VOLUNTARINESS OF CONSENT TO HIV CLINICAL RESEARCH: A CONCEPTUAL AND EMPIRICAL STUDY

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M Soc Sc (Research Psychology)

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Declaration

I, Nicole Mamotte, declare that

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2. This thesis has not been submitted for any degree or examination at any other university.

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Abstract

While obtaining voluntary informed consent for research participation is an ethical imperative, there appears to be little consensus regarding what constitutes a voluntary consent decision. As a result, considerable controversy exists in the research ethics literature, with researchers and ethicists advancing numerous concerns about the voluntariness of consent to research. For example, concerns about the voluntariness of consent to research are frequently raised when financial compensation or care and treatment are offered in return for research participation, when participants are recruited by their health care providers, when risks are more than minimal, and when research is conducted in developing countries by developed country researchers. However, without a valid conceptualisation of voluntariness and an appropriate means of assessing it is impossible to determine whether commonly expressed concerns about voluntariness are well founded. As such, a comprehensive conceptual and empirical review of voluntary consent was conducted. The conceptual and empirical review revealed that voluntary consent to research consists of a legal imperative that consent be free from controlling influences of other people and a moral imperative that consent be perceived as voluntary by the person providing consent. On the basis of this conceptualisation the Voluntariness Assessment Instrument was developed. The Voluntariness Assessment Instrument was piloted on 100 women enrolled in two South African HIV clinical trials. The study found high levels of perceived voluntariness. A desire to please the researchers, feelings of having no alternative to research participation as well as a need for money were significantly associated with lower perceived voluntariness. An absence of controlling influences from others was also observed for the overwhelming majority of research participants. Overall the data suggests that it is possible to obtain voluntary and valid consent from research participants in ethically complex HIV clinical trials in developing country contexts.

Dedication

For Mason

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Frequently Used Abbreviations

REC	Research Ethics Committee
BREC	Biomedical Research Ethics Committee
VNRI	Voluntariness Assessment Rating Instrument
SoI	Survey of Influences
DMCI	Decision Making Control Instrument

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Chapter 1: Introduction

"*There are always countless descriptions under which any voluntary act seems involuntary*" (*Feinberg, 1986, p. 284*).

1. Background and Rationale

South Africa bears an overwhelming proportion of HIV/AIDS infections, with unprecedented medical and socio-economic consequences (Abdool Karim & Abdool Karim, 2010; Kaleebu, Abimiku, El-Halabi et al., 2008). HIV research is imperative in South Africa so that at-risk populations are able to benefit from safe and effective behavioural and biomedical HIV prevention and treatment interventions. HIV research with vulnerable communities in developing countries is widely regarded as exceptionally ethically complex. This is evidenced by the development of special ethics guidance documents (cf. MRC, 2003; UNAIDS, 2012) to assist HIV researchers identify the critical ethical elements that need to be considered. One of the primary ethical challenges facing HIV clinical researchers is the need to obtain voluntary informed consent for research participation.

The importance of obtaining voluntary informed consent for research participation is rooted in the ethical principle of respect for autonomy. Respect for autonomy is the norm of respecting the dignity and decision-making capabilities of autonomous persons (NBAC, 1979). Informed consent allows research participants to make a meaningful choice whether or not to participate in research and should therefore reflect the will or intention of the consenter, not of other persons (Appelbaum, Lidz & Klitzman, 2009b). Every major research ethics guidance document drafted since World War II emphasises the importance of obtaining voluntary informed consent (Nelson & Merz, 2002), yet (as will be demonstratedin Chapter 2) these ethical guidelines repeatedly fail to appropriately clarify what constitutes voluntary consent or what factors are necessary and sufficient to undermine it.

Furthermore, there appears to be little theoretical consensus regarding what constitutes a voluntary decision to participate in research. Many maintain that voluntariness is a value-neutral concept whereby a person acts nonvoluntarily if exposed to a controlling influence (cf. Nelson et al., 2011) or if they have no acceptable alternatives to research participation (cf. Olsaretti, 1998). Conversely some argue that a more useful approach to the conceptualisation of voluntariness is to examine how voluntariness is understood in the legal context of informed consent (cf. Appelbaum, 2011). Others propose that only a moralised account of voluntariness can explain how a person's consent is nonvoluntary in a way that invalidates their consent (cf. Wertheimer, 2012).

As a result of discrepancies in ethical guidance and the lack of conceptual agreement around voluntary consent to research, considerable controversy exists in the research ethics literature, with researchers and ethicists advancing numerous concerns about the voluntariness of consent to research. For example, concerns about the voluntariness of consent to research are frequently raised when compensation is offered in return for research participation (Kass, Maman & Atkinson, 2005; Koen, Slack, Barsdorf & Essack, 2008; Kwagala, Wassenaar & Ecuru, 2010), when participants are recruited by their health care providers (Appelbaum, Lidz & Klitzman 2009a), when risks are more than minimal, when research is conducted in developing countries by developed country researchers (Marshall, Adebamowo, Adeyemo et al., 2006; Nelson & Merz, 2002), when care and treatment for a medical condition are offered in return for research participation or when potential participants lack alternate access to medical care (Kass, et al., 2005; Nelson & Merz, 2002; Pace, Emanuel, Chuenyam et al., 2005). Participants from developing countries, such as South Africa, are often described as vulnerable and more susceptible to coercion and undue influence because of male patriarchy (Nyika, Wassenaar & Mamotte, 2009), poverty, lack of education and a desperate need for health care (Barsdorf & Wassenaar, 2005). Studies on the voluntariness of consent conducted in South Africa suggest that participants may believe they are not free to make decisions to participate or to withdraw from studies (cf. Abdool Karim, Abdool Karim, Coovadia & Susser, 1998; Ramjee, Morar, Alary et al., 2000; Kilmarx, Ramjee, Kitayaporn & Kunasol, 2001; Joubert, Steinberg, van der Tyst & Chikobvu, 2003).

However, without a valid conceptualisation of voluntariness and an appropriate means of assessing it, it is impossible to determine whether commonly expressed concerns about voluntariness are well founded (Appelbaum et al., 2009a).

2. Aim

The principal objective of this study was therefore to identify a valid way of conceptualising voluntary informed consent and develop an appropriate means of assessing it. In order to achieve this, this study aimed to conduct a conceptual review and analysis of voluntary consent, followed by an empirical review of how voluntariness of consent has been assessed in the past. Finally, the study aimed to develop and pilot an instrument to assess voluntariness of consent in the context of HIV clinical research in South Africa.

3. Outline of Dissertation

In an effort to explicate the complexities surrounding the understanding of voluntariness as it relates to informed consent, this dissertation begins with a review of the literature on voluntary informed consent to research (Chapter 2). The literature review locates voluntary informed consent as a central requirement of ethical research and situates it in the substantive ethical principle of respect for autonomy. Ethical guidelines related to voluntary informed consent are presented and several definitions of voluntariness are introduced. Various factors thought to undermine the voluntariness of consent to research are deliberated and a rationale for the present study is provided. The specific aims of this study are then presented (Chapter 3). The following chapters address the three study aims. Chapter 4 presents the results of a conceptual review and analysis of voluntary consent to research. This review suggests researchers have a legal imperative to ensure informed consent is provided free from controlling influences of others and as such voluntary and valid. Researchers also have a moral imperative to ensure that research participants perceive their consent to be voluntary. Chapter 5 presents the results of a

review of previous empirical measures of voluntary consent to research and outlines the development of Voluntariness Assessment Instrument. The focus of this dissertation then shifts to the piloting of the Voluntariness Assessment Instrument. The methods and findings of the pilot study are presented in Chapters 6 and 7 respectively. Chapter 8 discusses the findings and implications of the pilot study. The Voluntariness Assessment Instrument was piloted on 100 women enrolled in two South African HIV clinical trials. The study found high levels of perceived voluntariness. A desire to please the researchers, feelings of having no alternative to research participation as well as a need for money were significantly associated with lower perceived voluntariness. An absence of controlling influences from others was also observed for the overwhelming majority of research participants. Overall the data suggest that it is possible to obtain voluntary and valid consent from research participants in ethically complex HIV clinical trials in developing country contexts.The final chapter (Chapter 9) of this dissertation brings the conceptual and empirical components of this study together, reflects on the implications of this work and proposes recommendations for future research on the voluntariness of consent to research.

