutions from the TSC a final email was received from the Chief PI which left no hope of ever proceeding with the study. In that email the Chief PI stated that:

We are all agreed that, having assured patients their anonymity and confidentiality regarding their disease, it would not be acceptable to reverse that assurance and reveal their identity to a third party who is not in any way connected to the trial. I am not even sure that any ethics committee would approve it. Under the circumstances, I very much regret that I cannot allow you any access to the ...patients. (Chief Principal Investigator, personal communication, March 15, 2011)

Incidentally, the international clinical trial was later asked to stop further recruitment in the country by the National Ethics Committee and the Medicines Control Authority of Zimbabwe due to ethical concerns.

Considerable efforts were made by the researcher, with the assistance of the BRTI Directorate; the SARETI Executive, in particular Professor Wassenaar and Dr Rossouw, to find an alternative study where participants could be accessible. Dr Paul Ndebele was also asked to assist based on his experience in research regulation in Zimbabwe and his professional networks. Of the three PIs who were approached through the BRTI Director General's office, one gave permission to the researcher to access trial participants in his study.

After permission was granted by the PI, the study had to be reviewed by the Institutional Review Board and the National Ethics Committee. Permission was also sought from the Harare City Council, being the custodian of the research sites for the primary study.

Results

Response Rate

A total of 150 participants were approached. However, only 100 participants agreed to be interviewed in the study, giving a response rate of 66.7%. Participants who refused to participate in the study cited three main reasons: (i) they were too sick to go through the questionnaire; (ii) they were hungry and needed to rush home after waiting at the study site for long; and lastly (iii) they had other commitments. It must be highlighted that the patients who refused to participate in the study might differ fundamentally from those who agreed to be interviewed. As such, the views obtained from the respondents might not represent the opinions of the actual population under study.

Socio-demographic Characteristics

Forty three males and 57 females were interviewed in the study. The mean age of the participants was 37.34 years and it ranged from 18 years to 80 years. Fifty nine percent of the participants were married whilst the remainder, 41 %, were either single, divorced, separated or widowed as shown in Figure 1.

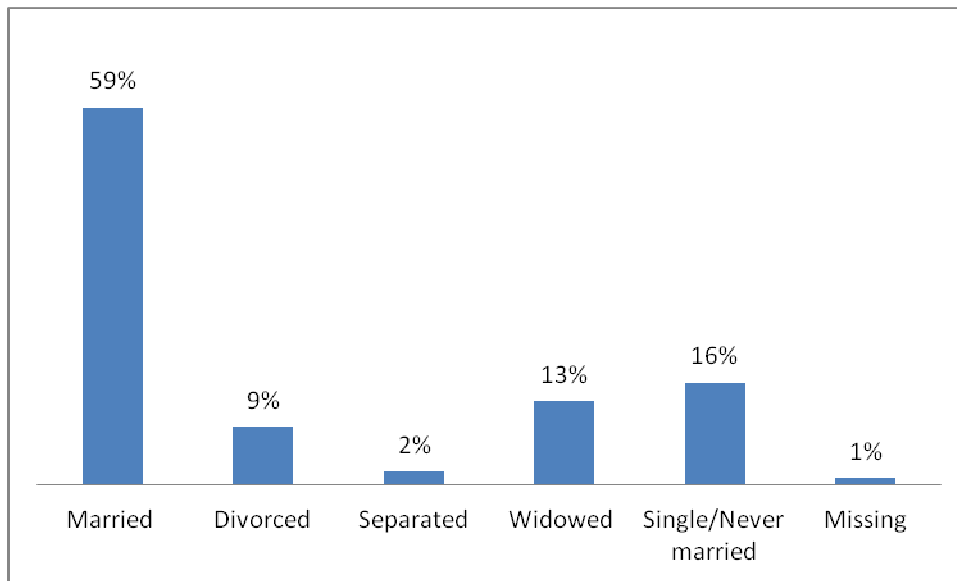


Figure 1: Percent Distribution of Respondents by Marital Status

The majority of the respondents (81%) had completed their secondary school education (Form Four). More than half (52%) of those respondents who were currently employed reported that they were formally employed. Of those employed, sixty seven percent were earning between US\$101 and US\$300 per month.

Research Experience

Participants were asked about their previous experience in research. The majority of the participants (87%) reported that they had never been involved in research. The majority of the participants (70%) were however not sure what the word research meant. With regards to duration of stay in the primary study, 72% of the respondents had been involved in the primary study for an average of 82 days from the date of enrolment. Less than half of the respondents (46%) reported that they first learnt about the primary study from a nurse at their local clinic whilst four percent and two percent learnt about the study from their doctor and community health worker respectively (see Figure 2). Forty eight percent of the respondents had learnt about the study from other sources that had not been pre-coded.

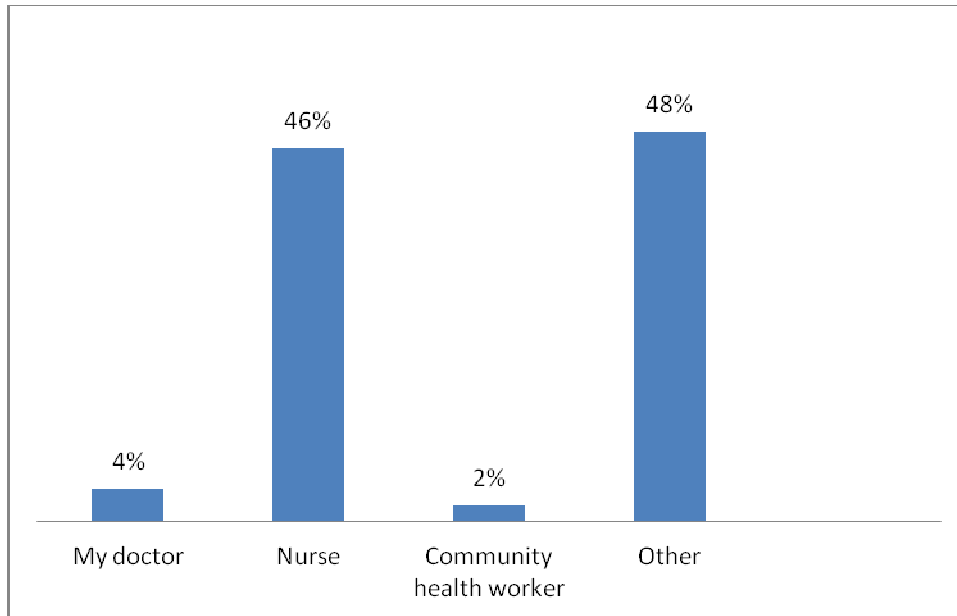


Figure 2: Percent Distribution of Respondents by Source of Information

The other category comprised of research assistants from the main study (89.8%), health officials from local clinics (8.2%) and community members (2.0%).

Motivations for Participation in Trial

Participants were first asked to state in general terms why they had decided to participate in the primary trial. Participants could give more than one answer. The responses were pre-coded into five main categories: (a) monetary incentives; (b) free treatment; (c) curiosity; (d) coerced and (e) other. Participants could select more than one answer. Table 1 shows the frequency distribution of participants' responses.

Table 1

Percent distribution of participants' by reason for enrolling in the clinical trial

Reason for enrolling in clinical trial	Percent
	<i>N</i> =100
	<i>n</i> (%)
Monetary incentives	0(0.0%)
Free treatment	4(4.0%)
Curiosity	43(43.0%)
Coerced	1(1.0%)
Other (Specify)	90(90.0%)

Ninety percent of the respondents cited “Other” reasons which were not pre-defined on the questionnaire. Of the 90% who cited “other” reasons, all indicated that they had enrolled in the trial for diagnosis and treatment of tuberculosis. It is worth noting that none of the participants mentioned altruistic motivations for participating in research.

Participants were further asked to choose from fourteen motivations that may or may not have influenced their decision to participate in the trial. They were asked the following question: “*Was your decision to participate in the study at all influenced by...*”. For each item that they identified as having influenced their decision to participate, they were asked to rate the degree of influence of that motivator on a scale ranging from 1 to 10. A score of 10 showed that the motivator was extremely important whilst a score of 1 meant that the motivator was not at all important in influencing the participant’s decision.

The most frequently cited motivators were: (i) diagnosis and treatment of tuberculosis (82.2%); (ii) how seriously the participants needed help for their condition (71%); (iii) advice from doctor or nurse (40%); (iv) the possibility of getting better care or follow up care (40%); and (v) access to treatment the participants could not get any other way (34 %). Table 2 shows the distribution of participants' motivations for enrolling in the clinical trial by the mean score for the degree of influence of each motivator. Participants could select more than one answer.

Table 2

Motivations for Subjects' Enrolment in Trial by Mean Score of Motivator

Item No.	Motivation	N=100 n (%)	Mean Score (1-10)
1.	The possibility of getting better care or follow up care	40(40.0%)	9.6
2.	Access to treatment you could not get any other way	34(34.0%)	9.5
3.	The availability of free treatment	15(15.0%)	9.2
4.	Getting something else for free	3(3.0%)	10
5.	Having something to occupy your time	0(0.0%)	
6.	Being able to stay in a hospital [for a longer time]	3(3.0%)	9
7.	How seriously you needed help for your condition	71(71.0%)	9.7
8.	Advice from your doctor or nurse [if yes: specify physician, nurse, other_____]	40(40.0%)	9.9
9.	Advice from other people	3(3.0%)	8.3
10.	Your trust in the people doing the research study	7(7.0%)	9.1
11.	The reputation of the institution where the research is being done	1(1.0%)	5.5
12.	Your curiosity about how the research study would work or what the results will be	9(9.0%)	8.8
13.	Your desire to help other people [with your condition	6(6.0%)	9
14.	The belief you're getting the active drug rather than the placebo	2(2.0%)	10

Offers to Participate in Research

Almost all the participants (93%) interviewed reported that they had been given an offer to participate in the study. Of those participants who reported that they were given an offer, all (100.0%) mentioned that they were offered bus fare to go to and from the research site. The

average amount of bus fare given to each participant per visit was US\$2. A small proportion of the participants also mentioned free treatment (5.4%) as an offer. Participants could give more than one answer.

Table 3

Percent Distribution of Participants by Offers to Participate in Research

N=100	
Participants offered something to participate	93(93.0%)
What were you offered?	n=93
Bus fare	93(100.0%)
Free treatment	5(5.4%)

When asked to state the importance of the offer of bus fare on their decision to participate in the clinical trial on a scale ranging from one to 10 (with 1 indicating that the offer was not at all important and 10 showing that it was extremely important) almost all the participants (99%) assigned a score of one meaning the offer of bus fare was not important in influencing their decision to participate in the study. Only one participant of those who mentioned bus fare as an offer assigned a score of two to the importance of this offer. All the participants who mentioned receiving an offer of free treatment however reported that it was extremely important in their decisions to participate in the study.

Participants were also asked to assess the fairness of the offers on a scale from 1 to 10 (with 1 showing that the offer was not at all fair and 10 showing that it was extremely fair). The majority of the participants (98.7%) gave a score of 10 for the offer of bus fare showing that the bus fare was extremely fair, whilst the remainder gave scores below five. Participants

viewed fairness of the bus fare in terms of its adequacy to take them back and forth from the research site. Free treatment was also rated as extremely fair by all the participants who cited it as an offer.

Pressures, Threats and Risks

Only a small proportion (2%) reported that they had been pressured or pushed to participate in the study. None of the respondents reported being threatened to participate in the clinical trial. On further questioning, one participant who reported that she had been pressured into the study revealed that she was pressured by her grandmother to enrol in the clinical trial due to her persistent illness. The second participant said that she was pressured by her doctor who argued that the new machine would quicken the diagnosis of her condition and thus enable her to get better treatment. When asked to rate the importance of the pressure with regards to their decision about participating in the trial, the two participants gave a score of one meaning that the pressure was not at all important in their decision to participate in the study.

Only one participant reported that the study was risky or uncomfortable giving a score of 6 on a scale of 1 to 10 (with 1 showing that the study was not at all risky or uncomfortable and 10 showing that it was extremely risky). The reason cited was that the researchers were taking too much blood for the first diagnostic tests. In spite of this risk in the study, the participant reported that she felt she had to enrol in order to be treated for her condition.

Perceptions on Coercion and Voluntariness

Respondents completed the Perceived Coercion Scale (PCS) as well as the Voluntariness Ladder, which are two global measures of voluntariness in the medical field. Coercion is regarded as the intentional use of a credible and severe threat of harm or force to control

another person (Beauchamp & Childress, 2009) or compel him or her to do something. For coercion to happen, three main things should be in place: (a) an unfavourably narrowed set of options; (b) that some human agents be limiting a person's options in an attempt to manipulate them; and (c) a threat (Hawkins & Emanuel, 2005).

On the PCS, respondents were asked whether five statements were true or false as they relate to their decisions to participate in the clinical trial. A true statement was given a score of 0 whilst a false statement received a score of 1. The scores from the five questions were then summed up to generate a single score for each respondent. A total score of 0 reflects a participant with the lowest perception of coercion whilst a score of 5 reflects the highest perception of coercion. Ninety eight percent of the respondents gave a total score of zero on the PCS, which reflects that the majority of respondents did not feel that they had been coerced to participate in the study.

Data generated from the Voluntariness Ladder confirmed the results from the PCS. The Voluntariness Ladder measures voluntariness on a scale that ranges from 1 to 10. A score of 1 shows that a participant's decision was not at all voluntary whilst a score of 10 shows that the decision was completely voluntary. The majority of respondents (98%) gave a score of 8 or above whilst 2% gave a score of 5 or less.

There was no significant relationship between most of the motivation factors and the PCS scores. The only significant relationships were found between low perceived coercion (lower scores on the PCS) and the following motivations: (i) trust in the people doing the research study ($p < 0.005$); (ii) the reputation of the institution where the research was being done ($p < 0.001$) and (iii) desire to help other people with a similar condition ($p < 0.001$).

Participants with no previous research experience had lower perceptions of coercion than those with previous research experience. As shown in Table 4, 89% of those participants who scored 0 — an indication of low perceptions of coercion — had no previous research experience compared to 11% with previous research experience ($p < 0.005$).

Table 4

Percent Distribution of Participants by Previous Research Experience and Levels of Perceived Coercion

Previous research experience	PCS Total Score			
	0 (n=97)	1 (n=1)	3 (n=1)	Missing (n=1)
Yes	11	100	0	100
No	89	0	100	0
Total	100	100	100	100

A significant inverse relationship was also found between the reputation of the institution where the research was being done and scores on the Voluntariness Ladder. For example, 96% of the respondents who gave a score of 10 (which shows high perceptions of voluntariness) reported that they had not been influenced by the reputation of the institution where the research was being done ($p < 0.001$).

There was no significant relationship between the following socio-demographic variables and scores from the Perceived Coercion Scale: age ($p = 0.182$); sex ($p = 0.506$); level of education; marital status ($p = 0.918$); employment status ($p = 0.389$); occupation ($p = 0.750$) and average monthly income ($p = 0.921$). The results also show a non-significant relationship between the same socio-demographic variables and scores from the Voluntariness Ladders: age ($p = 0.246$); sex ($p = 0.439$), level of education ($p = 0.981$); marital status ($p = 0.909$); employment status ($p = 0.303$); occupation ($p = 0.690$) and average monthly income ($p = 0.921$).

The findings from this study suggests that the following variables are predictors of diminished voluntariness: trust in people doing research, knowledge of the reputation of the institution conducting the research, previous research experience and the desire to help other people with a similar condition.

Discussion

Voluntariness of participation in research and its constraints have been poorly conceptualized and empirical evidence on this concept is still emerging. Although motivations for participation in research have been explored elsewhere, the literature on motivations to research participation in resource constrained settings is not conclusive.

Results obtained in this study in Zimbabwe showed that participants were influenced to participate in the study by five main motivations: (i) the need for diagnosis and treatment of tuberculosis, (ii) the extent to which they needed help for their condition, (iii) the advice received from a doctor or nurse, (iv) the possibility of getting better care or follow up care, and (v) the access to free and readily available treatment.

The only offers participants had received for participating in the trial were bus fare and free treatment. However, the offer of bus fare had no influence on participants's decisions to enrol in the study. The majority of the participants did not feel coerced, pressured or threatened to participate in the trial based on their self reported experiences and scores from the PCS. These results were also confirmed by data from the Voluntariness Ladder, which showed that participants had high perceptions of voluntariness.

There was no significant relationship between the socio-demographic variables and scores from the two measures of voluntariness; PCS and the Voluntariness Ladder. The only significant relationship was found between previous research experience and scores from the PCS and Voluntariness Ladder.