Chapter 2: Literature Review

This chapter reviews the literature on voluntary informed consent and in so doing provides the background and rationale for the study. First, voluntary informed consent is located as a central requirement of ethical research and is situated in the substantive ethical principle of respect for autonomy. Ethical guidelines related to voluntary informed consent are introduced and several definitions of voluntariness are reviewed. Various factors thought to undermine the voluntariness of consent to research are discussed and the importance of adequately conceptualising and assessing voluntary consent is then explained.

1. The Foundation of Voluntary Consent to Research

It is an ethical imperative that voluntary informed consent be obtained from potential research participants prior to participation. Obtaining voluntary informed consent reflects the substantive ethical principle of respect for autonomy and is emphasised in every major research ethics guideline since the Nuremburg Code (1949) (Nelson & Merz, 2002).

1.1 Autonomy

The ethical principle of respect for autonomy necessitates that voluntary informed consent be obtained prior to research participation. Respect for autonomy is one of the four widely accepted ethical principles along with nonmaleficence, beneficence and justice (Beauchamp & Childress, 2009). The four ethical principles are evident in most classical ethical theories and form the basis of most research ethics codes and guidelines. Nonmaleficence is concerned with avoiding the causation of harm while beneficence involves providing benefits and balancing those benefits against any risks (Beauchamp & Childress, 2009). Justice refers to the fair distribution of risks and benefits (NBAC, 1979). Respect for autonomy is the norm of respecting the dignity and decision-making capabilities of autonomous persons and protecting the rights of those with diminished

capacity (NBAC, 1979). Autonomy refers to an individual's personal freedom of thought and action (Beauchamp & Childress, 2009). Beauchamp and Childress (2009) outline two conditions of autonomy: Liberty (freedom from controlling influences) and agency (capacity for intentional action). According to Faden and Beauchamp (1986), however, a person acts autonomously only if they (a) act intentionally, (b) with understanding and (c) without controlling influences. Autonomous action as opposed to autonomous persons is the primary focus of research ethics. "The capacity to act autonomously is distinct from acting autonomously, and possession of the capacity is no guarantee that an autonomous choice has been or will be made" (Faden & Beauchamp, 1986, p. 237). That is, autonomous persons may perform nonautonomous acts and nonautonomous persons may act autonomously. Wertheimer (2012) identifies both positive and negative dimensions to respecting autonomy. Positive autonomy is the possibility of acting. A person's positive autonomy is respected by allowing them to authorise interventions or enter into binding agreements in order to enhance their interests or realise their fundamental purpose (Wertheimer, 2012). Negative autonomy is the presence of constraints to acting which protects the individual's fundamental interests. Consider the example of research participation: Allowing competent individuals to decide to participate in research emphasises their positive autonomy. However, preventing individuals who are less than fully competent (such as minors) from deciding to participate in research emphasises their negative autonomy. Protecting a person's negative autonomy may prevent them from exercising their positive autonomy and *vice versa*. It is, according to Wertheimer (2012), impossible to enhance respect for both dimensions at the same time and difficult to get the balance right between the two.

In research ethics the principle of respect for autonomy is operationalised by obtaining voluntary informed consent (NBAC, 1979). Respect for autonomy obliges researchers to disclose information, foster understanding and voluntariness and ensure adequate decision-making: all key elements of informed consent (Beauchamp & Childress, 2009).

1.2 Informed consent

Informed consent allows research participants to make a meaningful choice whether or not to participate in research and should therefore reflect the will or intention of the consenter, not of other persons (Appelbaum et al., 2009b). Two distinct meanings of informed consent have been advocated. First, informed consent may be viewed as an individual's 'autonomous authorisation' of research participation (Pedroni & Pimple, 2001). Used in this sense, informed consent transforms research participation into a morally acceptable, cooperative activity (Pedroni & Pimple, 2001). Second, informed consent may be viewed as a 'legally effective authorisation' of research participation (Pedroni & Pimple, 2001). In this sense, informed consent refers to the rules, regulations and practices that make it socially and legally acceptable to enroll people in research (Pedroni & Pimple, 2001).

It is widely accepted that for consent to be morally valid it must satisfy five criteria: competence, disclosure, understanding, voluntariness and formalisation of consent (Bosk, 2002). Beauchamp and Childress (2009) however recommend that seven elements be fulfilled in order to achieve adequate informed consent. According to their conceptualisation, there are two preconditions for meaningful informed consent to be achieved. First, the potential research participant must (1) have the competence to understand and decide and second, they must (2) make a voluntary decision (Beauchamp & Childress, 2009). Once these two threshold elements have been met, three informational elements are required. First there has to be (3) adequate disclosure of material information and this should be followed by (4) the recommendation of a plan (enrolment in research) (Beauchamp & Childress, 2009). Both the disclosed information and the recommended plan have to be (5) understood by the person consenting (Beauchamp & Childress, 2009). Cahana and Hurst (2008) provide a useful 'rule of thumb' for what constitutes acceptable levels of understanding. They state that at a minimum a participant should understand all the information that could lead an 'average or reasonable' person to refuse participation. Once the informational elements have been met the person consenting needs to (6) actually make a decision (in favour or against the

recommended plan) and then (7) authorise the chosen plan (which may include informed consent or informed refusal of research participation) (Beauchamp & Childress, 2009). If any one of these consent elements is not met, the consent obtained may not be morally valid (Agrawal, 2003).

While the importance of obtaining morally valid informed consent cannot be neglected, informed consent is in reality made operational by means of the legal doctrine of informed consent (Berg, Appelbaum, Lidz & Parker, 2001). The legal doctrine maintains that informed consent is to be obtained before a researcher is legally entitled to conduct research with a human participant (Berg et al., 2001). The legal doctrine of informed consent comprises two duties: the duty to disclose necessary information to potential research participants and the duty to obtain the participant's formal consent before commencing the research (Berg et al., 2001). The legal doctrine of informed consent does however take understanding and voluntariness into consideration in order for legally valid consent to be obtained (Berg et al., 2001).

From both moral and legal perspectives valid consent is morally transformative (Wertheimer, 2012). Valid informed consent renders it permissible for one person to do to another that which would not have been permissible without such consent (Wertheimer, 2012).

1.3 Defining voluntary consent to research

There is little consensus around what constitutes a voluntary decision to research participation. The most widely accepted definition of voluntariness is Beauchamp and Childress's (2009) definition whereby a person acts voluntarily "if he or she wills the action without being under the control of another's influence" (p. 132). Similarly, Nelson et al. (2011) state that for an action to be voluntary it must be intentional and free from the controlling influence of another person or condition. Wall (2001), on the other hand, theorises that voluntariness is the degree of control that an individual has over their own behaviour. While Graham (2010) theorises that voluntariness is the correspondence of

one's will with one's action. According to Olsaretti (1998) a decision may only be deemed voluntary if an acceptable alternative is available or, in the absence of an acceptable alternative, if a person would have made a given decision had an acceptable alternative been available (Olsaretti, 1998). Weiss Roberts (2002) defines voluntariness as a person's ability to act in accordance with their own authentic sense of self and what is best for them in light of their situation. Appelbaum et al. (2009a) hypothesise that a decision is nonvoluntary only if it is subject to an influence that is external, intentional, illegitimate and causally linked to the choice of the research participant.