The high levels of perceived voluntariness reported in this study might be due to the fact that participants might have understood voluntariness in the context of diagnosis and treatment of their condition as opposed to voluntary participation to be in a study. The study might also have been seen to carry low risk since no experimental treatment was involved.

Most of the participants had been presenting with TB symptoms for a long time but the TB could not be detected using conventional diagnostic techniques at their local clinics.

Participants might have thought that they had no option but to try a new diagnostic technique that was only available in the study with the hope that it would quicken the diagnosis and subsequent treatment of their condition. These sentiments are summed up by one of the participants in the following statement: *“I was sick for a long time and the TB was not being detected so I chose to get into the study”*. The question that remains to be asked is: how voluntary is the consent of a participant who has no other or limited diagnostic options besides participating in a clinical trial? This is a conceptual issue that needs to be dealt with when assessing voluntariness, especially in countries with limited resources.

The majority of the participants in the trial were TB patients or people presenting with TB symptoms. These participants were recruited from local clinics dotted around the city and referred to the research site, which is located at the national referral centre for infectious diseases. There was no clear distinction between the research site and the referral hospital and it is possible that participants might have thought that they had been referred for further management without realising that they were in fact being recruited for a trial of a new diagnostic technique. The location of the research site and the way participants were recruited might be viewed as manipulation resulting in a form of therapeutic misconception in the minds of the respondents.

A direct question asking participant's whether they were in a study or just in routine clinical care might have been useful in clarifying the differences between research and clinical care. Additionally, it might have been more interesting to compare participants' perceptions of treatment under the primary trial with that offered under routine care considering that the treatment offered outside the trial was also free.

When respondents were asked the question: "*Have you been involved in any research study before?*" most of them struggled to answer as they did not understand what research was. They thought that research was the same as diagnosis for a medical condition or participation in a health related project. This observation might support the idea that respondents in the trial might not have thought themselves as being involved in research even though their perceptions of voluntariness were high.

The most commonly used Shona words that describe research in Zimbabwe are either *tsvakurudzo* or *ongororo*. In the current study *ongororo* was used to describe research although the Research Assistant would also use *tsvakurudzo* when the respondent indicated that they did not know what *ongororo* meant.

Participants regarded offers of bus fare as well as pressures as insignificant in their decision to participate in the study. Some of the motivations were also rated low in terms of their importance in influencing the respondent's decision to enrol in the trial. These findings are in line with existing conceptual frameworks which assert that not all influences exerted on

another person are controlling and that the impact of an influence varies from one person to another (Appelbaum *et al.*, 2009a; Beauchamp & Childress, 2009; Nelson *et al.*, 2011).

It is also pertinent to highlight that the two participants who indicated that they had been pressured to participate in the study — one by her grandmother and the other by her doctor — might not have understood the distinction between being pressured and being persuaded. The distinction between these two terms needs to be clearly defined in future studies on voluntariness.

The results of this study show some common patterns as well as some differences when compared to those conducted in other contexts, both in developing and developed countries. For example, results from Appelbaum and colleagues showed that the decision to participate in a clinical trial is a function of more than one consideration (Appelbaum *et al.*, 2009b). These results were confirmed in the current study. However, whilst participants in the study by Appelbaum *et al* cited trust in the researchers and the reputation of the host institutions as important motivations for enrolling in a clinical trial, these motivations were not regarded as such in the current study. This could be explained by the fact that participants in the current study were TB patients or TB suspects desperate to get treatment for their condition. As such they were mainly concerned about direct benefits of access to diagnostic services and drugs and health care; hence the majority cited motivations that were closely related to access to treatment and care.

Consistent with the present study, results from both developed countries (Franck *et al.*, 2007; Knifed *et al.*, 2008; Marshall & Rotimi, 2001; Montgomery & Sneyd, 1998) and developing countries (Minnies *et al.*, 2008; Moodley *et al.*, 2005; Sarkar *et al.*, 2009) also show low

levels of perceived coercion across different clinical trials. In the few studies in which participants reported being pressured to participate in the trial, the source of the pressure was mainly the treating physician (Agrawal *et al.*, 2006; Lynoë *et al.*, 1991; Riecken & Ravich, 1982); spouses, family members, friends, members of the research team and village elders (Krosin *et al.*, 2006; Pace *et al.*, 2005) as well as negative consequences that could arise if they withdrew from the study (Karim *et al.*, 1998; Krosin *et al.*, 2006; Lynoë *et al.*, 2001). In the present study, there was little evidence to demonstrate that participants were ever pressured or coerced to participate in the study by other people.

Limitations

It is important to note that the study was conducted with a limited number of participants enrolled in a single trial of a new diagnostic technique for TB. The researcher had to conduct the study based on what was available as accessing participants in other trials was challenging. The data might thus be biased and may therefore not be generalized in other trials, for example, trials involving patients with non-curable diseases. The information generated on voluntariness was based on self-reports of the research participants, which might be difficult to validate.

The questionnaire used for the study was predominantly closed-ended with predetermined answers. Participants' responses could have been limited because of the nature of this instrument. Complementing the data collection tool with focus group discussions and in-depth interviews could have been useful in yielding more valuable data on this subject. It might also be useful to include additional items on the questionnaire, for example, questions which capture participants' understanding of research as well as their awareness to withdraw from research.

It must be highlighted that the design of rating scales has its own inherent challenges, which are further compounded by the lack of clarity on the concept of voluntariness. Of note is the fact that there are no clear guidelines on the optimum number of response categories needed for each rating scale. Whereas some researchers argue that the more the categories, the higher the reliability and precision of the measurement (Preston & Colman, 2000), others favour fewer response options arguing that they are less burdensome and have the potential of reducing respondent confusion (Viswanathan M, Begen M, Dutta S, & T, 1996). If the latter is true, it can be argued that the scales used for assessing the importance of fairness of a motivation, as well as the importance of pressures, threats and risks in participants' decision to enrol in a trial, which ranged from 1 to 10, were too wide for respondents to appreciate what each of the scores meant. Other contested issues on rating scales relate to the use of the same rating scale on all questions measuring the same trait as well as optimal features for question formatting, among other things (Khadka, Gothwal, McAlinden, Lamoureux, & Pesudovs, 2012).

In this study, the potential role of social desirability cannot be ruled out especially when one looks at the respondents' high perceptions of voluntariness. It is possible that even if the respondents participated in the primary study involuntarily they may have wanted to give the impression that the primary study satisfied all ethical obligations hence the high scores on the Voluntariness Ladder. More importantly, it is also worth noting that the psychometric properties of the study instruments, in particular their validity and reliability, is unknown.

The limitations notwithstanding, the views expressed by participants in this study provide insight into the current debates on voluntariness aimed at contributing to improvements in the

ethical recruitment and retention of research participants in clinical trials, particularly in developing countries.

Conclusion

The results from this study showed that participants were not influenced by offers, pressures and threats in their decision to enroll in the trial. The decision to enroll in a clinical trial was mainly influenced by immediate medical needs rather than altruism. The study also showed that participants had high levels of voluntariness based on scores from the PCS and the Voluntariness Ladder. However, more work still needs to be done on how best voluntariness can be conceptualized and measured. As long as there is no consensus on what constitutes voluntariness, different measures might be developed which may not be valid in measuring the construct.

Most participants did not understand what the word research meant. Although it could not be confirmed in this study, it is most likely that as a concept, research is not clearly understood within the Zimbabwean community. As demonstrated by examples in Africa, contextual factors, for example, understanding of research in general or the specific aspects of a protocol in particular are often the most dominant influences on voluntariness in informed consent (Kamuya et al., 2011). A poor understanding of the research can lead to serious challenges related to the therapeutic misconception, which may invalidate voluntariness as the individual might think that the research is meant for their individual benefit. Rumours which portray a negative image of the research as well as negative perceptions about the research, can also provide various degrees of control to the potential research participants and even to those already enrolled in the research resulting in the negation of voluntary participation (Molyneux, Wassenaar, Peshua, & Marsha, 2005).

Recommendations

In future studies assessing voluntariness among research participants, it is important that participants are asked whether they were aware that they were involved in research and whether they were told that participation in that study was voluntary. They should also be asked about their awareness to withdraw from the study anytime without suffering any negative consequences. In view of the difficulties expressed by respondents in answering the question related to the meaning of research, a study of the local meanings of the term research is recommended.

A three point scale might yield more valid data for assessing the importance and fairness of motivations, pressures, threats and risks in participants' decision to enroll in a trial. This is in view of the fact that most of the participants in this study had only gone as far as secondary school and that the subtleties of the differences between values on a wider scale, ranging from 1 to 10, might not have been clear to them.

Results from the study cannot confirm the validity and reliability of the PCS and Voluntariness Ladder as measures of voluntariness. As such, these tools need to be validated or complemented by other measures, for example, the recently developed Decision Making Control Instrument.

In future, voluntariness should be assessed in a broader context. It might be useful to first establish how research is understood in the local setting before assessing voluntariness. Furthermore, a comprehensive assessment of the informed consent process is essential rather than singling out one component, for example voluntariness. Future studies on voluntariness might yield more useful data by reviewing the consent documents of the primary study and

assessing participants' levels of comprehension. This is in view of the fact that it is possible that a person can give voluntary consent that is not informed. Further research is also required to establish perceptions of voluntariness and its constraints in other types of trials in resource constrained countries.

In their current form, the instruments used in this study as adopted from Appelbaum *et al* (2009b) may not have been adequate to measure the full scope of voluntariness in research contexts. The instruments, however, provide a useful starting point towards the development of comprehensive tools for assessing voluntariness in the context of both developing and developed countries. A composite tool, which combines items from the DMCI as well as the tool developed by Appelbaum and colleagues might be more appropriate for use in future studies assessing voluntariness in research settings.

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Appendices

Appendix 1: Questionnaire

Appendix 2: Perceived Coercion Scale

Appendix 3: Voluntariness Ladder

Appendix 4a: English Consent Form

Appendix 4b: Shona Consent Form

Appendix 5: UKZN Faculty of Development and Social Sciences Approval

Appendix 6: Medical Research Council of Zimbabwe Approval

Appendix 7: BRTI Institutional Review Board Approval

Appendix 8: Permission from City Health Department

Appendix 9: Permission from Principal Investigator of Primary Study

Running head: VOLUNTARINESS IN CLINICAL TRIALS

A Case Study to Assess Participants' Perceptions on Voluntariness and Motivations for
Participating in a Clinical Trial in Zimbabwe

By Farirai Mutenherwa

Submitted in partial fulfilment of the requirements for a Masters in Social Sciences- Health
Research Ethics, in the School of Psychology, University of KwaZulu-Natal.

Unless specifically indicated to the contrary, this dissertation is the result of my own work

Submitted: April 2012

STATEMENT OF ORIGINAL AUTHORSHIP

“I, FARIRAI MUTENHERWA, declare that the thesis titled: “A Case Study to Assess Participants’ Perceptions on Voluntariness and Motivations for Participating in a Clinical Trial in Zimbabwe”, which I hereby submit for the degree of Master of Social Science at the School of Psychology, Faculty of Humanities, Development and Social Science, University of KwaZulu-Natal, is my original work and has not previously been submitted by me for a degree at another university”.

Protocol number and date of the approval from the Faculty of Humanities, Development and Social Science Research Ethics Committee: **11 April 2011**

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Student’s Signature

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April 2012

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Abstract

Introduction: There is little empirical evidence on voluntariness of participation in clinical trials due to absence of acceptable measures and universally accepted conceptual frameworks of voluntariness. *Methods:* A cross-sectional study was conducted in Zimbabwe to examine participants' motivations, levels of voluntariness and perceptions about the effect of offers, pressures and threats on decision making. One hundred participants were recruited from an ongoing diagnostic trial. Questionnaires adapted from published research, the Perceived Coercion Scale and Voluntariness Ladder were used for data collection. *Results:* The need to access diagnostic services and treatment for tuberculosis was the main motivation for enrolment in the trial. Participants were not coerced to participate in the trial but were offered bus fare. The offer had no effect on their decision to enroll in the trial. *Conclusion:* Immediate health benefits have a key impact on participants' decisions to enrol in a clinical trial of a diagnostic technique. A comprehensive conceptual framework together with validated tools for assessing voluntariness in African contexts should be developed.

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Introduction

Informed consent is an essential element of ethical conduct in scientific research. Apart from being an ethical requirement, it is also a legal requirement that has its roots in the Nuremberg Code. Informed consent has five key elements namely: competence, disclosure, understanding, voluntariness and consent (Beauchamp & Childress, 2009; Sugarman, 2002). Competence and voluntariness are regarded as the threshold elements of informed consent (Beauchamp & Childress, 2009; Sugarman, 2002). This implies that before a person gives informed consent, s/he must have adequate decision-making capacity, or competency to do so, and must be in a position to make a voluntary choice about whether or not to participate in a clinical trial (Sugarman, 2002). Only after these two elements have been fulfilled can the other components of consent be considered.

The voluntary participation of subjects in research has been widely debated, especially in clinical trials (Appelbaum, Lidz, & Klitzman, 2009a, 2009b; Litton, 2011; Nelson & Merz, 2002). Ethical and moral questions arise in therapeutic clinical trials, particularly in instances where the drug is not yet widely available or its accessibility in the public health system is limited. In the 1980s, when HIV was first diagnosed, antiretroviral drugs were not widely available and HIV positive individuals could only access these drugs through participation in clinical trials. As such, participants could enrol in clinical trials simply because they were the only sources of the life-saving drugs. Furthermore, participants in clinical trials might receive better health care services during clinical monitoring of the drug compared to the “usual standard of care” that may be available in state hospitals. In settings with limited resources, participation in clinical trials may, therefore, result from inducement, which can be argued to be undue since it might compromise the participants’ ability to make a truly

voluntary decision to participate in the trial. It must be highlighted, however, that although need and limited options are important aspects in considering voluntariness in resource limited settings, these factors do not necessarily imply that voluntariness is compromised. The risks to the research participants should also be given prominence when issues about vulnerability are considered. If the risks are greater than the benefits and the participants are in dire need of the service available in the research project, then undue inducement might pose more of a concern than in the absence of these factors.

Socioeconomic and political factors can also expose individuals and communities to coercion and undue influences, thus complicating the ethical principle of voluntariness. Zimbabwe has been experiencing severe economic challenges which peaked in 2008. The economic downturn resulted in a sharp decrease in funding for social services leading to an unprecedented deterioration of health infrastructure, loss of experienced health professionals, drug shortages and a drastic decline in the quality of health services available for the population (Collaborating Centre for Operational Research and Evaluation, 2010; Ministry of Health and Child Welfare, 2009). There are therefore glaring inadequacies in the six health system building blocks in the country namely human resources, medical products, vaccines and technology, health financing, health information, service delivery and leadership and governance (Ministry of Health and Child Welfare, 2009). These building blocks are prerequisites for a functional health delivery system.

Trends in mortality and morbidity in Zimbabwe show that the population is still affected by common preventable and treatable diseases and conditions including nutritional deficiencies, communicable diseases, diseases associated with pregnancy and childbirth, and newborn-related conditions (Ministry of Health and Child Welfare, 2009). HIV and AIDS, tuberculosis

(TB), diarrhoea, childhood illness, malaria, malnutrition, injuries, selected non-communicable diseases and reproductive health and pregnancy related conditions are amongst the leading causes of morbidity in Zimbabwe. HIV prevalence amongst the 15 – 49 year age group in the country remains at an unacceptably high level of 13.7% (Ministry of Health and Child Welfare, 2009). By 2009, approximately 45 percent (180,000 of an estimated 400,000 persons) of those requiring antiretroviral therapy were actually receiving treatment (Ministry of Health and Child Welfare, 2009).

Tuberculosis is the second leading cause of death in Zimbabwe and is among the top five leading causes of hospital admission and outpatient consultation. Among the 22 high tuberculosis countries in the world, Zimbabwe stands at number 17 (Ministry of Health and Child Welfare, 2010) with an estimated incidence rate of 782 per 100 000 population (Ministry of Health and Child Welfare, 2010). The TB epidemic in the country is largely driven by HIV. It is estimated that of all patients with TB infections, 72% are co-infected with HIV (Ministry of Health and Child Welfare, 2010).

Efforts to control TB in Zimbabwe are hampered by socioeconomic factors coupled with limited access to diagnostic centres and lack of sensitive and rapid TB tests (Population Services International, 2011). Rapid diagnosis and early treatment are essential for effective control of TB in the community. The most commonly available diagnostic test for TB is smear microscopy. However, its sensitivity is below 50% (Population Services International, 2011) and TB suspects have to make frequent visits for complementary radiography tests before commencing TB treatment. Although the evidence is still emerging, there are growing concerns that some patients might be suffering from drug-resistant TB (DR-TB), which is both difficult and expensive to diagnose and to treat. The Zimbabwean national TB

programme is already stretched. Sensitive and rapid diagnostic tools for drug sensitive and DR-TB are therefore required in order to reduce the burden of TB in Zimbabwe.

The economic decline in the general population is evidenced by the corresponding rise in levels of poverty and unemployment. The majority of the population still lives below the poverty datum line and do not enjoy even the minimum standard of living. By 2008, the economic crisis resulted in an unemployment rate of 80% whilst inflation rates were estimated at over 231 million percent (Ministry of Health and Child Welfare, 2009). Most of the industries were unable to generate employment opportunities as they were operating below capacity.

The soaring inflation rates coupled with the high unemployment rate drastically eroded the purchasing power of the local currency, thus aggravating poverty within the population. Poor people are prone to have more health problems and, furthermore, struggle to access or afford healthcare services. The cost of getting a TB diagnosis can also be a deterrent to the early diagnosis of TB in the country. A study conducted in Harare in 2009, showed that only 20% of the TB suspects could afford to pay for radiography and clinical examination (Population Services International, 2011). In Zimbabwe, patients pay for consultation fees and for diagnosis of TB. However, once diagnosed with TB, treatment is given free of charge.

Access to health resources for both diagnosis and treatment in the developing world can differ significantly from the developed world. In developing countries, regular and quality health care might only be available in a study environment. The perspective of potential participants in the developing world setting on voluntariness might therefore differ from those in developed countries. A research participant in a developing country might arguably be more likely to be influenced to join a trial because of access to health care services offered

in the trial; as such services may not be available or affordable in the public system. It is therefore important to assess the perspectives of participants about voluntariness in a developing world context, bearing in mind that contextual and socioeconomic factors might have a significant impact on participants' decisions.

Appropriate measures of assessing voluntariness to consent to research are poorly developed (Appelbaum et al., 2009b; Mandava, Pace, Campbell, Emanuel, & Grady, 2012; Miller et al., 2011). Additionally, the elements of voluntariness are poorly conceptualized and have been subjected to considerable debate (Appelbaum et al., 2009a, 2009b; Kamuya, Marsh, & Molyneux, 2011; Miller et al., 2011; Nelson et al., 2011). Consequently, empirical studies on voluntariness have been difficult to design and conduct, leaving a very small body of evidence on the subject with little consensus on the findings from these studies (Appelbaum et al., 2009a, 2009b; Nelson et al., 2011). Against this background, it has been argued that the regulation of the consent process could be based on the wrong presumptions about conditions that may impair voluntariness (Appelbaum et al., 2009a).

In this study, the researcher therefore aimed to contribute to the emerging body of literature and debate on voluntariness, using a trial of a new TB diagnostic technique in Zimbabwe as a case study. The study sought to confirm or dispel factors that have traditionally been viewed as threats or constraints to voluntary participation in research in Zimbabwe. Specifically, the study set out to answer the following key questions:

- What motivates research participants to enrol in a clinical trial?
- To what extent do incentives, threats and pressures affect research participants' voluntary decision making?

A cross-sectional exploratory study was carried out to answer the above questions. A semi-structured questionnaire, as well as the Voluntariness Ladder and Perceived Coercion Scale (PCS), which are two global measures used for the assessment of voluntariness in hospital settings, were used during data collection. The questionnaire covered three areas: demographic data, motivations for participating in research, and experience of offers, pressures, or threats.

The research participants were recruited from participants enrolled in a randomized controlled trial assessing the impact of a new TB diagnostic technique in preventing adverse outcomes in smear negative TB suspects in Zimbabwe.

Literature Review

Voluntariness of informed consent has been less explored in the literature of bioethics compared to the other components of consent (Appelbaum et al., 2009a, 2009b; Barsdorf & Wassenaar, 2005; Nelson et al., 2011; Nelson & Merz, 2002). This could be partly due to the complex nature of the concept and difficulties in assessing how voluntariness could be impaired. As Appelbaum aptly puts it: “Getting a conceptual handle on voluntariness is no easy task” (Appelbaum, 2011, p. 18). Consequently, there is little empirical evidence and a lack of acceptable measures of voluntariness to guide policy-makers and ethical and regulatory authorities on how to ensure voluntary participation by research subjects. The lack of acceptable measures and empirical evidence on voluntariness has raised concerns over potential coercion and undue inducement by researchers during recruitment and retention of research participants, particularly in clinical trials in the developing world.

In this section, the concept of voluntariness and its measurement will be discussed together with a summary of studies conducted on this subject. Three main conceptual frameworks will be discussed. The first conceptual framework was developed by Appelbaum and colleagues (Appelbaum et al., 2009a), the second by Nelson and colleagues (Nelson et al., 2011) and the third by Bull and Lindegger (Bull & Lindegger, 2011).

The Concept of Voluntariness

The precise meaning of the term voluntariness is disputed (Appelbaum et al., 2009a; Kamuya et al., 2011; Litton, 2011; Nelson et al., 2011; Nelson & Merz, 2002). In some circles, voluntariness is viewed in terms of the absence or presence of sufficient knowledge, psychological pressure and external control (Feinberg, 1973). This view of voluntariness has

been widely criticised for being broad to the extent of equating voluntariness with autonomous action (Beauchamp & Childress, 2009; Nelson et al., 2011). For an autonomous action to take place the person should be independent from controlling influences and should have the capacity for intentional action (Beauchamp & Childress, 2009; Kukla, 2005).

According to Beauchamp and Childress, a person acts voluntarily “if he or she wills the action without being under the control of another’s influence” (Beauchamp & Childress, 2009, p. 132). External control can result from influences from a second person, accidents or unanticipated events. They also argue that *internal* influences such as debilitating illnesses, psychiatric disorders or drug addiction can also compromise voluntariness (Beauchamp & Childress, 2009) possibly by causing cognitive impairment. Thus, an adequate condition of voluntariness must take into account both internal and external controlling influences.

Beauchamp and Childress further assert that not all influences exerted on a person — whether internal or external — are controlling and that the impact of an influence varies from one person to another and depends on circumstances.

Appelbaum and colleagues present a conceptual framework of voluntariness based on the “legal doctrine of informed consent”(Appelbaum et al., 2009a, p. 37). They argue that choices are voluntary unless they are unduly influenced or coerced. Those influences which render decisions involuntary have four characteristics: they are (i) external, (ii) intentional, (iii) illegitimate, and (iv) causally linked to the choice of the person participating in research (Appelbaum et al., 2009a). These four characteristics should all be present for a decision to be regarded as involuntary (Appelbaum et al., 2009a). Borrowing from Talcott Parsons’ conceptualisation of the mechanisms by which an individual can exert influence on another

person's decisions, offers, pressures and threats were identified as forms of influence that meet these four criteria.

Nelson and colleagues provide a theoretical model of voluntary informed consent, which they claim is most applicable in the field of biomedical research (Nelson et al., 2011).

According to their account, two conditions are necessary for voluntary participation to take place: (i) intentionality and (ii) freedom from controlling influences. Intentionality involves acting according to plans. Accidental actions are not intentional and are therefore involuntary.

In their model, controlling influences can be understood according to two main components of control namely, internal and external influences as well as constraining situations. The category of internal influences comprises of biomedical conditions, for example psychiatric disorders, drug addiction and disease. External influences comprise of offers of payment, threats, education, deceit, manipulative advertising and emotional appeals, among other things. Constraining situations refer to the contextual or background situations of the person targeted for exploitation. Examples of contextual factors include social norms and understanding of research.

The model proposed by Nelson and colleagues has two key features. Firstly, it makes a distinction between *interactions* between two people — the one who is influencing and the other whose decision is to be impacted — on the one hand; and the *context* where the interaction happens on the other hand. Secondly, the model highlights that both the interaction between the two people and the context where the interaction is happening have the potential of exerting moral challenges to the informed consent process (Kamuya *et al.*, 2011).

In their model, Nelson and colleagues (Nelson *et al.*, 2011) illustrate the moral challenges that may arise between a physician and a patient both in terms of interaction and context. They argue that if a doctor or clinician orders a reluctant patient to undergo a diagnostic test or examination by threatening the patient with abandonment if the patient does not comply, the doctor's influence would have controlled the patient's choice through coercion. By contrast, if the physician were to persuade a patient who was initially unwilling to undergo the test, the physician's actions influenced but did not control the patient's decision. Influences can thus be controlling or non-controlling and some might be welcome whereas others might not.

Measurement of Voluntariness

In their model, Nelson and colleagues developed a nine-question Decision Making Control Instrument (DMCI) from the original 28 items. The instrument measures self-perception of voluntariness by measuring two components of voluntariness — intentionality and extent of control. Measurements of the extent of intentionality and control are scored on a 6-point Likert scale that ranges from “Strongly Disagree” (1) to “Strongly Agree” (6) (Miller *et al.*, 2011; Nelson *et al.*, 2011). An example of an item on intentionality is: “I made this decision”. Participants are asked to respond to the following nine statements:

1. I was powerless in the face of this decision
2. Someone took this decision away from me
3. I made this decision
4. I was passive in the face of this decision
5. The decision about the protocol was inappropriately influenced by others
6. I was not in control of this decision
7. Others made this decision against my wishes

8. I was not the one to choose
9. The decision was up to me.

Although this model is well thought through, Nelson *et al* seem to have downplayed the role of contextual factors in influencing decision making. In their model, contextual factors are captured as constraining situations. Based on experience in conducting clinical trials in Africa, it has been argued that contextual factors are the most dominant forms of influence on voluntariness in the informed consent process (Kamuya *et al.*, 2011). The danger in underplaying contextual factors is that researchers may be distracted from considering ways in which such challenges could be addressed in real life situations. Additionally, it has been argued that internal influences such as psychiatric disorders, drug addiction and disease are not threats to voluntariness but challenges to autonomy or competency (Kamuya *et al.*, 2011).

The requirement that a voluntary action must be “substantially” free from “controlling influences” is not clearly enunciated in Nelson and colleagues’ conceptual framework (Blumenthal-Barby (Swindell), 2011; Bull & Lindegger, 2011). Specifically, the distinction between “controlling” and “non-controlling” influences is not clear. Most cases of influences might fall between the lines of controlling and non-controlling and unfortunately, the authors do not offer a framework to classify actions that fall in-between these two categories. Furthermore, there is no guidance on whether/how/when a person is substantially free from these influences. In a way, the authors seem to acknowledge that the requirement for voluntary action is quite problematic as they did not attempt to “determine precisely the degree of control an agent must have over causal influences in order to act voluntarily” (Nelson *et al.*, 2011, p. 10).

Bull and Lindegger agree with Nelson and colleagues' assessment of voluntariness as well as Appelbaum's conceptual framework on the issue of intentionality and freedom from controlling influences (Bull & Lindegger, 2011). However, they argue that in as much as external influences are critical in determining voluntary action, authors should also focus on participants' "subjective experiences of voluntariness in decision making" (Bull & Lindegger, 2011, p. 27). Participants may still feel that their decisions were not voluntary even though they are not causally influenced by intentional, external and legitimate influences. Perceived constraints to voluntary participation also need to be taken into consideration even in the absence of evidence of external control. A comprehensive analysis of voluntariness should therefore factor in both participants' subjective experiences of voluntariness as well as objective external influence.

Evidence from the behavioural and cognitive sciences also challenge the notion that acting intentionally — a measure of voluntariness — requires acting according to plans. Rather, people act according to plans less often than is traditionally thought (Blumenthal-Barby (Swindell), McGuire, & Halpern, 2011). People are heavily influenced by subconscious cues in the environment, mood or affect, in addition to deliberative judgment. Most of our decisions and actions do not, therefore, meet the criteria for having been done according to plan (Blumenthal-Barby (Swindell), 2011). In light of the evidence from the behavioural and cognitive sciences, the reliability of Nelson and colleagues' proposed DMCI is challenged. Our perceptions about the intentionality and control of our own and others' decisions are remarkably skewed and un-insightful (Blumenthal-Barby (Swindell), 2011). Furthermore, the DMCI measures perceived *voluntariness* as opposed to *actual voluntariness* and there is no guidance on the relationship between the two.

The DMCI is designed to gather empirical data on perceived voluntariness by assessing whether participants felt they were in control of their decisions or that the decision was made on their behalf. The instrument might be useful in identifying a certain category of potential constraints, for example, social constraints on decision making. However, it might not be possible to identify subtle subjective experiences, for example those coming from the social desirability effect in research settings (Bull & Lindegger, 2011). Participants might also alter their behaviour or decisions as a result of their awareness that they are involved in an experimental study — a phenomenon popularly referred to as the “Hawthorne effect” (Shuttleworth, 2009). Such effects might even be more difficult to deduce from the DMCI.

An Alternative Conceptual Framework

Bull and Lindegger (2011) argue that although intentionality and freedom from control are critical, there is a need to consider the role of relationships and socio-cultural factors in decision making when assessing voluntariness. They propose that voluntariness be viewed as falling on a continuum which ranges from independent voluntariness on one extreme, to controlled decisions on the other extreme. In between the two extremes is cooperative decision making which is based on relational autonomy.

In independent voluntariness, a person makes an independent decision even though there is influence from other people. On the other extreme, a person makes a decision under the control of another without exercising their autonomy or voluntariness. In between is a third position which they regard as “cooperative decision making” which is based on relational autonomy (Bull & Lindegger, 2011, p. 29). In this form of voluntariness there is joint and collaborative decision making with regard to participation in research.

Independent voluntariness is believed to be common in individualistic societies, whilst collaborative decision making and controlled decision making might be found in communalistic societies where respect for persons is not understood in terms of individual autonomy and privacy but rather in terms of cohesion and wellbeing of the entire community. This is common in traditional African societies and East Asian societies where decisions about research participation and medical care may be made by family members or traditional leaders (Engelhardt, 1980; Mills, Nixon, Singh, Dolma, & Nayyar, 2006; Tan, Angeles, & Lunitao, 2001). For example, to access a prospective female participant in an African community, a researcher might need to get approval from a community leader, then the woman's husband, and in some cases approval from in-laws is also expected (Mills *et al.*, 2006; Nyika, Wassenaar, & Mamotte, 2009). This is because of the relational nature of personhood in the African context and the emphasis on consensus and community, which makes individual consent and voluntariness, as defined in Western cultures, virtually impossible in some cultural contexts.

A Comparison of the Three Frameworks: Appelbaum et al, Nelson et al and Bull and Lindegger's Conceptual Frameworks

Two notable differences exist in the frameworks discussed. Firstly, in Appelbaum's account, internal influences, for example psychiatric conditions, do not negate voluntariness. A person can only be deprived of voluntariness through external influences resulting from the deliberate actions of another person (Appelbaum *et al.*, 2009a). On the contrary, Nelson and colleagues suggest that, in addition to external influences like threats, internal influences such as mental illness can indeed render an action non-voluntary.

Secondly, whilst Appelbaum asserts that an illegitimate influence is a requirement for involuntariness, this notion is excluded from Nelson *et al*'s analysis. Instead, Nelson and colleagues argue that it is not the *illegitimacy of an influence* that renders an action involuntary but rather the *controlling effect of that influence*. In Nelson *et al*'s account there is a distinction between the legitimacy of an influence and whether or not it causes a voluntary or involuntary decision (Nelson *et al.*, 2011).

The main distinction between Bull and Lindegger's model and the other two models (Nelson *et al* and Appelbaum *et al*'s conceptual frameworks) is that Bull and Lindegger view voluntariness as falling on a continuum from independent voluntariness to total control. Bull and Lindegger also highlight that social-cultural factors play a significant role in influencing participants' decisions. They also give room for collaborative decision making which they argue could still be considered as voluntary. Bull and Lindegger's model has a lot of appeal in African settings where cohesion and communal stability take precedence over individual autonomy.

The differences notwithstanding, there seems to be consensus in the three accounts that voluntary decisions should reflect the will of the decision-maker rather than of another person. Additionally, influences exerted on a person by another are not always controlling and may or may not render decisions involuntary.

Forms of Influence

Influences range from acts of love, threats, education, lies, manipulation and emotional appeals. For the purposes of this study, three categories of influence will be discussed: coercion, persuasion and manipulation (Beauchamp & Childress, 2009; Nelson *et al.*, 2011).