These definitions of voluntariness will be elaborated on and their appropriateness discussed in Chapter 4 when the results of a conceptual review and analysis of voluntariness are presented. The issue highlighted above is that much discrepancy exists in existing definitions of voluntariness. These discrepancies are also evident in ethical guidelines on voluntary consent which are outlined below.

1.4 Ethical guidelines

Every major research ethics guidance document drafted since World War II emphasises the importance of obtaining voluntary informed consent (Nelson & Merz, 2002). However, review of these guidelines reveals a failure to consistently describe what factors are necessary and sufficient to undermine voluntary consent.

The Nuremburg Code (1949) states that:

> "The voluntary consent of the human subject is absolutely essential. This means that the person involved should … be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion" (p. 1).

Likewise, the Belmont Report (1979) emphasises that:

> "In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily … an agreement to participate in

> research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence" (NBAC, 1979, p. 7).

The Declaration of Helsinki specifies that:

> "Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees" and "When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress" (World Medical Association, 2013, p. 2–4).

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guidelines for Good Clinical Practice (ICH GCP) (1996) states that:

> "Freely given informed consent should be obtained from every subject prior to clinical trial participation" (Principle 2.9. p. 9) "[and] that neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or continue to participate in a trial" (Principle 4.8.3, p. 15).

Guideline 4 of the Council for International Organizations of Medical Sciences (CIOMS) (2002) International Ethical Guidelines for Biomedical Research Involving Human Subjects states that:

> "For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject … [the volunteer should have] arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation" (p. 32).

The US Department of Health and Human Services Regulations for the Protection of Human Research Subjects (45 CFR 46) (The Common Rule) section 46.116 states that:

> "An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence" (p. 7).

The United Nations Educational, Scientific and Cultural Organisation (UNESCO) Universal Declaration on Bioethics and Human Rights Article 6.2 states that "scientific research should only be carried out with the prior, free, express and informed consent of the person concerned" (p. 7).

The South African Department of Health (2004) Ethics in Health Research: Principles, Structures and Processes section 2.6 states that, "investigators must assure potential participants that participation is voluntary, and that refusal to participate, or a decision to discontinue participation, will not involve any form of penalty" (p. 4). Furthermore, the South African Medical Research Council's (2003) Guidelines on Ethics for Medical Research: HIV Preventive Vaccine Research states that: "Consent must be voluntary and freedom of choice must be safeguarded (12.8) [and that] undue inducements, offers that persuade participants to volunteer against their better judgment or to assume risks they would not otherwise have assumed, should be avoided" (12.8.3) (p. 24).

In addition to these ethical guidelines, regulatory agencies and research ethics committees have implemented policies and practices to enhance voluntary consent, such as implementing special protections for vulnerable participants (cf. UNAIDS GPP, 2011), reducing the amount of compensation offered (cf. NHREC, 2012) and discouraging physicians from recruiting their own patients into research (Appelbaum et al., 2009a).

Britz and le Roux-Kemp (2012) argue that with regard to voluntary informed consent South African and international ethical guidance documents are not only different but sometimes contradictory. They maintain that international ethical guidance on voluntary

informed consent is not always in line with the South African Constitution and legislation concerning informed consent (Britz & le Roux-Kemp, 2012). The doctrine of informed consent is set out in sections 6, 7 and 8 of the South African National Health Act (Britz & le Roux-Kemp, 2012). The South African National Health Act (sections 6, 8 and 71) also covers research on human participants and is therefore crucial to good practice in clinical trials (Britz & le Roux-Kemp, 2012). According to Britz and le Roux-Kemp (2012), the ICH GCP and SA GCP require the researcher to attempt to find out why a research participant withdraws from a trial, while respecting the research participant's right to not offer a reason. Britz and le Roux-Kemp (2012) argue that this guideline does not respect participants' rights to voluntarily withdraw and may even leave participants feeling that they are not allowed to withdraw. The authors conclude that ICH GCP and SA GCP therefore contradict the notion of voluntary research participation (Britz & le Roux-Kemp, 2012).

The above ethical guidelines and regulatory policies claim that force, fraud, deceit, duress, over-reaching (Nuremburg Code, 1949), intimidation (CIOMS, 2002), coercion and undue influence (CIOMS, 2002; NBAC, 1979) compromise the voluntariness of consent to research participation. Some guidelines include voluntariness-reducing factors that are a little more controversial, such as a dependent relationship with the physician (World Medical Association, 2013), inducements, offers that persuade participants to volunteer against their better judgment or to assume risks they would not otherwise have assumed (South African Medical Research Council, 2003). What any of these 'voluntariness reducing' factors actually entail is not evident from the guidelines. Furthermore, while ethical guidelines and regulatory policies clearly view an absence of these factors as necessary for consent to be voluntary, it is not clear whether absence of these factors is sufficient for consent to be voluntary.

2. Concerns about the Voluntariness of Consent to Research

As argued above, ethical guidelines fail to appropriately clarify what constitutes voluntary consent or what factors are necessary and sufficient to undermine it. As a result, considerable controversy exists in research ethics literature, with researchers and ethicists advancing numerous concerns about the voluntariness of consent to research. These concerns are reviewed and discussed below.

2.1 Coercion

One area in which there is widespread consensus is that coercion is incompatible with voluntary choice. "The principle that coercion undermines voluntariness may be uncontroversial, it is less clear what constitutes the coercion … that violates the voluntariness principle" (Wertheimer, 1987, p. 4). Emanuel, Currie and Herman (2005) define coercion as "threats that make a person choose an option that necessarily makes him or her worse off and that he or she does not want to do" (p. 337). Coercion, according to this conceptualisation, requires a person's options to be narrowed unfavourably by another person who is trying to get them to do something they would not ordinarily do, by means of a threat. The threat ensures that the person will be left worse off regardless of which option they choose (Hawkins & Emanuel, 2005). It seems reasonable for coercion to involve a threat of harm that unfavourably narrows a person's options. However, Emanuel, Currie and Herman's (2005) requirement that coercion necessarily leaves a person worse off is problematic. According to this definition, a Professor who threatens to fail a student who does not complete a course evaluation is not coercing that student if the student's subsequent forced completion of the five-minute evaluation does not in any way leave the student worse off. A more appropriate criterion of coercion is provided by Wertheimer (1987) who states that "A makes a threat when, if B does not accept A's proposal, B will be worse off than in the relevant baseline position" (p. 204). Wertheimer's (1987) definition assumes that the coercee will only be made worse off if he fails to comply with the coercer's threat. According to this

definition the above example of the Professor and the student would constitute a case of coercion.

Similarly, according to Faden and Beauchamp (1986) "coercion occurs if one party intentionally and successfully influences another by presenting a credible threat of unwanted and avoidable harm so severe that the person is unable to resist acting to avoid it" (Faden & Beauchamp, 1986, p. 261). This definition requires one person to intentionally influence another. That is, another person has to be in control of the threat. Likewise, Birnbacher (2009) states that coercion necessarily involves human agency. Another person has to intervene between a person's situation and a person's decision. According to this definition, unintentional or situational influences or perceived coercion are not truly coercive as they do not force a person to make an 'eliminable' choice or leave the person worse off (Faden & Beauchamp, 1986). This is not to say that these factors do not undermine voluntariness, only that they cannot be considered coercive.