Coercion is the intentional use of a credible and severe threat of harm or force to control another person (Beauchamp & Childress, 2009) or compel him or her to do something. Coercion, therefore, requires the presence of three main aspects: (a) an unfavourably narrowed set of options; (b) that some human agents be limiting a person's options in an attempt to manipulate him or her; and (c) a threat (Hawkins & Emanuel, 2005). A classic case of coercion is as follows: A wants B to do X. If B does not do X, A will make B worse off than B was before the interaction. If B either accepts or refuses, B will be worse off than if A had never approached him (Wertheimer, 1987). A practical example of a coercive action would be withholding treatment from participants enrolled in a therapeutic study in order for them to continue with the study up to its end. Withholding treatment is a threat that will narrow the participants' options thereby forcing them to comply. It will also make the participants worse off than they were before if they do not comply. Like undue inducement, coercion can be understood as a threat to voluntary informed consent as it renders the actions of the coerced person non-autonomous.

Whether or not coercion occurs is a function of the subjective responses of the person targeted for coercion (Beauchamp & Childress, 2009). Coercion does not occur in circumstances where a person complies because they feel threatened but in actual fact no threat has been issued. Similarly, persons may feel pressured to enrol in a study because they are desperately in need of money or other goods from the study or simply have no option because of severe illness, lack of food or shelter. Although they might feel constrained by these influences to enrol in the study, their decision to enrol cannot be attributed to coercion. For coercion to occur, the self-directed course of action of the target of the coercive action should be displaced by a credible and intended threat (Beauchamp & Childress, 2009). In the

constraining situations such as illness and poverty, there is no coercion because no one has issued a threat in order to gain their compliance or enrolment in the study.

In *persuasion*, a person is encouraged to believe in something through the merit of the reasons proposed by another person (Beauchamp & Childress, 2009; Nelson *et al.*, 2011).

Manipulation is a generic term which encompasses several forms of influence that can neither be regarded as coercive nor persuasive. In manipulation, a person is swayed to do what the manipulator desires through other means besides coercion or persuasion. In clinical trials, manipulation might occur through manipulation of information or manipulation of options. Information can be manipulated through the ways a researcher presents information — tone of voice, forceful gestures, and the way information is framed. Researchers may also lie, withhold or exaggerate critical information required by prospective participants to make informed decisions. For example, instead of presenting to potential participants the failure rate of an investigational drug as 25%, a researcher might choose to say: “The success rate of the drug is 75%”.

Options can be manipulated through offers of rewards or benefits promised to prospective subjects (Beauchamp & Childress, 2009; Nelson *et al.*, 2011). Compensation for participation, provision of financial incentives, access to drugs or medical care or presentation of limited choices during the enrolment process can also affect a person’s perception of the study, thereby affecting understanding and voluntariness. Investigators may also manipulate trust (Brown *et al.*, 1989) or create a sense of false security for those enrolling in the study in order to increase enrolment.

Studies on Voluntary Participation in Clinical Trials

Voluntariness of research participation has been poorly conceptualised in the literature, making it difficult to design and conduct empirical studies on the subject (Appelbaum *et al.*, 2009a; Barsdorf & Wassenaar, 2005; Beauchamp & Childress, 2009; Nelson *et al.*, 2011). A few studies have been conducted, mostly in the developed world, but there is no evidence suggesting that studies to assess participants' voluntariness in clinical trials have been conducted in Zimbabwe.

Studies on voluntariness can be classified into two broad categories: (i) those that focus on participants' perceptions on pressures and (ii) those that ask participants about their knowledge about their right to refuse to participate or to withdraw as and when they wish to do so without suffering any adverse consequences. With regard to the first category, studies conducted in the United States of America, Canada and the United Kingdom across a range of clinical trials revealed that between 90% and 99% of the participants were not pressured to participate in the clinical trials they enrolled in (Franck, Winter, & Oulton, 2007; Knifed, Lipsman, & Mason, 2008; Marshall & Rotimi, 2001) or that their participation was voluntary (Montgomery & Sneyd, 1998).

In the context of developing countries, studies in Africa show similar patterns of voluntariness among clinical trial participants. For example, 95% of women whose children were enrolled in a paediatric trial conducted in Ghana (Sarkar, Grandin, & Gladstone, 2009) and 99% of participants in an influenza vaccine trial in South Africa (Moodley, Pather, & Myer, 2005) reported that their participation in the respective trials was voluntary. Similar results were obtained in an Indian paediatric trial where 98% of the women enrolled reported

that they did so without any pressures or compulsion (Minnies, Hawkrige, & Hanekom, 2008).

In the few cases where participants felt pressured to participate in clinical trials, the source of pressure was mainly their health condition or other constraining situations (Mandava et al., 2012). In the developed countries, pressure from another person was rarely reported and, when reported, the source of the pressure was the treating physician (Agrawal, Grady, & Fairclough, 2006; Lyno'e, Sandlund, & Dahlqvist, 1991; Penman, Holland, & Bahna, 1984; Riecken & Ravich, 1982). Similarly, in the developing countries, pressure from other people was reported by few respondents ranging from six percent to 26%, depending on the type of trial (Mandava et al., 2012). Spouses, family members or friends, members of the research team and village elders were cited as the sources of pressure (Krosin, Klitzman, & Levin, 2006; Pace et al., 2005).

The majority of participants (87%) in a clinical trial in Bangladesh reported that they felt pressured by the fear of the negative consequences that could arise if they withdrew from the study (Lyno'e, Hyder, & Chowdhury, 2001). They reported that the trial offered so many advantages making it difficult to refuse enrolling. Similarly, in a perinatal HIV transmission trial conducted in South Africa, 32% and 23% of participants in the evaluation study group and sensitization group respectively thought that care would be compromised if they refused to participate in the study (Karim, Karim, Coovadia, & Susser, 1998). Furthermore, 44% of parents enrolled in a paediatric malaria vaccine clinical trial in Mali, thought that they would be deprived of healthcare services should they refuse to participate in the study (Krosin et al., 2006).

Studies that investigated whether participants knew that they could refuse or withdraw to participate in the trial demonstrate the clearest differences in perceptions of participants in developing and developed countries. Out of the 18 countries that measured voluntariness in terms of whether or not participants knew they could withdraw or refuse to participate, in 15 studies at least 75 percent of the participants in developed countries were aware that they could withdraw or refuse. Furthermore, in 10 of these studies 90% or more reported that they were not only aware but believed that they could actually withdraw from research if they wished. In contrast, less than 50% of the participants in five of the 15 studies conducted in developing countries that measured knowledge of withdrawal or refusal, knew they could withdraw from research (Mandava et al., 2012).

It is pertinent to highlight that there are also differences between and within developing countries. For instance, in some developing countries, high proportions of participants knew that they could withdraw or refuse to participate in the trial. In a malaria vaccine trial conducted in Mali, more than 90% of adults and parents of children enrolled in the trial were aware that they could withdraw from the trial (Ellis, Sagara, & Durbin, 2010). Similarly, 88% of participants enrolled in a vaccine trial in Thailand knew that they had a right to refuse participation as they wished (Pitisuttithum, Migasena, & Laothai, 1997) whilst 93% of the women in a South African HIV trial reported that they had the right to quit (Verheggen & van Wijmen, 1996). However, 10% of mothers in a malaria vaccine trial conducted in Mali knew that they could withdraw their child from the trial any time (Krosin et al., 2006). Knowledge to refuse or withdraw in a clinical trial was also recorded in a study in an HIV vaccine trial conducted in Côte d'Ivoire, in which 27% of the participants knew they could withdraw any time (Ekouevi, Becquet, & Viho, 2004).

In a study, conducted in South Africa, the results showed that there were racial differences in the public's perceptions of voluntariness in medical research. Specifically, Black participants had the lowest scores on voluntariness compared to both Indians and Whites (Barsdorf & Wassenaar, 2005). This could partly be explained by the systematic human rights abuses and violations perpetrated on the Black community during the apartheid era, resulting in Black people being apprehensive of any medical research targeting them.

A preliminary empirical investigation conducted by Appelbaum *et al* among clinical trial participants at a university medical centre in the United States of America on voluntariness and motivations for participating in different clinical trials, revealed that participants have diverse reasons for wanting to participate in a clinical trial (Appelbaum *et al.*, 2009b). The study also showed that participants' decisions to enrol are affected by more than one consideration. Participants cited the possibility of better care, trust in the researchers and the reputation of the host institutions as important motivations for their participation. However, participants placed different values on their motivations for participation depending on the nature of the clinical trial they were enrolled in and their health condition. For example, respondents who were enrolled in substance abuse trials placed less emphasis on altruism as a motivation for participation and placed more emphasis on the availability of free treatment and the seriousness of their need for treatment. On the other hand, those faced with life-threatening conditions, for example participants enrolled in oncology trials, placed the greatest weight on advice from their medical caregivers.

With regards to constraints to voluntary participation, the study revealed little evidence of constraints to voluntary participation. Where constraints to voluntary participation were reported, they were perceived as rarely playing a significant role in influencing the decisions

of the participants on whether to participate or not. However, participants who cited that they received advice from a physician or nurse had a high score on the Perceived Coercion Scale suggesting that participants might have been constrained to say no.

It is pertinent to highlight that the findings from studies on voluntariness have been criticized on methodological and conceptual grounds (Appelbaum *et al.*, 2009a, 2009b; Mandava *et al.*, 2012; Pace, Grady, & Emanuel, 2003). Specifically, there is presently neither an agreed conceptual framework to guide research on voluntariness nor standard and reliable techniques for its assessment (Appelbaum *et al.*, 2009a; Pace *et al.*, 2003). Different studies were thus using different measurement techniques for assessing voluntariness and, consequently, the body of data collected on the subject are hardly comparable and to a greater extent inconclusive.

Efforts to establish participants' motivations and possible constraints of voluntariness in clinical trials are essential if one acknowledges the fact that informed consent is a process of shared decision making between the researcher and the participant (Lindegger *et al.*, 2006; Lindegger & Richter, 2000; Sastry *et al.*, 2004). This entails a two way process in which the researcher should first understand the needs, values and motivation of the participants, and how best to inform them and optimize their involvement in the research study (Lindegger & Richter, 2000). Consistent with this conception of informed consent, Mkhize (2006) argues that informed consent should in fact be viewed as a semiotic process whereby all concerned parties negotiate the processes and procedures to be followed. Although this might be the ideal situation, it might not be possible to achieve in real life situations.

Against this background, a new agenda has been set for health researchers to come up with reliable assessment techniques for assessing constraints to voluntariness and to study the epidemiology of these constraints. The ultimate objective of this research agenda is to develop ways of preventing constraints to voluntariness with a view to enhancing the voluntary participation of research subjects in research (Appelbaum *et al.*, 2009a).

Calls have also been made to understand the perceptions of potential research participants about health research (Barsdorf & Wassenaar, 2005; Benatar, 2002). It has been argued that health research in developing countries should in fact be preceded by social science research in order for health researchers to understand the culture, customs, attitudes and perceptions of local communities (Barsdorf & Wassenaar, 2005; Mills *et al.*, 2006). Such information would be critical in providing insights into the presence or absence of constraints to voluntariness within a given society and inform remedies to deal with these constraints.

As with participants in other developing countries, and in particular post colonial African countries, research participants in Zimbabwe are vulnerable to unethical research due to deprivation of educational opportunities, lack of political power, poverty, unfamiliarity with medical interventions and dire need for medical care (Teays & Purdy, 2001). Consequently, they may view health research participation as mandatory and non-voluntary. Their vulnerability might potentially make them more susceptible to coercion, threats, deception and manipulation. It is against this background that an exploratory descriptive study was conducted to understand in detail the prevailing situation with regards to voluntariness of participation in clinical trials in Zimbabwe.

Of the three conceptual frameworks described in this paper, Bull and Lindegger's account is arguably the best. However, there were neither previous studies nor validated data collection tools tied to their model, which could be adapted for the current study. In order to overcome the conceptual and methodological shortcomings of previous studies on voluntariness and to enhance comparability of research results, this study adopted the conceptual framework and tools developed by Appelbaum *et al* (2009a).

Aims and Objectives

The overall objective of this study was to ascertain research participants' views regarding the presence and importance of offers, pressures, and threats to their decisions about enrolling in a diagnostic trial.

Specifically, the study set out to answer the following key questions:

- i. What are the key factors that influence research subjects' decisions to participate in a clinical trial of a new TB screening and diagnostic technique?
- ii. What is the role of offers, pressures and threats on research subjects' decisions to enrol in a clinical trial?
- iii. What proportion of research subjects perceive themselves as having volunteered to participate in the clinical trial?
- iv. Is there an association between the factors that influence participants' decisions to enrol in a clinical trial and levels of voluntariness? If so, what is the level of association?
- v. What are the predictors of diminished voluntariness?

Method

In this section, the materials and methods used to collect the data are presented. For clarity, the source of research subjects for the current study will be referred to as the *primary study*. The current study will be referred to as the *sub-study*.

Study design

A cross-sectional descriptive study design was used.

Subjects

Respondents for this study were recruited from participants enrolled in a randomized controlled trial of the impact of a new diagnostic test for TB in Zimbabwe, referred to as the primary study.

The Primary Study

Background of the primary study

The aims of the primary study were to prevent adverse outcomes in primary health clinic smear negative tuberculosis suspects. The sample size for the primary study was 766 participants aged 16 years and above. The study design was a randomised controlled trial with two arms. In the first arm (routine arm) participants were offered the standard of care and in the intervention arm GeneXpert (GXP) testing was offered to smear negative TB suspects. GeneXpert is a new molecular diagnostic test used to detect *Mycobacterium tuberculosis* (MTB) and resistance to rifampicin. It is easy to use, has minimal requirements

and produces results within minutes (Helb, Jones, Story, & Boehme, 2010). The study was conducted in Zimbabwe at a TB referral centre.

Procedure

The TB suspects presenting for investigation at the primary health clinics in Harare were offered to join the study. Specimens were collected from suspects after obtaining their written informed consent. On the first day, participants were requested to provide two spot sputum specimens, a urine specimen and whole blood for HIV, CD4 cell count and interferon gamma assays. On the second day, patients were asked to come back to the clinic to provide one morning sputum and one additional spot sputum. One spot sputum specimen from the smear negative participants was subsequently randomised to GXP (Intervention arm) or fluorescence smear microscopy testing (control arm).

GeneXpert Intervention

Specimens randomised to this arm were tested for TB with the GeneXpert. Participants with positive GeneXpert results were referred for TB treatment whilst those with negative GeneXpert results would continue with their standard of care provided through the routine clinical care from clinics. The study also provided transport costs for these patients to visit the Infectious Diseases Hospital and get a chest X-ray, at no cost, for routine investigations.

Fluorescence Microscopy Arm

Specimens randomised to the fluorescence microscopy arm were tested with fluorescence smear microscopy. Participants with positive fluorescence screen were referred for TB

treatment and those with negative fluorescence screening continued with their routine standard of care as provided by the clinics.

Smear Negative TB Suspects

All smear negative TB suspects who tested positive on GXP or fluorescence microscopy were followed-up and referred for treatment. Smear negative TB suspects who failed to return to collect their results at their local clinic and were negative on all TB tests were followed up to establish the reason for not collecting results and reinvestigated for TB if they were still symptomatic.

HIV Testing and Counselling

Diagnostic HIV testing and counseling were offered to participants in both the GeneXpert intervention and Fluorescence microscopy arms. Participants not wishing to know their results were asked to consent to anonymised testing for study purposes. All trial participants found to be HIV-positive were started on cotrimoxazole (if WHO stage 2 to 4) and referred to the HIV clinic.

The Sub-Study

Sample Size

Assuming a prevalence of involuntariness of 8 percent, a sample size of 100 was calculated. The prevalence of involuntariness was based on studies conducted in developing countries which showed that levels of involuntariness ranged from five to 10% (Ellis et al., 2010; Sarkar et al., 2009; Verheggen & van Wijmen, 1996). The inclusion criterion was that the participant needed to be 18 years of age and be a current study participant in the primary

study. Participants were approached when they came for their research visits for the primary study.

Data Collection Instrument

A set of three data collection tools were used. These instruments were first used by Appelbaum and colleagues in a study conducted at a major university medical centre in the United States of America (Appelbaum *et al.*, 2009b). Their study sought to generate preliminary data on the extent and correlates of limitations on voluntariness across different clinical trials, which included trials on substance abuse, cancer, HIV, interventional cardiology, or depression.