In addition to being intentional, the influence also has to successfully get the coercee to do what the coercer wants (Faden & Beauchamp, 1986). The threat has to actually control the other person (Nelson et al., 2011). If the person subjected to the credible threat of unwanted and avoidable harm is able to resist it, then the influence exerted cannot be said to be coercive and it therefore does not undermine voluntariness. The person being coerced has to be unable to resist acting to avoid the threat of harm for it to qualify as coercion (Faden & Beauchamp, 1986). Furthermore, the threat of harm has to be credible, the coercer has to be able to carry out the threat of harm and the coercee has to believe that they will do so (Faden & Beauchamp, 1986). Coercion makes even intentional and well-informed decisions nonvoluntary (Beauchamp & Childress, 2009). For example, when a mugger says 'your money or your life', the person being threatened is still able to make a well-informed and intentional decision to hand over his money. Despite this, the decision is nonvoluntary as it is irresistible and therefore a controlled action. Stated differently coercion requires the presence of (a) two unrelated alternatives (Birnbacher, 2009) such as 'option 1 – your money' or 'option 2 – your life' (the alternatives of

‘cancer’ or ‘chemotherapy’ would, for example, not classify as unrelated alternatives), and (b) for option 2 to be artificially made a condition of option 1.

When coercion is attempted, one person intentionally threatens another with what the coercer believes the coercee will view as serious harm in order to induce compliance (Faden & Beauchamp, 1986). Coercion however only occurs if the coercee finds the threat irresistible and therefore complies. As such, Faden and Beauchamp’s (1986) analysis relies on a subjective interpretation of irresistibility. Coercion depends on the subjective response of the person being influenced (Beauchamp & Childress, 2009). The person who is the target of attempted coercion has to find the threat irresistible for coercion to occur.

Secondly, only threats that are irresistible qualify as coercive. Resistible threats and offers are forms of manipulation. If a person was able to resist a threat (even if they chose not to), they were not coerced, their consent was voluntary (Faden & Beauchamp, 1986). For example, a physician may say to patients A and B, “I will no longer treat you if you do not enroll in my research study”. If patient A lives in a rural area and the physician threatening him is the only physician he is able to access, he may very well find the threat irresistible and be forced to enroll in the research; in this case coercion would have taken place. If patient B, on the other hand, lives in an urban area with easy access to several physicians, he may find the threat resistible as he is able to find a new physician with relative ease. As such, even if patient B decides to enroll in the research, it could not be said that patient B was coerced.

In contrast, Feinberg (1986) differentiates between ‘coercion proper’ and ‘coercive pressure’. Coercion proper is the provision of a credible threat that renders alternatives unreasonable (in the money or your life example, the victim in theory does have a choice between his money or his life but the choice is so unreasonable it effectively renders the alternative impossible) or it renders combinations of alternatives impossible (again using the money or your life example, the threat makes it truly impossible to retain both your money and your life). Coercive pressure on the other hand is when the threat is “credible,

and in fact believed, but nonetheless it constitutes for the coercee a cost that he is willing to pay in preference to submitting to the alternative" (Feinberg, 1986, p. 193). For example, person C may be coerced by a robber who threatens 'your money or I will shoot you' he may however not be coerced by a kidnapper who threatens 'hand over your child or I will shoot you'. In both situations the threat is credible and it renders the alternative (of death) unreasonable. However, in the second example not even the threat of death is sufficient to get person C to submit to the alternative of handing his child over to a kidnapper. Feinberg (1986) concludes that whether a threat results in coercion proper or merely coercive pressure is a result of the subjective experience and values of the coercee. The extent of coercion "is a function of how much [a person] wants X, or fears Y, and how he ranks his preferences" (Feinberg, 1986, p. 199). While coercive pressure is morally problematic and researchers and third parties should be prohibited from applying coercive pressure to potential research participants, it is less of a concern for the voluntariness of informed consent to research in the sense that the person exposed to the coercive pressure is essentially able to resist it, meaning his consent remains voluntary.

Coercion in the sense explained above, also needs to be distinguished from what Feinberg (1986) refers to as 'compulsion' or what Birnbacher (2009) calls 'direct coercion', that is, the use of force that does not present hypothetical alternatives. Rather, a person is literally or physically made to do something they do not want to do. An example of compulsion would be when one person physically pushes another person off a bridge.

While coercion is the most commonly expressed concern in voluntariness literature, empirical studies of voluntariness seldom reveal evidence of coercion. In Appelbaum et al.'s (2009b) study of the voluntariness of consent to research of 88 US research participants, no participants reported the presence of threats. The study also found that the majority of participants did not perceive their decision to have been coerced in any way (Appelbaum et al., 2009b). Similarly, Lansimies-Antikainen et al.'s (2010) study of informed consent in a randomised controlled trial on exercise and diet in Finland found that 99% of the 1324 respondents surveyed reported that they enrolled in the study without the presence of coercion.

2.2 Persuasion

Concern has also been expressed that attempting to persuade people to participate in research may place too much pressure on participants to enroll or result in them acting in what they perceive to be a socially desirable way thereby preventing participation from being sufficiently self-directed (Wertheimer, 2012). According to Faden and Beauchamp (1986), persuasion "is the intentional and successful attempt to induce a person, through appeals to reason, to freely accept – as his or her own – the beliefs, attitudes, values, intentions, or actions advocated by the persuader" (Faden & Beauchamp, 1986, p. 261–2). In their conceptualisation of persuasion, Faden and Beauchamp (1986) emphasise that the persuader merely brings "the persuadee's attention to reasons for acceptance of the desired perspective" (p. 348). The reasons themselves have to exist independently of the persuader. The persuader must not control them and they must be believed by the persuader (Faden & Beauchamp, 1986). If the persuader somehow has control over the factors offered as reasons, the influence is more likely to be manipulative than persuasive (Faden & Beauchamp, 1986). For example, an appeal to pre-existing shared beliefs would constitute persuasion. If a researcher were to indoctrinate a person with a certain belief, with the sole intention of getting the person to consent to research, it would constitute a form of psychological manipulation and undermine voluntary consent. Moreover, according to Faden and Beauchamp (1986) warnings and predictions also constitute persuasion, while appeals to false beliefs or deception are not considered persuasion. Persuasion improves a person's understanding of their options and choices; it does not undermine their understanding (Faden & Beauchamp, 1986). The persuadee should be free to decide whether or not to accept the reasons advocated by the persuader (Faden & Beauchamp, 1986). However, persuasion depends on the subjective response of the person being influenced. What may rationally persuade one person may overwhelm and confuse another preventing a reasonable decision from being made (Beauchamp & Childress, 2009).

Similarly, persuasion, according to Mandava and Millum (2012), is when one person motivates another to make a decision by presenting relevant information or highlighting

the connections between the decision–maker's existing set of desires (e.g., to advance scientific knowledge) and the decision to be made (i.e., to enroll in research). As the decision-making process of the person deciding is not illegitimately interfered with, persuasion does not undermine voluntaries (Mandava & Millum, 2012).

2.3 Inducements

Concern about the voluntariness of consent to research is also often raised when substantial financial or medical inducements (including care and treatment) are offered in return for research participation (Appelbaum et al., 2009; Emanuel et al., 2005; Kass et al., 2005). According to the Belmont Report undue influence "occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance" (NBAC, 1979).