The first instrument (Appendix 1) is a structured questionnaire that addresses three areas: socio-demographic data, motivations for participating in research, and experience of offers, pressures, or threats. The structured questionnaire was adopted with some modifications to suit the Zimbabwean context and for relevance to the current study. For example, questions from the original instrument that was developed by Appelbaum *et al* (2009b), which were deemed irrelevant to the Zimbabwean context, were excluded in the current tool. These included, Question 6 on the background section (What study are you currently involved in?) together with questions 5a (Do you have any pending legal cases or criminal charges?), 5b (Are you currently on parole or probation?) and 5c (Did your legal case/criminal charges/being on parole or probation influence your decision to participate in the study?) under Part II of the same tool.

Additional questions were also included in the questionnaire to capture information on the socioeconomic status of the research subjects, in particular, their income and level of education. The specific questions that were added are the following:

- What is your current marital status?
- What is the highest level of formal school that you have completed?
- What is your occupation?
- On average, what is your monthly salary?

These questions were added with a view to explore any associations between the socioeconomic factors, motivations to participate in a trial and the levels of voluntariness.

The other two instruments that were used were the Perceived Coercion Scale (PCS) (Appendix 2) and the Voluntariness Ladder (Appendix 3), which are global measures of voluntariness in hospital settings. The PCS was a modified version of the MacArthur Perceived Coercion Scale (MPCS) (Gardner, Hoge, & Bennett, 1993). The original MacArthur Perceived Coercion Scale was used to measure patients' perceptions of coercion during admission in a hospital. The original questions in the (MPCS) were as follows:

1. I felt free to do what I wanted about coming into the hospital.
2. I chose to come into the hospital.
3. It was my idea to come into the hospital.
4. I had a lot of control over whether I went into the hospital.
5. I had more influence than anyone else on whether I came into the hospital.

In the current and modified version of the PCS the five questions were phrased as above except that, instead of making reference to hospital admission, the questions were referring to the participant's involvement in research. Respondents were asked whether the five

statements were true or false with regards to their decisions to participate in the trial. The five questions used in the current study were phrased as follows:

1. I felt free to do what I wanted about signing up for the research project.
2. I chose to sign up for the research project
3. It was my idea to sign up for the research project.
4. I had a lot of control over whether I signed up for the research
5. I had more influence than anyone else on whether I signed up for the research project

A true statement was given a score of zero (0) whilst a false statement received a score of one (1).

The Voluntariness Ladder is a modified version of the Coercion Ladder (Hoyer, Kjellin, & Engberg, 2002). The Coercion Ladder is a visual analogue scale shown to patients so as to assess the degree of coercion prior to hospital admission. Each step on the ladder corresponds to the degree of pressure that a patient might have been subjected to. Patients are asked to put a mark on any one of the ladder steps that corresponds to their degree of perceived coercion. The steps range from 1 to 10. A score of 10 represents maximum perception of coercion whilst a score of 1 shows minimum perception of coercion.

The difference between the original Coercion Ladder and its modified version that was used in the current study is that instead of asking participants about perceptions of coercion with regards to hospital admission, participants were asked about their perceptions of voluntariness with regards to participation in a trial. Thus the Voluntariness Ladder was used to measure how voluntary a participant's decision was by asking each participant to circle a number on a ladder that best matched their decision. A score of 10 represented a completely voluntary decision whilst a score of 1 showed that a decision was not at all voluntary.

It is worth mentioning that there is no evidence that the questionnaire, the PCS and Voluntariness Ladder have been formally validated or used in a different cultural context apart from their use in the United States of America.

Measures

Participants completed a questionnaire which captured socio-demographic information (age, sex, education, marital status, income) as well as their experiences with offers, threats and pressures.

Voluntariness was assessed using the PCS as well as the Voluntariness Ladder. The Voluntariness Ladder is a simple measure that asks subjects to rate how voluntary their decision was on a “Ladder” ranging from 1 to 10. A score of 1 indicates a choice that is not at all voluntary and a score of 10 reflects a completely voluntary choice.

Scores on the PCS ranged from zero (0) to five (5) and were based on true or false responses to five questions. A score of 5 on the PCS indicates a high perception of coercion whilst a score of zero reflects perceptions of non-coercion.

Procedure

Recruitment took place when participants came for their routine clinic visits in the primary study. Participants were only referred to the sub-study after finishing the business of their visit in the primary study. A research nurse in the primary study introduced participants to the sub-study and requested the participants’ permission to be accessed by research assistants from our research team. Those interested in participating in the sub-study were asked to make arrangements with a research assistant at a convenient time. They were then taken through

the consent process and only after they had consented to participate in this study, were interviews conducted by the researcher and one trained research assistant.

A question that often arises on studies on voluntariness in research is the voluntariness of the research participants taking part in such studies. Although no specific measures were done to assess the levels of voluntariness of the respondents in the current study, efforts were made by the researcher to enhance voluntary participation. For example, during the consent process, participants were informed that they did not have to take part in the sub-study if they did not want to. If they decided not to participate in the sub-study that decision would not in any way affect their regular benefits and medical care from the primary study. They were also told that they could withdraw from the study at any time if they so wished. It must be highlighted, however, that even though prospective participants were provided with the relevant information to improve their voluntariness, there is no guarantee that such efforts resulted in voluntary participation.

After expressing their willingness to participate in the sub-study and signing the consent form (Appendix 4b), participants were asked to choose from among 14 possible motivations for enrolling in research. If they identified a motivation as having played a role in their decision to participate, they were asked to indicate the degree of influence associated with that motivation on a scale ranging from 1 to 10. Respondents were also asked whether they had been subjected to offers, pressures and threats in the clinical trial. If they indicated that they had been subjected to these influences, they were asked to describe (i) what happened, (ii) the extent to which it influenced their decisions, and (iii) the degree to which they considered the offer, pressure, or threat to have been unfair. Influence was again indicated on a scale ranging from 1 to 10.

Respondents were also asked about the risks they perceived to be associated with the primary study and the role of offers, pressures, or threats in making the risks worth accepting. Finally, respondents completed a modified version of the MacArthur Perceived Coercion Scale (Appelbaum *et al.*, 2009b; Gardner *et al.*, 1993) and a Voluntariness Ladder, which is a modification of the Coercion Ladder (Hoyer *et al.*, 2002). These two instruments are published measures of voluntariness of decisions in treatment contexts.

All the three instruments were pilot-tested on ten respondents to ensure understanding of the questions by participants and relevance to the study and cultural context. This is particularly important in view of the fact that the same tools were first used in a developed country set up and have neither been formally validated nor used in a different cultural context. The instruments were also translated into Shona, the language spoken by most people in the town where the primary study was conducted.

Ethical approval was obtained from the University of KwaZulu-Natal Faculty of Development and Social Sciences (Appendix 5), Medical Research Council of Zimbabwe, which serves as the National Ethics Committee (Appendix 6) as well as the Biomedical Research and Training Institute Institutional Review Board (Appendix 7). Written permission to access patients was obtained from the City Health Department (Appendix 8) as well as from the Principal Investigator of the primary study (Appendix 9). In the letter written to the PI of the primary study requesting permission to access study participants (see Appendix 9), the researcher indicated that information generated from the current study would only be used for academic purposes. Additionally, the letter also stated that the study as well as the participants to be interviewed would not be identified in the research report or in any

publications that might come out of the study. Instead of specifying the exact name or title of the primary study, it shall be reported that data came from participants in a diagnostic trial in Zimbabwe.

Challenges

It must be highlighted that getting permission to access clinical trial participants was a major challenge. During research proposal development, the researcher was given assurance by the Clinical Trial Manager in Zimbabwe that he could access participants of an international randomised clinical trial in Zimbabwe. The only condition given for accessing clinical trial participants in this study was that the student gets approval from the local Principal Investigator of the trial. The proposal was thus finalised with this study in mind. The proposal was developed and finalised whilst the student was still in South Africa.

The main reason why the study was chosen was that the trial had two sites in Zimbabwe, one in an urban area, and the other in a small farming town. As such it was hoped that comparisons would be made between participants in the two groups in terms of their motivations and opinions on voluntariness. Furthermore, the study was conveniently chosen because it was administered by the institution where the student was employed at that time. Previous attempts to access clinical trials conducted under the auspices of other organisations that the researcher was not affiliated with had not been successful and it was hoped that this clinical trial would be the best option.

Upon return to Zimbabwe, an application for permission was made to the local PI of the international clinical trial as per agreement and conditional approval was granted on 11

January 2011. The approval was given on the condition that the Chief Principal Investigator approves the study, hence an application was also sent to the Chief PI, who was based in the United Kingdom, on 17 January 2011. In response, the chief PI indicated that the sub-study needed to be approved by the Technical Steering Committee (TSC) and hence the researcher had to wait until he received feedback. The Chief PI had also hinted that there could be concerns about confidentiality.

Against that background, the researcher had to write a letter to assure the TSC and Chief PI that confidentiality and anonymity would be guaranteed and that the study would only be used for academic purposes. In response the Chief PI indicated that she was going to organise a meeting between the Project Manager of the clinical trial and the researcher in order to get more insight into the proposed study. That meeting never took place. In a sudden turn of events, the Chief PI sent an email advising the researcher to consider doing the research “on other trials of which there must be several in South Africa and Zimbabwe” (Chief Principal Investigator, personal communication, March 15, 2011). Following the resolutions from the TSC a final email was received from the Chief PI which left no hope of ever proceeding with the study. In that email the Chief PI stated that:

We are all agreed that, having assured patients their anonymity and confidentiality regarding their disease, it would not be acceptable to reverse that assurance and reveal their identity to a third party who is not in any way connected to the trial. I am not even sure that any ethics committee would approve it. Under the circumstances, I very much regret that I cannot allow you any access to the ...patients. (Chief Principal Investigator, personal communication, March 15, 2011)

Incidentally, the international clinical trial was later asked to stop further recruitment in the country by the National Ethics Committee and the Medicines Control Authority of Zimbabwe due to ethical concerns.

Considerable efforts were made by the researcher, with the assistance of the BRTI Directorate; the SARETI Executive, in particular Professor Wassenaar and Dr Rossouw, to find an alternative study where participants could be accessible. Dr Paul Ndebele was also asked to assist based on his experience in research regulation in Zimbabwe and his professional networks. Of the three PIs who were approached through the BRTI Director General's office, one gave permission to the researcher to access trial participants in his study.

After permission was granted by the PI, the study had to be reviewed by the Institutional Review Board and the National Ethics Committee. Permission was also sought from the Harare City Council, being the custodian of the research sites for the primary study.

Results

Response Rate

A total of 150 participants were approached. However, only 100 participants agreed to be interviewed in the study, giving a response rate of 66.7%. Participants who refused to participate in the study cited three main reasons: (i) they were too sick to go through the questionnaire; (ii) they were hungry and needed to rush home after waiting at the study site for long; and lastly (iii) they had other commitments. It must be highlighted that the patients who refused to participate in the study might differ fundamentally from those who agreed to be interviewed. As such, the views obtained from the respondents might not represent the opinions of the actual population under study.

Socio-demographic Characteristics

Forty three males and 57 females were interviewed in the study. The mean age of the participants was 37.34 years and it ranged from 18 years to 80 years. Fifty nine percent of the participants were married whilst the remainder, 41 %, were either single, divorced, separated or widowed as shown in Figure 1.

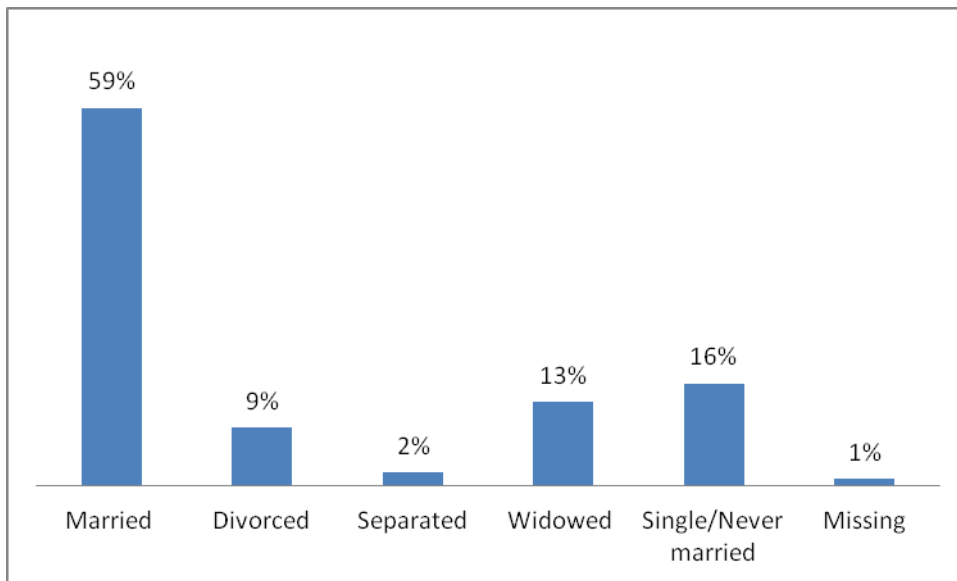


Figure 1: Percent Distribution of Respondents by Marital Status

The majority of the respondents (81%) had completed their secondary school education (Form Four). More than half (52%) of those respondents who were currently employed reported that they were formally employed. Of those employed, sixty seven percent were earning between US\$101 and US\$300 per month.

Research Experience

Participants were asked about their previous experience in research. The majority of the participants (87%) reported that they had never been involved in research. The majority of the participants (70%) were however not sure what the word research meant. With regards to duration of stay in the primary study, 72% of the respondents had been involved in the primary study for an average of 82 days from the date of enrolment. Less than half of the respondents (46%) reported that they first learnt about the primary study from a nurse at their local clinic whilst four percent and two percent learnt about the study from their doctor and community health worker respectively (see Figure 2). Forty eight percent of the respondents had learnt about the study from other sources that had not been pre-coded.

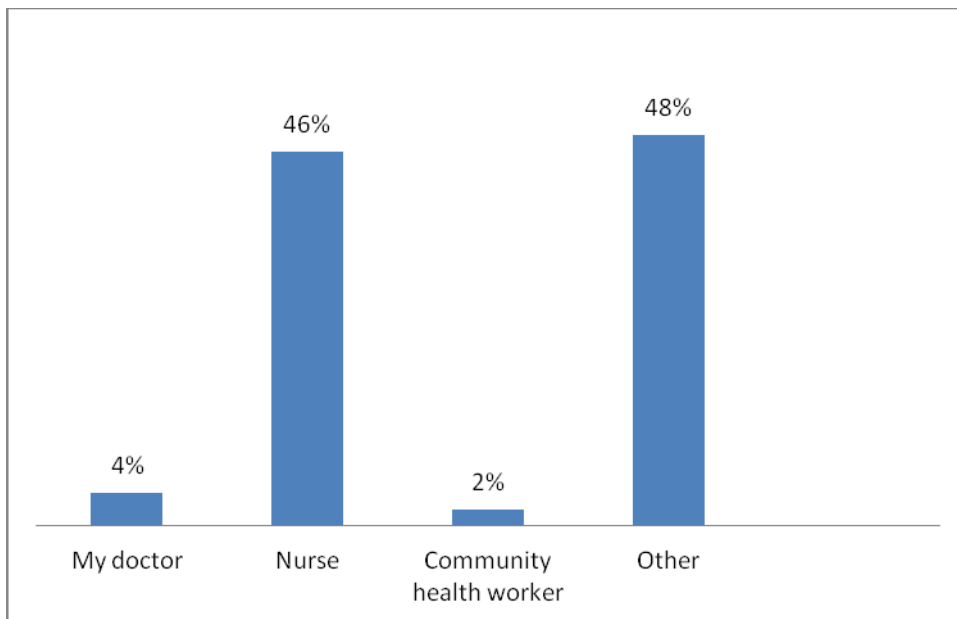


Figure 2: Percent Distribution of Respondents by Source of Information

The other category comprised of research assistants from the main study (89.8%), health officials from local clinics (8.2%) and community members (2.0%).

Motivations for Participation in Trial

Participants were first asked to state in general terms why they had decided to participate in the primary trial. Participants could give more than one answer. The responses were pre-coded into five main categories: (a) monetary incentives; (b) free treatment; (c) curiosity; (d) coerced and (e) other. Participants could select more than one answer. Table 1 shows the frequency distribution of participants' responses.