There are four primary objections to offering incentives to research participants. First, some (cf. Bosk, 2002) see the provision of inducements in return for research participation to be in direct contrast to the altruistic ideals that should motivate research participation. Second, inducements for research participation are thought to be more attractive to individuals with low income or limited access to health services (Nelson & Merz, 2002) leading to the over-representation of and disproportionate burden on such individuals (Koen, Slack, Barsdorf & Essack, 2008). Third, inducements may lead potential participants to be dishonest about information that may lead to their exclusion from the study (Koen et al., 2008). Lastly, there is concern that inducements may lead to hasty decision-making, resulting in the decision-maker sacrificing their long-term interests to gain a short-term good (Hawkins & Emanuel, 2005) or failing to accurately assess the level of risk the study poses (Bentley & Thacker, 2004). Similarly, Wertheimer and Miller (2008) state that inducements may compromise the voluntariness of consent if potential research participants are unable to respond to the incentive in a rational manner.

Several empirical studies have examined the effects of inducements on research participation. For example, Dugosh, Festinger, Croft and Marlow (2010) found that 38%

of 84 substance abusing criminal offenders surveyed reported that financial incentives were the main reason they joined the study. In contrast, Appelbaum et al. (2009b) found that 35% of the 88 research participants they surveyed reported the presence of offers but that the majority of these respondents rated the offers as having little influence on their decision to enroll in the research. Similarly, Bentley and Thacker's (2004) study of the effects of payment on potential participants' risk evaluations and willingness to participate in research found that monetary payment had positive effects on respondents' willingness to participate, regardless of the level of risk. However, higher monetary payments did not appear to blind respondents to the risks of a study (Bentley & Thacker, 2004).

According to Appelbaum et al. (2009a), offers are acceptable insofar as they expand a person's options without limiting their choice. Offers however become problematic if they cause a person to ignore the risks associated with an action (Appelbaum et al., 2009a). Emanuel et al. (2005) argue that providing offers such as payment or medical care that are beneficial, wanted and reasonable as part of an 'otherwise ethical research study' cannot constitute an undue inducement and as such cannot undermine the voluntariness of consent. According to Emanuel et al. (2005) the purpose of inducements is to change behaviour. As such, providing a person with an inducement that encourages them to do something they would otherwise not do is not enough to render an inducement undue (Emanuel et al., 2005). In order to change behaviour, inducements also change how people balance risks and benefits. For example, a higher salary offer may encourage a person to accept a job that involves greater risk, risk they would be unwilling to accept for lower pay (Emanuel et al., 2005).

Emanuel et al. (2005) argue that there are four necessary conditions that must be met for an inducement to be undue. First, a desirable good has to be offered in return for a specified action. Second, the offered good must be so excessive that it cannot be resisted. Third, the offer has to result in a person making a poor judgment in relation to the specified action. Finally, the person's poor judgment must result in a high probability that they will experience serious harm that threatens their interests. Although the

reasonableness of risks is subjective, Emanuel et al. (2005) argue that undue inducements apply only when risks are undoubtedly unreasonable. While unfortunate circumstances may make certain offers irresistible, they only become undue inducements when a "person's unfortunate circumstances and compromised judgment are combined with accepting a seriously unfavourable risk-benefit ratio that threatens fundamental interests" (Emanuel et al., 2005, p. 338). The authors conclude that if a research study fulfils all the other ethical requirements and an efficient and competent research ethics review committee has found the risk-benefit ratio to be favourable then undue inducement cannot occur as the risk of "serious harm that threatens fundamental interests" is precluded even if participants exercise poor judgment (Emanuel et al., 2005, p. 338).

It could however be argued that the notion that a person has to be left worse off for undue inducement to have occurred should be rejected. While the 'risk of serious harm' is precluded in otherwise ethical studies, should not deprivations of voluntariness also be of moral concern when an offered good is provided in excess, leading to poor judgment that threatens the participant's fundamental interests even in the absence of the risk of serious harm? Inducements would then be considered to be of ethical concern if they cause a person to do something they do not want to do, irrespective of the risk of harm.

According to Feinberg (1986), offers encourage a person to do something by introducing an alternative into a given situation making a certain action more appealing than the unacceptable status quo. For example, if person D is unemployed, with no means to provide for her family, she may feel she has no choice but to take the only low paying, menial job offered to her or enroll in research that offers financial reimbursement. The offer of a job or research participation provides a means for her to provide for her family, it adds something positive to her desperate situation making her better off, not worse. Offers do not disrupt a person's status quo. The choice whether to accept the offer or maintain the unacceptable status quo is entirely up to person D. If a threat were presented instead of an offer, person D would have no way of returning to the status quo unless the threat were removed.

Faden and Beauchamp (1986) address the issue of whether offers can be coercive. Firstly, according to their conceptualisation, threats are coercive as they provide severe negative consequences, while offers do not. There is no negative consequence to turning down an offer; doing so merely leaves the individual with the existing status quo (although the existing status quo may be deemed unacceptable to begin with) (Faden & Beauchamp, 1986). For example, a hijacker with a gun may threaten motorist E, 'hand over your car or I will shoot you'. Regardless of which option motorist E chooses he will face a severe negative consequence that will disrupt his existing status quo. If however person F offers motorist E R100,000 to buy his car, neither option will result in a severe negative consequence that disrupts his status quo. If motorist E decides to sell his car he will receive R100,000 but if he decides to keep his car he will be left as he was before the interaction occurred. According to Nelson et al. (2011), offers or inducements for research participation are not problematic if a potential participant welcomes them, does not want to resist them and the risks are no more than those of everyday life.

2.4 Difficult or desperate background conditions

Difficult or desperate background conditions such as illness, poverty and lack of access to health care are frequently cited as having the potential to undermine voluntary decision-making (Barsdorf & Wassenaar, 2005; Kass et al., 2005). It is argued that offering potentially effective treatment to a terminally ill person or offering free health care or payment in return for research participation to participants from impoverished communities leaves the potential participant with no meaningful choice but to enroll in the research (Olsaretti, 1998). According to Sears (2005) it is possible for a person to be capable of voluntary decision-making yet vulnerable to contextual influences, such as poverty. Contextual vulnerabilities, according to Sears (2005), can cause a person to misinterpret the purpose of research to fit in with their own needs and priorities.

Terminally ill patients, for example, are often seen as desperate, vulnerable and unable to make free choices (Agrawal, 2003). For some authors (cf. Bosk, 2002; Nelson & Merz, 2002) illness has the potential to undermine the voluntariness of consent to research

participation, especially for the terminally ill for whom research participation may represent the last hope of cure or relief. According to Bosk (2002) while desperately ill patients are capable of assessing their own best interests and making decisions, they do not meet the standards of a fully rational decision-maker required by the practice of informed consent. This is because a desperately ill person's continued existence is threatened and they are fatigued by illness and anxious about recovery, factors which affect judgment and patients' decision-making abilities (Bosk, 2002). Bosk (2002) concludes that consent to research necessitates desperately ill patients be given information at a stage when they are least able to process it and requires an independent decision when they are most dependent on others for care and support. Bosk (2002) argues that ill patients may not rationally consider the information disclosed during consent if they want to do everything they can to overcome their illness and not give up. As a solution to the problem of voluntariness being compromised by illness, Bosk (2002) suggests that the patient's eagerness to volunteer needs to be reduced. Their trust in physicians and hope for cure or relief, need to be placed second to reason, instead of the other way round. In contrast, Agrawal (2003) argues that choices made by terminally ill patients may be difficult due to their unfortunate situation, but they are still capable of being free and voluntary. If terminally ill patients were to be regarded as incapable of making voluntary decisions they would not be allowed to make decisions about their treatment or estate wills (Agrawal, 2003). Choosing the most reasonable option out of a range of unfavourable options when a person is forced to by illness by no means undermines the validity of the consent provided.

In a study of the decision-making process of 163 phase 1 oncology trial participants Agrawal et al. (2006) found that 75% of respondents reported experiencing moderate to a lot of pressure to enroll in the study because their cancer was growing. Similarly, Pace et al., (2005) found that of the 141 participants surveyed in a randomised HIV treatment controlled trial in Thailand, 43 reported feeling pressurised to participate due to their health-related circumstances. Of these, 10 respondents reported that the trial was the only way for them to access treatment (Pace et al., 2005). In contrast, Mutenherwa (2012) assessed the perceived voluntariness of the enrolment of Zimbabwean clinic patients in a

randomised controlled trial of the impact of a new diagnostic test for tuberculosis. This poor and ill research population would, by traditional accounts (cf. Bosk, 2002; Olsaretti, 1998), be seen to be incapable of making a voluntary decision to participate in research. Yet Mutenherwa's (2012) research found that the majority (98%) of respondents perceived their participation to be voluntary and uncoerced. Such research discounts the commonly held assumption that poverty and illness necessarily undermine voluntary consent.

Nelson et al. (2011) refer to illness and poverty as "constraining situations" (p. 9). They explain that these non-intentional coercion-like conditions may make a person feel controlled situationally. While Nelson et al. (2011) state that the absence of options brought about by constraining situations cannot render consent nonvoluntary, they can "lead to deprivations of voluntariness that are morally problematic" (p. 9) such as undue inducements.

Feinberg (1986) on the other hand argues that unfortunate circumstances and situational constraints such as poverty may influence a person's choice or even limit their range of options but cannot make a choice nonvoluntary. Feinberg (1986) argues that one has to "accept the circumstances of the consenter exactly as we find them and ask whether in those circumstances, or against that background, the consenter's choice is free, or whether some further factor has intervened to vitiate it" (p. 149). Two examples can be provided to illustrate this point. If a robber points a gun at person G and says 'hand over your wallet or I will shoot you', the decision made by person G to hand over his wallet is nonvoluntary. This is because it results from the robber's *intrusive behaviour* imposed on person G's *normal background* that *forced* him to consent. On the other hand, person H is unemployed with no means of providing for his family and a researcher invites him to participate in a clinical trial offering financial reimbursement in return for participation. According to Feinberg (1986) it would still be possible for person H to make a voluntary decision whether or not to enroll in the research, as person H's unemployment and financial circumstances have to be taken as given, as part of his normal background against which consent is given rather than an intervening force that deprives him of

voluntary choice (Feinberg, 1986). A person who chooses research participation in order to receive financial reimbursements may be in desperate circumstances, may feel their choice is forced, and may have no other feasible alternatives, but Feinberg (1986) argues that it cannot be claimed that such a choice is not voluntary. Choosing the most reasonable option out of a range of unfavourable options when a person is forced to by unfortunate circumstances by no means undermines the voluntariness of the consent provided. Essentially, in the first example a threat is made which will leave person G worse off, while in the second example an alternative to an unfortunate situation is provided in the form of research participation making the bleak situation potentially better not worse. Similarly, Faden and Beauchamp (1986) argue that a person may be restricted by their circumstances, without any feasible alternatives but they can still carefully deliberate about their situation and reach a voluntary decision. As long as controlling influences of another person are not present it is possible to deliberately choose the best option when only unfavourable options are available (Faden & Beauchamp, 1986).

Faden and Beauchamp (1986) give the label "situations of desperate need" (p. 357) to situations where a person needs something, without which there is a strong likelihood that the person or someone close to them will be seriously harmed, for example, an invitation to participate in an experimental HIV treatment trial when participation presents the only hope of possible treatment as HIV treatment is not yet publically available. Even in these situations, Faden and Beauchamp (1986) believe that if an offer (be it financial reimbursement or treatment) is welcome or resistible the person deciding can make a voluntary decision. Similarly, Wertheimer (1987) argues that "if B's unfortunate circumstances are not due to A and if A's proposal violates none of B's rights, B's agreement is not made under duress" (p. 64). As such Nelson et al. (2011) argue that "denial of research opportunities to desperate persons would be to refuse them, in many cases, the very conditions they seek to increase their degree of control and to make voluntary choice meaningful" (p. 16).

While Faden and Beauchamp (1986), Feinberg (1986) and Wertheimer (1987) argue that neither situational constraints nor unfortunate circumstances alone can render a choice nonvoluntary, this does not mean that voluntariness should not be closely examined when desperate or difficult conditions are present.

First, situational constraints can make intentional influences more difficult to resist or make those influences harder to identify (Appelbaum et al., 2009a). Birnbacher (2009) provides an example of person I who is lost in a desert and is dying from dehydration when he is offered a glass of water in return for a 'disproportionally high sum of money'. In this context, Person I is manipulated into agreeing to the offer. As such his consent to the transaction is not sufficiently voluntary. However, *why* his consent is nonvoluntary needs to be closely examined. His *unfortunate situation* (dying of thirst in a desert) does not make him incapable of providing voluntary consent. He could, for example, quite voluntarily decide whether or not to follow the direction of another person he comes across in the desert or continue on his own. Similarly the *offer* itself is not inherently voluntariness depriving. If the same offer of water for a disproportionally high sum of money were made to a runner at the end of a race he would likely find the offer resistible. What is problematic is that the situational constraint made person I more susceptible *to intentional manipulation*. It is therefore the intentional manipulation in the form of an exploitative offer by the other person that undermined voluntariness, not just the unfortunate circumstances of the decision-maker.

Second, situations or circumstances are also of concern for voluntariness when one person has brought about the situation in which another person finds himself in order to gain that person's consent for a specific activity. For example, if an ill patient were to enroll in a phase II experimental drug trial in the hope of receiving potentially effective treatment for a condition for which existing treatment is absent or proving ineffective, it is possible for the patient to voluntarily choose research participation as opposed to the alternative of deteriorating health. The patient's illness may not be seen as limiting the voluntariness of his consent. If however a physician first deceptively gave an ill patient a placebo instead of the standard treatment so that his condition would worsen and he

would then enroll in the experimental drug trial, the patient's enrolment would be nonvoluntary because the physician is intentionally controlling it, through the use of deception.

2.5 Addictions and psychiatric disorders

Concerns about impaired voluntariness have also been raised when research is conducted with psychiatric or substance abuse patients (Appelbaum, 1995). Concern is also raised when drug abusers are recruited for studies that involve the administration of their drug of choice or monetary payments where participants may use the payments to purchase drugs (Mamotte, 2012).

Nelson et al. (2011) argue that certain actions performed by a drug addict or a psychotic schizophrenic will be nonvoluntary if the action, although intentional, is caused by the person's addiction or disorder. For example, while an alcoholic may intentionally pour himself a drink, the action is argued by Nelson et al. (2011) to be nonvoluntary as the alcoholic's behaviour is controlled by his addiction. This is of course not to say that persons with disorders and addictions are not capable of making voluntary decisions in certain contexts. For example, (a) person J, a drug addict, may not voluntarily decide to take an illicit drug because he is compelled to do so by his addiction, (b) he may not even be able to voluntarily enter a treatment facility because he is forced by his addiction to continue drug use despite his desire to quit but (c) he may be able to voluntarily decide to enroll in an HIV vaccine trial. In other words, according to Nelson et al.'s (2011) conceptualisation, addictions and disorders are only likely to infringe voluntariness in certain domains of a person's life.