Table 1

Percent distribution of participants' by reason for enrolling in the clinical trial

Reason for enrolling in clinical trial	Percent
	<i>N</i> =100
	<i>n</i> (%)
Monetary incentives	0(0.0%)
Free treatment	4(4.0%)
Curiosity	43(43.0%)
Coerced	1(1.0%)
Other (Specify)	90(90.0%)

Ninety percent of the respondents cited “Other” reasons which were not pre-defined on the questionnaire. Of the 90% who cited “other” reasons, all indicated that they had enrolled in the trial for diagnosis and treatment of tuberculosis. It is worth noting that none of the participants mentioned altruistic motivations for participating in research.

Participants were further asked to choose from fourteen motivations that may or may not have influenced their decision to participate in the trial. They were asked the following question: “*Was your decision to participate in the study at all influenced by...*”. For each item that they identified as having influenced their decision to participate, they were asked to rate the degree of influence of that motivator on a scale ranging from 1 to 10. A score of 10 showed that the motivator was extremely important whilst a score of 1 meant that the motivator was not at all important in influencing the participant’s decision.

The most frequently cited motivators were: (i) diagnosis and treatment of tuberculosis (82.2%); (ii) how seriously the participants needed help for their condition (71%); (iii) advice from doctor or nurse (40%); (iv) the possibility of getting better care or follow up care (40%); and (v) access to treatment the participants could not get any other way (34 %). Table 2 shows the distribution of participants' motivations for enrolling in the clinical trial by the mean score for the degree of influence of each motivator. Participants could select more than one answer.

Table 2

Motivations for Subjects' Enrolment in Trial by Mean Score of Motivator

Item No.	Motivation	N=100 n (%)	Mean Score (1-10)
1.	The possibility of getting better care or follow up care	40(40.0%)	9.6
2.	Access to treatment you could not get any other way	34(34.0%)	9.5
3.	The availability of free treatment	15(15.0%)	9.2
4.	Getting something else for free	3(3.0%)	10
5.	Having something to occupy your time	0(0.0%)	
6.	Being able to stay in a hospital [for a longer time]	3(3.0%)	9
7.	How seriously you needed help for your condition	71(71.0%)	9.7
8.	Advice from your doctor or nurse [if yes: specify physician, nurse, other_____]	40(40.0%)	9.9
9.	Advice from other people	3(3.0%)	8.3
10.	Your trust in the people doing the research study	7(7.0%)	9.1
11.	The reputation of the institution where the research is being done	1(1.0%)	5.5
12.	Your curiosity about how the research study would work or what the results will be	9(9.0%)	8.8
13.	Your desire to help other people [with your condition	6(6.0%)	9
14.	The belief you're getting the active drug rather than the placebo	2(2.0%)	10

Offers to Participate in Research

Almost all the participants (93%) interviewed reported that they had been given an offer to participate in the study. Of those participants who reported that they were given an offer, all (100.0%) mentioned that they were offered bus fare to go to and from the research site. The

average amount of bus fare given to each participant per visit was US\$2. A small proportion of the participants also mentioned free treatment (5.4%) as an offer. Participants could give more than one answer.

Table 3

Percent Distribution of Participants by Offers to Participate in Research

N=100	
Participants offered something to participate	93(93.0%)
What were you offered?	n=93
Bus fare	93(100.0%)
Free treatment	5(5.4%)

When asked to state the importance of the offer of bus fare on their decision to participate in the clinical trial on a scale ranging from one to 10 (with 1 indicating that the offer was not at all important and 10 showing that it was extremely important) almost all the participants (99%) assigned a score of one meaning the offer of bus fare was not important in influencing their decision to participate in the study. Only one participant of those who mentioned bus fare as an offer assigned a score of two to the importance of this offer. All the participants who mentioned receiving an offer of free treatment however reported that it was extremely important in their decisions to participate in the study.

Participants were also asked to assess the fairness of the offers on a scale from 1 to 10 (with 1 showing that the offer was not at all fair and 10 showing that it was extremely fair). The majority of the participants (98.7%) gave a score of 10 for the offer of bus fare showing that the bus fare was extremely fair, whilst the remainder gave scores below five. Participants

viewed fairness of the bus fare in terms of its adequacy to take them back and forth from the research site. Free treatment was also rated as extremely fair by all the participants who cited it as an offer.

Pressures, Threats and Risks

Only a small proportion (2%) reported that they had been pressured or pushed to participate in the study. None of the respondents reported being threatened to participate in the clinical trial. On further questioning, one participant who reported that she had been pressured into the study revealed that she was pressured by her grandmother to enrol in the clinical trial due to her persistent illness. The second participant said that she was pressured by her doctor who argued that the new machine would quicken the diagnosis of her condition and thus enable her to get better treatment. When asked to rate the importance of the pressure with regards to their decision about participating in the trial, the two participants gave a score of one meaning that the pressure was not at all important in their decision to participate in the study.

Only one participant reported that the study was risky or uncomfortable giving a score of 6 on a scale of 1 to 10 (with 1 showing that the study was not at all risky or uncomfortable and 10 showing that it was extremely risky). The reason cited was that the researchers were taking too much blood for the first diagnostic tests. In spite of this risk in the study, the participant reported that she felt she had to enrol in order to be treated for her condition.

Perceptions on Coercion and Voluntariness

Respondents completed the Perceived Coercion Scale (PCS) as well as the Voluntariness Ladder, which are two global measures of voluntariness in the medical field. Coercion is regarded as the intentional use of a credible and severe threat of harm or force to control

another person (Beauchamp & Childress, 2009) or compel him or her to do something. For coercion to happen, three main things should be in place: (a) an unfavourably narrowed set of options; (b) that some human agents be limiting a person's options in an attempt to manipulate them; and (c) a threat (Hawkins & Emanuel, 2005).

On the PCS, respondents were asked whether five statements were true or false as they relate to their decisions to participate in the clinical trial. A true statement was given a score of 0 whilst a false statement received a score of 1. The scores from the five questions were then summed up to generate a single score for each respondent. A total score of 0 reflects a participant with the lowest perception of coercion whilst a score of 5 reflects the highest perception of coercion. Ninety eight percent of the respondents gave a total score of zero on the PCS, which reflects that the majority of respondents did not feel that they had been coerced to participate in the study.

Data generated from the Voluntariness Ladder confirmed the results from the PCS. The Voluntariness Ladder measures voluntariness on a scale that ranges from 1 to 10. A score of 1 shows that a participant's decision was not at all voluntary whilst a score of 10 shows that the decision was completely voluntary. The majority of respondents (98%) gave a score of 8 or above whilst 2% gave a score of 5 or less.

There was no significant relationship between most of the motivation factors and the PCS scores. The only significant relationships were found between low perceived coercion (lower scores on the PCS) and the following motivations: (i) trust in the people doing the research study ($p < 0.005$); (ii) the reputation of the institution where the research was being done ($p < 0.001$) and (iii) desire to help other people with a similar condition ($p < 0.001$).

Participants with no previous research experience had lower perceptions of coercion than those with previous research experience. As shown in Table 4, 89% of those participants who scored 0 — an indication of low perceptions of coercion — had no previous research experience compared to 11% with previous research experience ($p<0.005$).

Table 4

Percent Distribution of Participants by Previous Research Experience and Levels of Perceived Coercion

Previous research experience	PCS Total Score			
	0 (n=97)	1 (n=1)	3 (n=1)	Missing (n=1)
Yes	11	100	0	100
No	89	0	100	0
Total	100	100	100	100

A significant inverse relationship was also found between the reputation of the institution where the research was being done and scores on the Voluntariness Ladder. For example, 96% of the respondents who gave a score of 10 (which shows high perceptions of voluntariness) reported that they had not been influenced by the reputation of the institution where the research was being done ($p < 0.001$).

There was no significant relationship between the following socio-demographic variables and scores from the Perceived Coercion Scale: age ($p = 0.182$); sex ($p = 0.506$); level of education; marital status ($p = 0.918$); employment status ($p = 0.389$); occupation ($p = 0.750$) and average monthly income ($p = 0.921$). The results also show a non-significant relationship between the same socio-demographic variables and scores from the Voluntariness Ladders: age ($p = 0.246$); sex ($p = 0.439$), level of education ($p = 0.981$); marital status ($p = 0.909$); employment status ($p = 0.303$); occupation ($p = 0.690$) and average monthly income ($p = 0.921$).

The findings from this study suggests that the following variables are predictors of diminished voluntariness: trust in people doing research, knowledge of the reputation of the institution conducting the research, previous research experience and the desire to help other people with a similar condition.

Discussion

Voluntariness of participation in research and its constraints have been poorly conceptualized and empirical evidence on this concept is still emerging. Although motivations for participation in research have been explored elsewhere, the literature on motivations to research participation in resource constrained settings is not conclusive.

Results obtained in this study in Zimbabwe showed that participants were influenced to participate in the study by five main motivations: (i) the need for diagnosis and treatment of tuberculosis, (ii) the extent to which they needed help for their condition, (iii) the advice received from a doctor or nurse, (iv) the possibility of getting better care or follow up care, and (v) the access to free and readily available treatment.

The only offers participants had received for participating in the trial were bus fare and free treatment. However, the offer of bus fare had no influence on participants's decisions to enrol in the study. The majority of the participants did not feel coerced, pressured or threatened to participate in the trial based on their self reported experiences and scores from the PCS. These results were also confirmed by data from the Voluntariness Ladder, which showed that participants had high perceptions of voluntariness.

There was no significant relationship between the socio-demographic variables and scores from the two measures of voluntariness; PCS and the Voluntariness Ladder. The only significant relationship was found between previous research experience and scores from the PCS and Voluntariness Ladder.

The high levels of perceived voluntariness reported in this study might be due to the fact that participants might have understood voluntariness in the context of diagnosis and treatment of their condition as opposed to voluntary participation to be in a study. The study might also have been seen to carry low risk since no experimental treatment was involved.

Most of the participants had been presenting with TB symptoms for a long time but the TB could not be detected using conventional diagnostic techniques at their local clinics.

Participants might have thought that they had no option but to try a new diagnostic technique that was only available in the study with the hope that it would quicken the diagnosis and subsequent treatment of their condition. These sentiments are summed up by one of the participants in the following statement: *“I was sick for a long time and the TB was not being detected so I chose to get into the study”*. The question that remains to be asked is: how voluntary is the consent of a participant who has no other or limited diagnostic options besides participating in a clinical trial? This is a conceptual issue that needs to be dealt with when assessing voluntariness, especially in countries with limited resources.

The majority of the participants in the trial were TB patients or people presenting with TB symptoms. These participants were recruited from local clinics dotted around the city and referred to the research site, which is located at the national referral centre for infectious diseases. There was no clear distinction between the research site and the referral hospital and it is possible that participants might have thought that they had been referred for further management without realising that they were in fact being recruited for a trial of a new diagnostic technique. The location of the research site and the way participants were recruited might be viewed as manipulation resulting in a form of therapeutic misconception in the minds of the respondents.

A direct question asking participant's whether they were in a study or just in routine clinical care might have been useful in clarifying the differences between research and clinical care. Additionally, it might have been more interesting to compare participants' perceptions of treatment under the primary trial with that offered under routine care considering that the treatment offered outside the trial was also free.

When respondents were asked the question: "*Have you been involved in any research study before?*" most of them struggled to answer as they did not understand what research was. They thought that research was the same as diagnosis for a medical condition or participation in a health related project. This observation might support the idea that respondents in the trial might not have thought themselves as being involved in research even though their perceptions of voluntariness were high.

The most commonly used Shona words that describe research in Zimbabwe are either *tsvakurudzo* or *ongororo*. In the current study *ongororo* was used to describe research although the Research Assistant would also use *tsvakurudzo* when the respondent indicated that they did not know what *ongororo* meant.

Participants regarded offers of bus fare as well as pressures as insignificant in their decision to participate in the study. Some of the motivations were also rated low in terms of their importance in influencing the respondent's decision to enrol in the trial. These findings are in line with existing conceptual frameworks which assert that not all influences exerted on

another person are controlling and that the impact of an influence varies from one person to another (Appelbaum *et al.*, 2009a; Beauchamp & Childress, 2009; Nelson *et al.*, 2011).

It is also pertinent to highlight that the two participants who indicated that they had been pressured to participate in the study — one by her grandmother and the other by her doctor — might not have understood the distinction between being pressured and being persuaded. The distinction between these two terms needs to be clearly defined in future studies on voluntariness.

The results of this study show some common patterns as well as some differences when compared to those conducted in other contexts, both in developing and developed countries. For example, results from Appelbaum and colleagues showed that the decision to participate in a clinical trial is a function of more than one consideration (Appelbaum *et al.*, 2009b). These results were confirmed in the current study. However, whilst participants in the study by Appelbaum *et al* cited trust in the researchers and the reputation of the host institutions as important motivations for enrolling in a clinical trial, these motivations were not regarded as such in the current study. This could be explained by the fact that participants in the current study were TB patients or TB suspects desperate to get treatment for their condition. As such they were mainly concerned about direct benefits of access to diagnostic services and drugs and health care; hence the majority cited motivations that were closely related to access to treatment and care.

Consistent with the present study, results from both developed countries (Franck *et al.*, 2007; Knifed *et al.*, 2008; Marshall & Rotimi, 2001; Montgomery & Sneyd, 1998) and developing countries (Minnies *et al.*, 2008; Moodley *et al.*, 2005; Sarkar *et al.*, 2009) also show low

levels of perceived coercion across different clinical trials. In the few studies in which participants reported being pressured to participate in the trial, the source of the pressure was mainly the treating physician (Agrawal *et al.*, 2006; Lynoë *et al.*, 1991; Riecken & Ravich, 1982); spouses, family members, friends, members of the research team and village elders (Krosin *et al.*, 2006; Pace *et al.*, 2005) as well as negative consequences that could arise if they withdrew from the study (Karim *et al.*, 1998; Krosin *et al.*, 2006; Lynoë *et al.*, 2001). In the present study, there was little evidence to demonstrate that participants were ever pressured or coerced to participate in the study by other people.

Limitations

It is important to note that the study was conducted with a limited number of participants enrolled in a single trial of a new diagnostic technique for TB. The researcher had to conduct the study based on what was available as accessing participants in other trials was challenging. The data might thus be biased and may therefore not be generalized in other trials, for example, trials involving patients with non-curable diseases. The information generated on voluntariness was based on self-reports of the research participants, which might be difficult to validate.

The questionnaire used for the study was predominantly closed-ended with predetermined answers. Participants' responses could have been limited because of the nature of this instrument. Complementing the data collection tool with focus group discussions and in-depth interviews could have been useful in yielding more valuable data on this subject. It might also be useful to include additional items on the questionnaire, for example, questions which capture participants' understanding of research as well as their awareness to withdraw from research.

It must be highlighted that the design of rating scales has its own inherent challenges, which are further compounded by the lack of clarity on the concept of voluntariness. Of note is the fact that there are no clear guidelines on the optimum number of response categories needed for each rating scale. Whereas some researchers argue that the more the categories, the higher the reliability and precision of the measurement (Preston & Colman, 2000), others favour fewer response options arguing that they are less burdensome and have the potential of reducing respondent confusion (Viswanathan M, Begen M, Dutta S, & T, 1996). If the latter is true, it can be argued that the scales used for assessing the importance of fairness of a motivation, as well as the importance of pressures, threats and risks in participants' decision to enrol in a trial, which ranged from 1 to 10, were too wide for respondents to appreciate what each of the scores meant. Other contested issues on rating scales relate to the use of the same rating scale on all questions measuring the same trait as well as optimal features for question formatting, among other things (Khadka, Gothwal, McAlinden, Lamoureux, & Pesudovs, 2012).

In this study, the potential role of social desirability cannot be ruled out especially when one looks at the respondents' high perceptions of voluntariness. It is possible that even if the respondents participated in the primary study involuntarily they may have wanted to give the impression that the primary study satisfied all ethical obligations hence the high scores on the Voluntariness Ladder. More importantly, it is also worth noting that the psychometric properties of the study instruments, in particular their validity and reliability, is unknown.

The limitations notwithstanding, the views expressed by participants in this study provide insight into the current debates on voluntariness aimed at contributing to improvements in the

ethical recruitment and retention of research participants in clinical trials, particularly in developing countries.

Conclusion

The results from this study showed that participants were not influenced by offers, pressures and threats in their decision to enroll in the trial. The decision to enroll in a clinical trial was mainly influenced by immediate medical needs rather than altruism. The study also showed that participants had high levels of voluntariness based on scores from the PCS and the Voluntariness Ladder. However, more work still needs to be done on how best voluntariness can be conceptualized and measured. As long as there is no consensus on what constitutes voluntariness, different measures might be developed which may not be valid in measuring the construct.