Alternatively, it may be argued that addictions and disorders do not affect voluntariness as conceptualised by Nelson et al. (2011). Rather, addictions and disorders may be more appropriately considered under the condition of *competence* to make a voluntary decision rather than a factor that mitigates the voluntariness of a decision. Competence to provide voluntary informed consent is defined by the NBAC (1998) as the ability to understand

the nature of research participation, appreciate the consequences of participation as well as the ability to consider alternatives and make a reasoned choice. In scenario (b), for example, it may be argued that because of his drug addiction person J does not have the competence to make a voluntary decision about entering a treatment facility; the decision will therefore be taken away from him and he may be involuntarily admitted by his family or a court order. If however he is deemed to have the competence to make a decision about entering a treatment facility or enrolling in HIV vaccine research, his decision to not enter the facility or to enroll in the HIV vaccine trial cannot then be said to be nonvoluntary because of his drug addiction, although it may be nonvoluntary for other reasons. The UNAIDS (2012) guidance document on *Ethical considerations in biomedical HIV prevention trials* has recently been amended to include a guidance point on recruiting people who inject drugs into HIV prevention trials. Although UNAIDS (2012) describes people who inject drugs as vulnerable and in need of special protections, it regards voluntary participation of such populations as possible.

2.6 Social roles, norms and inequalities

Faden and Beauchamp (1986) argue that role constraint can impact voluntariness in a way that situational factors cannot. "A person's role can carry with it certain expectations for behaviour and consequent intentional actions that function to limit or constrain that person's autonomous expression" (Faden & Beauchamp, 1986, p. 368). Dependent relationships are a concern for voluntariness insofar as a person in a dependent relationship may submit to the *perceived desires* of the other person even when it conflicts with their own will and desires (Agrawal, 2003). Similarly, institutionalised persons are often subject to the formal or legal authority of those representing the institution (Agrawal, 2003). The central issue is the relative powerlessness that accompanies certain roles in society: When people are in a dependent role, such as hospitalised patients, they may not act as they would prefer or as they otherwise would. Roles such as the hospitalised patient are defined by their passivity and dependency on powerful medical professionals so when people find themselves in these roles they may have less opportunity to act voluntarily than when they are in other roles (Faden &

Beauchamp, 1986). It is for this reason that the voluntariness of ill or previously disadvantaged persons' consent is frequently questioned. For example, ill persons may not realise that the social norms that govern their behaviour as patients may be very different to those that govern the role of research participants, or that the roles and responsibilities of a researcher and a physician are different (Bosk, 2002). The greater the disparity in power between research participants and researchers, the more likely participants are unable to make a voluntary decision, even if objective evidence of controlling influences is absent (Bull & Lindegger, 2011). At the same time, this greater likelihood does not rule out the possibility of voluntary decisions being made in such circumstances.

The different role of men and women in African cultures is another example of how powerlessness can raise concerns for voluntary consent. The patriarchal social system present in most African countries means that men are often viewed as the head of the family and are responsible for making important decisions on behalf of their family (Nyika, Wassenaar & Mamotte, 2009). As such, women may not be allowed to express themselves even on personal matters over which they ought to have control (Nyika et al., 2009). This utilitarian practice may be seen as a violation of women's rights to self-determination which would prevent them from making voluntary decisions on personal matters such as research participation (Nyika et al., 2009). It is possible for conflict to exist between the wishes and desires of a female research participant and what is expected of her by her patriarchal society (Nyika et al., 2009). In addition, expectations of men and family may pressure women not to effect their right to self-determination (Nyika et al., 2009). Molyneux, Wassenaar, Peshu and Marsh (2005), for example, found that mothers of child participants considered decision-making by the child's father to be the social norm. Kamuya, Marsh and Molyneux (2011) argue that this social norm undermines women's voluntariness as they may simply be following their social obligation to defer decision-making.

To ensure that people in positions of relative powerlessness realise their ability to make voluntary decisions, most ethical guidance documents such as the *Good participatory*

practice guidelines for biomedical HIV prevention trials (UNAIDS, 2011) emphasise the importance of empowering research participants via participatory practices and encourage the employment of recruiters from target populations in order to reduce the power differentials between participants and research staff.

In contrast, others (cf. Millum, 2011) argue that powerlessness and role constraints are only perceived influences and as such cannot undermine voluntariness as no one is actually attempting to control another. While people in dependent relationships or positions of relative powerlessness may believe that they are unable to make a voluntary decision, this does not mean that they are actually incapable of making a voluntary decision. This is in direct contrast to Bull and Lindegger (2011) who argue that internalised powerlessness can undermine the voluntariness of consent to research. According to Millum (2011) certain roles in society, be it a hospitalised patient or an African woman in a patriarchal society, may make it more difficult for the person occupying that role to exert their right to autonomy or express their voluntary choice, but that difficulty cannot be equated with an inability to make voluntary decisions. Of course, if there are severe negative consequences (such as being ostracised or beaten) to acting outside prescribed social roles it would constitute coercion and be nonvoluntary as a result of the threat of harm. Millum (2011) states that if a person is acting purely on the basis of perception and an internalised social role in the absence of real negative consequences, voluntariness is not compromised. As long as people in positions of relative powerlessness have the competence to act voluntarily they cannot be denied the opportunity to make a decision on the presumption that that decision may be less than fully voluntary. From this perspective, unequal power differentials can make people more susceptible to intentional influences or make those influences harder to identify. In the absence of intentional influences (such as coercion), however, people in positions of relative powerlessness cannot be assumed to be incapable of making voluntary decisions. According to Mandava and Millum (2012) potential participants' consent may still be valid despite the influence of social roles, norms and inequalities. If researchers disclose everything that they need to, the participants are capable of understanding what is being

proposed, and refusal is a reasonable option, even if the potential participants' value system inclines them against it.

2.7 Social desirability and trust

Ajzen (2001) identified the important role of normative beliefs in the prediction of behaviour. Normative beliefs refer to an individual's beliefs about the expectations of others and their motivation to conform to these expectations (Ajzen, 2001). The potential for impaired voluntariness resulting from social desirability or trust has been raised when participants are recruited by their health care providers or from facilities where they are receiving care and treatment (Appelbaum et al., 2009). In these situations potential participants may not want to disappoint health care providers or they may feel that they are not entitled to refuse participation (Appelbaum et al., 2009; Kamuya, Marsh & Molyneux, 2011). A patient's trust in their physician may also override their desire to provide informed and truly voluntary consent (Bosk, 2002). According to Mandava and Millum (2012) trust is only problematic when it is unwarranted and is illegitimately used to induce someone to make a decision they would not otherwise make. Bosk (2002) claims that it is possible that the patient's existing relationship with their physician or the patient's belief that research reflects their last or best hope for cure or relief negatively impacts the voluntariness of their decision to participate. Bosk (2002) further argues that informed consent protects the public's interest in being able to freely make their own choices but that patients' interests may differ completely. Patients want to be relieved of their illness and, failing that, be taken care of. Informed consent does not enhance these interests (Bosk, 2002). As a solution to the concern that being recruited into research by one's physician may compromise voluntariness, Bosk (2002) suggests that research conducted by one's physician should be proposed and discussed by external, non-medical personnel and patients should be given sufficient time to weigh up their options.

Similarly, Abdool Karim, Abdool Karim, Coovadia and Susser (1998) argue that the social context of hospitals where medical professionals are held in high esteem may negatively impact participants' freedom to refuse research participation. Furthermore,

patients' perception that medical professionals expect them to participate may also mitigate the voluntariness of consent (Abdool Karim et al., 1998; Hewlett, 1996). In Abdool Karim et al.'s (1998) study of the voluntariness of informed consent to HIV testing within a South African perinatal HIV transmission study, 32% of the 56 women in the study group and 23% of the 56 women in the control group felt that the care they received would be compromised if they did not participate in the study. Abdool Karim et al. (1998) suggest two solutions to the potential lack of voluntariness of consent to research conducted in hospital settings. First, more explicit information should be included in consent forms about how refusal to participate in research will not compromise care received (Abdool Karim et al., 1998). Second, it is suggested that researchers and medical professionals are sensitised to the elements that may undermine voluntariness in a hospital setting (Abdool Karim et al., 1998).