Most participants did not understand what the word research meant. Although it could not be confirmed in this study, it is most likely that as a concept, research is not clearly understood within the Zimbabwean community. As demonstrated by examples in Africa, contextual factors, for example, understanding of research in general or the specific aspects of a protocol in particular are often the most dominant influences on voluntariness in informed consent (Kamuya et al., 2011). A poor understanding of the research can lead to serious challenges related to the therapeutic misconception, which may invalidate voluntariness as the individual might think that the research is meant for their individual benefit. Rumours which portray a negative image of the research as well as negative perceptions about the research, can also provide various degrees of control to the potential research participants and even to those already enrolled in the research resulting in the negation of voluntary participation (Molyneux, Wassenaar, Peshua, & Marsha, 2005).

Recommendations

In future studies assessing voluntariness among research participants, it is important that participants are asked whether they were aware that they were involved in research and whether they were told that participation in that study was voluntary. They should also be asked about their awareness to withdraw from the study anytime without suffering any negative consequences. In view of the difficulties expressed by respondents in answering the question related to the meaning of research, a study of the local meanings of the term research is recommended.

A three point scale might yield more valid data for assessing the importance and fairness of motivations, pressures, threats and risks in participants' decision to enroll in a trial. This is in view of the fact that most of the participants in this study had only gone as far as secondary school and that the subtleties of the differences between values on a wider scale, ranging from 1 to 10, might not have been clear to them.

Results from the study cannot confirm the validity and reliability of the PCS and Voluntariness Ladder as measures of voluntariness. As such, these tools need to be validated or complemented by other measures, for example, the recently developed Decision Making Control Instrument.

In future, voluntariness should be assessed in a broader context. It might be useful to first establish how research is understood in the local setting before assessing voluntariness. Furthermore, a comprehensive assessment of the informed consent process is essential rather than singling out one component, for example voluntariness. Future studies on voluntariness might yield more useful data by reviewing the consent documents of the primary study and

assessing participants' levels of comprehension. This is in view of the fact that it is possible that a person can give voluntary consent that is not informed. Further research is also required to establish perceptions of voluntariness and its constraints in other types of trials in resource constrained countries.

In their current form, the instruments used in this study as adopted from Appelbaum *et al* (2009b) may not have been adequate to measure the full scope of voluntariness in research contexts. The instruments, however, provide a useful starting point towards the development of comprehensive tools for assessing voluntariness in the context of both developing and developed countries. A composite tool, which combines items from the DMCI as well as the tool developed by Appelbaum and colleagues might be more appropriate for use in future studies assessing voluntariness in research settings.

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Appendices

Appendix 1: Questionnaire

Appendix 2: Perceived Coercion Scale

Appendix 3: Voluntariness Ladder

Appendix 4a: English Consent Form

Appendix 4b: Shona Consent Form

Appendix 5: UKZN Faculty of Development and Social Sciences Approval

Appendix 6: Medical Research Council of Zimbabwe Approval

Appendix 7: BRTI Institutional Review Board Approval

Appendix 8: Permission from City Health Department

Appendix 9: Permission from Principal Investigator of Primary Study

Appendix 2: Perceived Coercion Scale (PCS)

Now I'm going to read some statements about your decision to sign up for the RIFAQUIN project. Please tell me whether each statement is true or false as it relates to your decision.

Parizvino ndave kuda kukuverengerai zvinotevera maererano nepfungwa yekupinda muongororo yeRIFAQUIN. Mungandiudzawo kuti zvinotevera ichokwadi here kana kuti kunyepa zvichienderana nekufunga kupinda muongororo iyi.

		True	False
1.	I felt free to do what I wanted about signing up for the research project. <i>Ndakanzwa kusununguka kuita zvandaida maererano nekupinda muongororo iyi.</i>		
2.	I chose to sign up for the research project. <i>Ndakasarudza kupinda muongororo iyi</i>		
3.	It was my idea to sign up for the research project. <i>Kupinda muongororo iyi dzainge dziri pfingwa dzangu.</i>		
4.	I had a lot of control over whether I signed up for the research project. <i>Ndainge ndiine simba rakawanda pasarudzo yekupinda muongororo iyi?</i>		
5.	I had more influence than anyone else on whether I signed up for the research project. <i>Ndainge ndiine simba rakawanda kudarika munhu wese pasarudzo yekupinda muongororo iyi</i>		
	Total score		

Appendix 3: Voluntariness Ladder

43. Now I'd like you to think again about your decision to enter the clinical trial you are enrolled. Use the ladder of numbers below to show me how **voluntary** (willing to participate) your decision was. Circle the number that best matches your decision, from completely voluntary (10) to not at all voluntary (1). *Pari zvino ndave kuda kuti mufunge zvakare nezvesarudzo yenyu yekupinda muongororo yamuri. Shandisai danho remanhamba riri pasi kuti mundiratidze kuti sarudzo yenyu yekupinda muongororo iyi yange iri sarudzo yenyu isina kumanikidzwa, kutyityidzirwa kana kunyengetedzwa. Tenderedzai nhamba inonyatsoenderana nesarudzo yenyu yekupinda muongororo iyi, gumi ichimirira kuti makapinda muongororo iyi nesarudzo yenyu pasina kumanikidzwa, kutyityidzirwa kana kunyengetedzwa, motsi achimirira kuti kupinda muongororo iyi yakange isiri sarudzo yenyu zvachose.*

Completely voluntary choice

10
9
8
7
6
5
4
3
2
1

Not at all voluntary choice

APPENDIX 4a: English consent form

PARTICIPANT INFORMATION SHEET

Study title: A case study to assess participants' perceptions on voluntariness and motivations for participating in a clinical trial in Zimbabwe

Principal investigator: Mr. Farirai Mutenherwa

Cell phone: 0774 600 155

Introduction

You are invited to volunteer for a research study. Before you decide to take part in the study it is important for you to understand why the research is being done and what it will involve. The purpose of this information leaflet is therefore, to help you to decide if you would like to participate in this study. If you have any questions about this study please do not hesitate to ask the investigator. You should not agree to take part unless you are completely satisfied with all the procedures involved. Please take time to read the following information carefully. You may consult other people about the study if you wish. If you agree to participate in this study, you will be requested to sign the consent form to show that you have understood the nature of the study.

What you should know about this research study:

- We give you this consent so that you may read about the purpose, risks, and benefits of this research study.
- You have the right to refuse to take part, or agree to take part now and change your mind later.
- Whatever you decide, it will not affect your regular care.
- Please review this consent form carefully. Ask any questions before you make a decision.
- Your participation is voluntary.

Nature and purpose of the study

The aim of this study is to assess your motivations for participating in a clinical trial and your perceptions on voluntary participation. The study is being done as part of my academic studies for a Masters degree in Health Research Ethics. It is hoped that the information that you are going to share with me will help to identify constraints of voluntariness in Zimbabwe.

Why you have been chosen?

We are inviting you to join this study because you are currently enrolled in the GeneXpert clinical trial in Zimbabwe. If you choose to take part in this study, you will be one of approximately 197 research subjects who are currently enrolled in the clinical trial to join this study.

Do I have to take part ?

We hope that you will agree take part in this study. However, you do not have to take part in the study if you do not want to. If you decide that you do not want to participate in this study, that decision will not affect your health care or daily life in any way. If you decide that you

want to take part now but then change your mind later you may withdraw from the interview at any time without having to give a reason.

What are the procedures involved in the study?

If you agree to take part in this study, I will ask you to sign a consent form to be interviewed. Again, if you agree to be in this study, a questionnaire will be administered to you by a trained interviewer. If you are willing to take part but unable to be interviewed at this time, we will arrange an appointment at a later date. If you decide not to be in this study you will not lose any of your regular benefits, and medical care from the main study.

The questions will address the following: demographic data, motivations for participating in GeneXpert clinical trial, and experience of offers, pressures, or threats related to your participation in the GeneXpert clinical trial. This will take about forty minutes. If you are not comfortable to answer some questions, you are free not to answer them.

What are the possible disadvantages and risks of taking part?

Being involved in this study involves minimum to low risk. You may experience some discomfort when answering questions about your health condition, socioeconomic status and experience with clinical trials.

What are the possible benefits of taking part?

There will be no direct benefit to you from taking part in this study. However, the information we get from you might help to improve the ethical recruitment and retention of clinical trial participants in future studies in Zimbabwe.

Will my taking part in the trial be kept confidential?

All information obtained during the course of this study, including personal data and research data (transcripts and notes) will be kept strictly confidential. However, your personal information may be given out if required by law.

Your name or address will not be included on any questionnaire or notes. Instead your study number from the GeneXpert study will be used. In this type of study it is helpful to quote in reports some of the exact things people have said in the interview, and we would like your permission do this. Data from this study that may be reported in scientific journals or reports will not include any information that identifies you. Data will be kept for at least five years after the study is finished for possible checking or further analysis. It will then be destroyed.

Has the study received ethical approval?

This Protocol was submitted to the Medical Research Council of Zimbabwe, Biomedical Research and Training Institute Institutional Review Board and the University of KwaZulu-Natal Ethics Committee and written approval has been granted by these three committees. The study is also structured in accordance with the Declaration of Helsinki, which deals with the recommendations guiding doctors in biomedical research involving human subjects. A copy of the Declaration may be obtained from the investigator, Farirai Mutenherwa should you wish to review it.

Offer to answer questions: Before you sign this form, please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think it over. For any other questions that you may have about this study, please contact the principal

investigator, Farirai Mutenherwa on the phone numbers listed at the top of this page. If you have any questions about this study or this consent form beyond those answered by the research team, including questions about the research, your rights as a research participant, or if you feel that you have been treated unfairly and would like to talk to someone other than a member of the research team, please feel free to contact the Medical Research Council of Zimbabwe using the contact information below:

Medical Research Council of Zimbabwe,c/o National Institute of Health Research Cnr Mazowe Street and Josiah Tongogara,Harare,Phone: 791193 or 791792

CONSENT TO PARTICIPATE IN THIS STUDY.

1. I have read the information sheet concerning this study [or have understood the verbal explanation] and I understand what will be required of me and what will happen to me if I take part in the study

YES
NO

2. I understand that any time I may withdraw from this study without giving a reason and without affecting my normal care and management.

YES
NO

3. My questions concerning this study have been answered

YES
NO

4. I agree to take part in this study by completing the questionnaire

YES
NO

5. I agree to anonymous quoting of any information I give

YES
NO

Full name of participant: _____

Date _____ Month _____ Year: _____

Signature of participant: _____

Full name of Independent witness (*Optional*): _____

Signature of Independent witness: _____

Relationship of participant to witness: _____

Full name of researcher: _____

Signature of researcher _____

The date you sign this document to enrol in this study, that is, today's date, **MUST** fall between the dates indicated on the approval stamp affixed to each page. These dates indicate that this form is valid when you enrol in the study but does not reflect how long you may participate in the study. Each page of this Informed Consent Form is stamped to indicate the form's validity as approved by the MRCZ. **YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.**

IDENTIFICATION	Interviewee Number	Interviewer Code	PROJECT: Voluntariness Study
			Date: _____/_____/2012

Appendix 4b: Shona Consent Form

GWARO REKUTSANANGURA ONGORORO

Study title: A case study to assess participants' perceptions on voluntariness and motivations for participating in a clinical trial in Zimbabwe

Principal investigator: Mr. Farirai Mutenherwa

Cell phone: 0774 600 155

Nhanganyaya

Muri kukokwa kuti mupinde mutsvakurudzo iri kuitwa. Musati mabvuma kupinda mutsvakurudzo iyi, zvakakosha kuti munzwise maererano nezvetsvakurudzo iyi. Naizvozvo, gwaro iri nderekukubatsirai mukuita sarudzo yekupinda mutsvakurudzo iyi kana kuti kwete. Kana muine mibvinzo maererano nezveongororo iyi makasununguka kubvunza munhu ari kukurukura nemi. Hamufanirwi kubvuma kupinda mutsvakurudzo iyi kunze kwekunge magutsikana nezviri kuitwa mutsvakurudzo iyi. Munokumbirwa kuti muwane nguva yokuverenga gwaro rino nemazvo. Makasununguka kubvunza vamwe vanhu pamusoro pezvetsvakurudzo iyi kana muchida. Kana mabvuma kupinda mutsvakurudzo iyi, munokumbirwa kuti musaine gwaro iri sechiratidzo chokuti manzwisira nezvetsvakurudzo

Zvemunofanira kuziva pamusoro petsvagurudzo ino:

- Tamupa gwaro rino kuti muriverenge, muzive nezvechinangwa chetsvagurudzo, njodzi dzingangosanganikwa nadzo uye zvichawanikwa mutsvagurudzo ino.
- Mune kodzero yekuramba kupinda mutsvagurudzo ino kana yekubvuma kupinda mutsvagurudzo parizvino mozoshandura pfungwa dzenyu panguva inotevera.
- Zvipi zvazvo zvamuchafunga kuita hazvikanganisi mabafirwo enyu emazuva ese.
- Ndapota nyatsoverengai gwaro rino. Bvunzai mibvunzo ipi zvayo yamunayo musati mafunga kuti moita zvipi.
- Isarudzo yenyu yakasununguka kubvuma kana kuramba kupinda mutsvagurudzo.

Chinangwa chetsvagurudzo

Tsvakurudzo iyi iri maererano nokuona zvikonzero zvinoita kuti vanhu vapinde mutsvakurudzo dzezveutano uye kuti tizive maonero amunoita sarudzo yenyu yekupinda mutsvakurudzo yeGeneXpert. Tsvakurudzo iyi iri kuitirwa kuti ndikwanise kupedza zvidzidzo zvangu zvekuitwa kwakanaka kwetsvakurudzo dzezveutano. Ndinotarisa kuti zvatichakurukura zvichabatsira kuti tione zvikonzero zvinoita kuti vanhu vapinde mutsvakurudzo dzezveutano dzinoitwa munyika ino vasina kuzvisarudzira pachavo asi kuti vamanikidziwa, vavhundutsirwa kana kuti vakwezva zvisina kufanira kuti vapinde mutsvakurudzo idzi.

Chikonzero chaita kuti mukumbirwe kupinda mutsvagurudzo

Muri kukokwa kuti mupinde mutsvakurudzo iyi nekuti muri mutsvakurudzo yeGeneXpert iri kuitwa munyika ino. Kana mukabvuma kupinda mutsvagurudzo yandiri kuda kuita iyi, muchange muri mumwe wevanhu zana nemakumi mapfumbamwe ane nomwe vachapinda mutsvagurudzo iyi kubva mutsvagurudzo ye GeneXpert.

Kupinda mutsvagurudzo pasina kumanikidzwa, kutyisidzirwa kana kunyengedzerwa

Tinovimba kuti muchabvuma kupinda mutsvagurudzo ino. Kunyangwe zvazvo tichikukumbirai kuti mupinde mutsvagurudzo ino, hamumanikidzwi kupinda mutsvagurudzo iyi kana musingadi zvenyu. Kana masarudza kuti hamudi kupinda mutsvagurudzo ino, sarudzo yenyu haikanganisi mabafirwo enyu amuri kuitwa mutsvagurudzo ye geneXpert panyaya dzezveutano kana upenyu hwenyu hwemazuva ose. Kana mukasarudza kupinda mutsvagurudzo ino, mozoshandura pfungwa dzenyu, munogona kuzongobuda mutsvagurudzo chero nguva ipi zvayo pasina kupa chikonzero.

IDENTIFICATION	Interviewee Number	Interviewer Code	PROJECT: Voluntariness Study
			Date: _____/_____/2012

Zvichaitika uye nguva yazvichatora:

Kana mabvuma kupinda mutsvakurudzo iyi, ndichakumbira kuti musaine gwaro iri kuti tikwanise kuzokurukura nemi. Zvakare kana mabvuma kupinda mutsvakurudzo iyi muchakurukura naResearch Assistant akadzidzira kuita hurukuro dzakadai. Kana muchida kupinda mutsvakurudzo asi musina kusununguka parizvino, tinokwanisa kubvumirana rimwe zuva rokuzosangana. Kana masarudza kusapinda mutsvakurudzo iyi muchamgoramba muchiwana zvose zvamaiwana mutsvakurudzo yeGeneXpert uye mucharamba muchingorapwa nekuonekwa neveveutano sezvamange muchingoitwa.

Muhurukuro yamuchaita muchakurukura maererano nezvinotevera: Nhorondo yezveupenyu hwenyu, zvikonzero zvakaita kuti mupinde mutsvakurudzo yeGeneXpert, zvamakaona kana kuitirwa maererano nesarudzo yenyu yekupinda mutsvagurudzo yeGeneXpert tichitarisa kukwezvwa, kumanikidzwa, kana kuvhundutsirwa kuti mupinde muongororo iyi. Hurukuro iyi ingangotora maminitisi makumi mana neshanu. Kana pane mibvunzo yamusingadi kupindura makasunguka kusaipindura.

Njodzi:

Hapana njodzi yakanyanya ingawanikwa nokupinda mutsvakurudzo iyi asi kuti munogona kushungurudzika zvisihoma nezvamuchataura maererano nekurwara kwenyu, mararamire enyu uye nhorondo yenyu yekupinda mutsvagurudzo yeGeneXpert.

Zvamuchawana uye/kana kuripwa:

Hapana zvichanyatsowanikwa nevanhu vachapinda muongororo ino. Ruzivo rwamuchatipa rwuchabatsiridza pakuvandudza kupinda kwakanaka kwevanhu mutsvakurudzo dzezveutano kumopa ruremekedzo kukodzero dzavanhu.

Zvakavanzika:

Ruzivo rwe rwatichawana kubva kwamuri ruchachengetedzwa zvakavanzika kunyangwe zvazvo rwuchikwanisa kuzivikanwawo nevamwe vashandi vari kuita tsvakurudzo ino. Hatishandisi mazita kana kero yepamunogara, tinoshandisa nhamba kuvanza zita renyu. Mutsvakurudzo yakadai, zvakakosha kunyora zvimwe zvezvinenge zvataurwa sezvazviri. Naizvozvo tinokumbira mvumo yenyu kuti tikwanise kuita saizvozvo. Ruzivo rwamuchatipa runogona kuzonyorwa mune mamwe magwaro asi zvose zvinoita kuti muzivikanwe hazvinyorwi mumagwaro aya. Zvamuchatipa muhurukuro idzi zvichachengetwa kwemakore mashanu zvisati zvaraswa.

Mvumo

Tsvakurudzo iyi yakabvumirwa neve Medical Research Council of Zimbabwe, Biomedical Research and Training Institute Institutional Review Board and the University of KwaZulu-Natal Ethics Committee. Zvakare tsvakurudzo iyi iri kuitwa maererano negwaro reDeclaration of Helsinki rinova gwaro rinoshandiswa kubatsira vana chiremba kuti vaite tsvagurudzo dzezveutano. Gwaro re Declaration of Helsinki munokwanisa kuriwana kubva kuna Farirai Mutenherwa

Kupa mukana wekupindura mibvunzo: Musati masaina gwaro rino, ndapota bvunzai mibvunzo ipi zvayo pamusoro pechinhu chipi zvacho chetsvagurudzo ino chisina kujeka kwamuri. Munogona kutora nguva yose yamunoda kuti mufunge nezvazvo. Kana muine mimwe mibvunzo yakanangana netsvagurudzo ino, sunungukai kutaura nemukuru wetsvagurudzo, Farirai Mutenherwa panhamba dzenhare dzakanyorwa nechekumusoro kwegwaro rino. Kana muine mibvunzo ipi zvayo yakanangana netsvagurudzo ino kana gwaro rino, yakasiyana neyapindurwa nemunhu ari kuita tsvagurudzo, kusanganisira mibvunzo yakanangana netsvagurudzo, kodzero dzenyu semunhu ari kupinda mutsvagurudzo kana kukuvara kwakanangana netsvagurudzo; kana kuti muchifunga kuti hamuna kubatwa zvakanaka uye muchida kutaura nemumwe munhu asiri kuita tsvagurudzo ino, sunungukai kutaura neveMedical Research Council of Zimbabwe panhamba dzenhare dziripazasi: Medical Research Council of Zimbabwe, c/o National Institute of Health Research Cnr Mazowe Street and Josiah Tongogara, Harare, Phone: 791 193 or 791 792

IDENTIFICATION	Interviewee Number	Interviewer Code	PROJECT: Voluntariness Study
			Date: _____/_____/2012

GWARO REKUBVUMA

Study title: A case study to assess participants' perceptions on voluntariness and motivations for participating in a clinical trial in Zimbabwe

Principal Investigator: Mr. Farirai Mutenherwa

Cell phone: 0774 600 155

1. Ndaverenga gwaro riri maererano nechirongwa (kana kunzwisisa tsanangudzo yandapihwa) uye ndanzwisisa zvinotarisirwa kwandiri nezvichaitika kwandiri kana ndapinda muchirongwa.
 1. HONGU
 2. KWETE
2. Ndanzwisisa kuti ndinogona kusarudza kusapinda mutsvagurudzo iyi chero nguva ipi zvayo ndisingapi chikonzero uye zvisingakanganisi marapirwo angu amazuva ose.
 1. HONGU
 2. KWETE
3. Mibvunzo yangu maererano nechirongwa chino yapindurwa
 1. HONGU
 2. KWETE
4. Ndabvuma kupinda muchirongwa chino nekuzadzisa mibvunzo
 1. HONGU
 2. KWETE
5. Ndabvuma kupinda muchirongwa chino uye kubvumira kuti zvandinenge ndataura zvinyorwe asi zvisingagone kuzivikanwa kuti ndiyani azvitaura
 1. HONGU
 2. KWETE

Zita rizere remunhu ari kubvuma : _____

Zuva ranhasi _____ Mwedzi _____ Gore: _____

Runyoro Rwenyu: _____

Zita remufakazi (*Kana muchida kuti pave nemufakazi*): _____

Runyoro rwemufakazi : _____

Ukama nemunhu apinda muongororo : _____

Zita remuongorori : _____

Runyoro rwemuongorori _____

Zuva ramunoisa runyoro pagwaro rino kuti mupinde mutsvagurudzo ino, rinova dheta ranhasi, RINOFANIRA kunge riri pedyo nedheti riri pachidhindo chakadhindwa papeji imwe neimwe yegwaro rino. Dheta iri rinoratidza kuti gwaro rino richiri kushanda pamunopinda mutsvagurudzo ino asi hariratidzi kuti munofanira kunge muri mutsvagurudzo kwenguva yakareba sei. Peji imwe neimwe yegwaro rino yakadhindwa kuratidza kuti gwaro rino riri kushanda sezvakabvumirwa neMRCZ. MUCHAPIHWA GWARO RAKAFANANA NERINO REKUCHENGETA.

Student Number : 210556043

11 April 2011



Faculty of Development and Social Sciences **UNIVERSITY OF KWAZULU-NATAL**

King Edward Avenue, Scottsville, Pietermaritzburg
Private Bag X01, Scottsville, 3209, South Africa

Telephone (033) 260-5699

Fax (033) 260-6327

Email: jacobsen@ukzn.ac.za

Mr F Mutenherwa
SARETI
School of Medicine
University of Pretoria
Pretoria
0001

Dear Mr Mutenherwa

Re: ETHICAL APPLICATION: A case study to assess participants' perceptions on voluntariness and motivations for participating in a clinical trial in Zimbabwe

This is to advise that the Faculty has approved your request for ethical clearance, and that you may proceed with your research project.

This permission is subject to review by the University Research Committee, who will be sending you a letter in due course.

Please let me know **if you change your title** before submitting your dissertation for examination, as your new title will also have to be submitted to the Faculty Higher Degrees Committee for approval.

Yours sincerely

MRS BE JACOBSEN
HIGHER DEGREES OFFICE

Cc Prof J Armstrong



APPROVAL LETTER

Ref: **MRCZ/B/267**

10 October 2011

Mr Farirai Mutenherwa
BRTI, Ethics
Nicoz Diamond Building
Samora Machel Avenue
BOX CY 1753, Causeway
Harare



RE: A Case Study to Assess Participants' Perceptions on Voluntariness and Motivations for Participating in a Clinical Trial in Zimbabwe.

Thank you for the above titled proposal that you submitted to the Medical Research Council of Zimbabwe (MRCZ) for review. Please be advised that the Medical Research Council of Zimbabwe has **reviewed** and **approved** your application to conduct the above titled study. This is based on the following documents that were submitted to the MRCZ for review:

a) Study protocol

• **APPROVAL NUMBER** : **MRCZ/B/267**

This number should be used on all correspondence, consent forms and documents as appropriate.

(i) **EFFECTIVE APPROVAL DATE** : **10 October 2011**

(ii) **EXPIRATION DATE** : **9 October 2012**

(iii) **TYPE OF MEETING** : **Expedited Review**

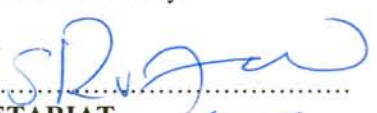
After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the MRCZ Offices should be submitted one month before the expiration date for continuing review.

- **SERIOUS ADVERSE EVENT REPORTING:** All serious problems having to do with subject safety must be reported to the Institutional Ethical Review Committee (IERC) as well as the MRCZ within 3 working days using standard forms obtainable from the MRCZ Offices.
- **MODIFICATIONS:** Prior MRCZ and IERC approval using standard forms obtainable from the MRCZ Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
- **TERMINATION OF STUDY:** On termination of a study, a report has to be submitted to the MRCZ using standard forms obtainable from the MRCZ Offices.
- **QUESTIONS:** Please contact the MRCZ on Telephone No. (04) 791792, 791193 or by e-mail on mrcz@mrczimshared.co.zw.

Other

- Please be reminded to send in copies of your research results for our records as well as for Health Research Database.
- You're also encouraged to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study.

Yours Faithfully


.....
**MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE**

PROMOTING THE ETHICAL CONDUCT OF HEALTH RESEARCH

Registered with the USA Office for Human Research Protections (OHRP) as an International IRB (Number
IRB00002409 IORG0001913)



BIOMEDICAL RESEARCH AND TRAINING INSTITUTE

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Tel: 263 4708544 / 708554
732894/735000/2/4/9
Fax: 263 4 735033
E-Mail: rpjike@brti.co.zw
Website: <http://www.brti.co.zw>

ANGOLA	MAURITIUS	SWAZILAND
BOTSWANA	MOZAMBIQUE	TANZANIA
LESOTHO	NAMIBIA	ZAMBIA
MALAWI	SOUTH AFRICA	ZIMBABWE

29 September 2011

Mr. Farirai Mutenherwa
BRTI
4th Floor NICOZ Diamond Building
Corner S. Machel /Park Street
Harare

Dear Mr. Mutenherwa

RE: AP104/2011 - A case study to assess participants' perceptions on voluntariness and motivations for participating in a clinical trial in Zimbabwe

Thank you for your letter dated 12 September 2011 in response to comments raised by the Board.

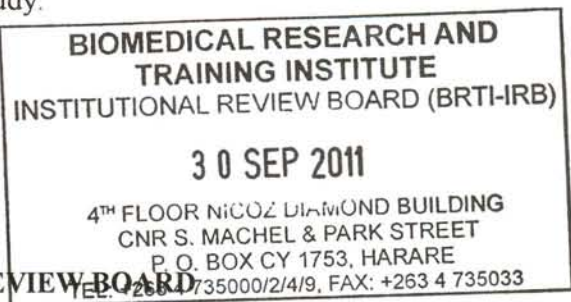
Further to the revisions incorporated in the submission, the above referred application is approved by Chairman's action with effect from 28 September 2011.

The approval awaits ratification by the full Board at the next IRB meeting.

We wish you well in the completion of this study.

Yours sincerely,

Professor Valerie J. Robertson
CHAIRPERSON, BRTI INSTITUTIONAL REVIEW BOARD



A Non-Profit Organization for Southern Africa Promoting Health and Medical Research for Development in the Africa Region

Directors: Mr T. Rwodzi (Chairman), Prof P R Mason (Director General), Prof C J Shiff (International), Dr S Guramatunhu (Director), Mrs S. Munyati (Director of Training) Prof. L Zijena (Scientific Director), Mr Nduna (Director), Prof L. Gwanzura (Laboratory Director), Mr C. Samkange (Director), Prof S.A Gregson (Director)



CITY OF HARARE

Director of Health Services

DR STANLEY MUNGOKA
MD (Cuba) MPH (Zim)

All correspondence to be addressed to the
DIRECTOR OF HEALTH SERVICES

Ref:.....

Your Ref:.....

DIRECTOR OF HEALTH SERVICES

Rowan Martin Building,
Civic Centre,
Pennefather Avenue,
off Rotten Row,
Harare, Zimbabwe.

P. O. Box 596
Telephone: 753326
753330/1/2
Fax: (263-4) 752093

26 September 2011

Farirai Mutenhera
Biomedical Research and Training Institute
P O Box CY 1753
Causeway
HARARE

Dear Sir

**Re: PERMISSION TO CONDUCT A STUDY AT HARARE CITY COUNCIL'S
PRIMARY HEALTH CLINICS**

I refer to the above.

Permission is hereby granted for you to carry out your research. Could you kindly liaise with the Assistant Director of Health Services (Nursing).

Yours faithfully

DIRECTOR OF HEALTH SERVICES
SM/gm

Cc - ADHS (Nursing)

Carla Pettit

From: farirai mutenherwa <fmutenherwa@yahoo.co.uk>
Sent: 08 September 2011 10:47 AM
To: farirai m
Subject: Fw: Request for permission to access study participants

----- Forwarded Message -----

From: Reggie Mutetwa <mutetwar@gmail.com>
To: farirai mutenherwa <fmutenherwa@yahoo.co.uk>
Sent: Thursday, 8 September 2011, 9:17
Subject: Re: Request for permission to access study participants

Dear Mr Mutenherwa,

As indicated in our discussions I'm happy with you accessing our study participants, and I give my permission on condition that your study is approved by the IRB and MRCZ.

Reggie

On 12 Aug,2011, at 9:41 PM, farirai mutenherwa wrote:

Dear Mr. Mutetwa

I trust this email finds you well. Further to our discussion on the above referred subject, I am writing to formally seek permission to access study participants currently enrolled in your research study entitled "**Impact of new TB diagnostic tools**".

My proposed study is in fulfillment of the requirements of a Masters degree in Social Sciences (Health Research Ethics at the University of KwaZulu-Natal. The study aims at assessing participants' motivations for enrolling in a clinical trial and their perceptions on voluntariness. Specifically, the study seeks to ascertain respondents' views regarding the presence and importance of offers, pressures and any form of undue influence (if any) as regards their decisions about enrolling in a clinical trial. By identifying influences that constrain voluntary participation or strategies that positively affect recruitment; the study seeks to provide guidance to researchers, regulatory bodies and Institutional Review Boards in Zimbabwe on appropriate safeguards for the voluntary participation of research subjects in clinical trials in our country.

I wish to assure you that the information generated from the proposed study will be used purely for academic purposes. Additionally, the study as well as the participants to be interviewed will not be identified in the research report or in any publications that may come out of the study. It shall be reported that data came from participants in a clinical trial in Zimbabwe, instead of specifying the exact name or title of the particular trial. Furthermore, all information coming out of the study will be fed back to you. I will also be keen to assist in ways to address any ethical issues/ concerns that may come out of the trial and all this will be done in consultation with you.

For more details, please find attached protocol, study summary, data collection tools and approval letter for the proposed study from the Faculty of Development and Social Sciences Academic Committee. Should you require further information, please do not hesitate to contact me.

The deadline for the submission of the final dissertation is October 2011. In view of the time limits, I would sincerely appreciate your response concerning this request at your earliest convenience.

I look forward to hearing from you soon.

Yours sincerely,

Farirai Mutenherwa

----- Forwarded Message -----

From: farirai mutenherwa <fmutenherwa@yahoo.co.uk>

To: fmutenherwa@yahoo.co.uk; nyamukapaconnie@gmail.com; cmakina@forbeszim.co.zw; pmason@brti.co.zw; robertson@uz-ucsf.co.zw; tmapako@bloodbank.co.zw; smunyati@brti.co.zw; Mr. Charles Makina <makinas@iwayafrica.co.zw>; farirai m <fmutenherwa@brti.co.zw>

Sent: Fri, 12 August, 2011 21:33:20

Subject: Application for ethical approval

Dear IRB Board Members

Please find attached application documents for ethical review.

Sincerely,

Farirai.

<questionnaire.doc><Voluntariness instrument .docx><Voluntariness Ladder.doc><APPLICATION FOR ETHICAL REVIEW.docx><BRTI_STUDY SUMMARY.docx><Ethical clearance.docx><Final_proposal.docx><Info sheet_Consent.docx><Shona Consent.docx>

Reggie

Mr Reggie Mutetwa

PhD fellow

Impact of new TB Diagnostic tools

CIDRI (Clinical Infectious Diseases Research Initiative) Fellowship

University of Capetown, Cape Town

and

Biomedical Research and Training Institute, Harare (Centre for TB Diagnostics and Interventions)

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