Even in situations where the researcher is not the potential participant's physician, participants may feel that they cannot say no to researchers (Hewlett, 1996; Kass et al., 2005). Kass et al. (2005) argue that informed consent must be sensitive to the trust participants place in the researchers and the research enterprise. A study by Appelbaum et al. (2009b) found that trust in the researchers and the reputation of the host institution were the most frequently cited motivations for research participation. When power disparities exist between researchers and participants, it is possible that participants may feel unable to make a voluntary decision about research enrolment, even in the absence of objective controlling influences being exerted by the researcher (Bull & Lindegger, 2011; Nelson & Merz, 2002). Participants may feel obliged to participate in research out of reverence for researchers or perceived negative consequences of refusal (Bull & Lindegger, 2011). For example, Lansimies-Antikainen et al. (2010) found that 10% of 1324 research participants in a randomised control trial on exercise and diet in Finland enrolled because of a willingness to please research personnel.

2.8 Emotions, perceptions, internal representations and personal beliefs

Some authors associate nonvoluntary consent with the consenter's emotional or mental state at the time of consent. This view assumes that consenting reluctantly or grudgingly is to do so nonvoluntarily (Wertheimer, 2012). Moreover, Nelson and Merz (2002) argue that "the fear of loss of health care benefits or retribution for refusal to participate render any given decision [nonvoluntary], regardless of the researcher's intention, and this may be so even if the patients are vulnerable to imagined threats that would not be credible or could be resisted under other circumstances or by other people" (p. 75). Bull and Lindegger (2011) argue that psychological research demonstrates the powerful influence of internal representation of external persons. The authors cite the case of a pregnant woman whose partner wants her to have an abortion. "While he may not threaten her with abandonment if she goes ahead with the pregnancy, her memory of previous experiences of abandonment when she failed to please her partner, and the fear of recurrence of such abandonment, may internally pressure her to agree to an abortion" (Bull & Lindegger, 2011, p. 27).

In contrast, Appelbaum et al. (2009a) argue that feelings, perceptions or internal representations may alter a person's ability to make a decision in line with their desires or lead to unwise decisions but they cannot make a choice nonvoluntary. If a person is deemed to have the capacity to make a voluntary decision "then there is no reason why his or her foolish or neurotic decision cannot be a sufficiently voluntary one … [people have] the right to decide foolishly in self-regarding matters" (Feinberg, 1986, p. 301). For example, a physician may recommend surgery as the only chance of survival and it may be assumed that any reasonable person would consent to the surgery. A particular patient, however, may be too terrified of the procedure to provide consent to the surgery. While to external observers this may be foolish, it cannot be said to render her decision nonvoluntary.

Similarly, Feinberg (1986) argues that when appropriate information is provided, mistaken beliefs or mistaken expectations of the future are not sufficient to render consent nonvoluntary. For example, a surgeon may explain to her patient that there is only a 50% chance that the surgery will be a success. Despite understanding this

information, the patient may be very optimistic and honestly believe that he will certainly (as opposed to might) be one of the 50% for whom the surgery is a success. According to Feinberg (1986) consent provided as a result of this factually mistaken belief (the patient did not consent to surgery with a 50% success rate because he mistakenly believed that he consented to surgery that for him would in fact be 100% successful) is not enough to render consent nonvoluntary. As long as the person deciding is deemed competent to make the decision, appropriate information is disclosed and the person deciding is given adequate opportunity to understand, the resultant decision can be deemed voluntary yet misinformed (Nelson & Beauchamp, 2011).

2.9 Actions of a third party

So far the potential impairments to voluntariness discussed have focused on actions of the researcher, influences from conditions such as poverty or illness or internal influences such as social desirability. However, actions of a third party, such as a spouse, often influence potential research participants' decision whether or not to enroll in research. Agrawal et al. (2006), for example, studied the decision-making process of 163 patients enrolling in five phase I oncology studies across the US. The study found that 11% reported a little pressure and 9% reported a moderate or large amount of pressure from family to join the study (Agrawal et al., 2006). Pace et al. (2005) studied the quality of informed consent in a randomised HIV control trial in Thailand and found that of the 38 respondents who reported feeling pressure from others to enroll, that pressure was felt to come from friends (n=21), from family (n=10) and a personal physician (n=3). Whether pressure from family and friends compromises voluntary consent is debatable, Miller and Wertheimer (2010) argue that pressure from third parties does not undermine voluntary consent. Millum (2011) however claims that third party pressure can undermine consent as the person who has the authority to make the decision (the research participant) has to actually make the decision for the decision to be voluntary. In African contexts, a communitarian culture of relational decision-making may mean that family and community members may play a central role in research participants' consent decisions (Osamor & Kass, 2012).

2.10 African communitarian culture and relational decision-making

Researchers have expressed concern that when Western-sponsored clinical trials are conducted in African communitarian cultures it may be inappropriate to meet the ethical requirement of voluntary informed consent which is construed as fundamentally rooted in Western individualistic culture (Frimpong-Mansoh, 2008; Mkhize, 2006), where the self is viewed as being independent from others (Nyika et al., 2009). While African culture is heterogeneous, the perception of 'self in relation to others' is typical of all African cultures (Nyika et al., 2009). African communitarian culture is described by Mbiti (1969) as a culture in which it is only through other people that an individual becomes conscious of his own will or desires. This results in individuals acting according to both their own wishes and those of others (Nyika et al., 2009). Although African communitarian culture does not preclude individuality, it may discourage the individual from taking priority over the community (Jensen & Gaie, 2010). Respecting African participants' autonomy means allowing them to follow the decision-making process of their choice (Nyika et al., 2009). While decision-making practices may differ between cultures, the principle of autonomy and the operational requirement of voluntary consent should be universal (Nyika et al., 2009). Bull and Lindegger (2011) argue that for voluntary consent to be compatible with African communitarian culture it is necessary to view independent and relational decision-making as equally voluntary and equally valid forms of decision-making. As such, they propose a continuum of voluntariness that takes the degree of relationships with others into consideration. At one end of the continuum is 'independent consent' whereby a person makes an independent decision even in the presence of influence by others (Bull & Lindegger, 2011). On the other end is what the author's term 'proxy consent', when a person provides consent that is completely controlled by others (Bull & Lindegger, 2011). In between the two extremes of 'independent consent' and 'proxy consent' Bull and Lindegger (2011) locate 'cooperative consent' based on relational autonomy in which "a person makes a joint decision in collaboration with others" (p. 28). Bull and Lindegger (2011) argue that this consent decision is voluntary but made together with others on the basis of shared values. Similarly, the Declaration of Helsinki states that

participants should be able to consult family members or community leaders regarding research participation as long as the potential participant makes the final decision (World Medical Association, 2013). Empirical research supports the hypothesis that potential research participants in African contexts often ask permission from family or their spouse prior to making a decision about research participation. Recently, Osamor and Kass (2012) studied the decision-making practices of Nigerian men and women who had previously participated in biomedical research. The authors found that 39 of the 100 participants surveyed requested permission from a spouse or family member before participating in the study (Osamor & Kass, 2012). The authors concluded that "informed consent in this community is understood and practised as a relational activity that involves others in the decision making process" (Osamor & Kass, 2012, p. 89).

3. Degrees of Voluntariness

While the above review suggests that there is little agreement in terms of what factors impair voluntariness, many authors agree that voluntariness should be measured in degrees (Faden & Beauchamp, 1986; Feinberg, 1986; Nelson et al., 2011). Acts or decisions are never simply voluntary or nonvoluntary. A decision may be more or less voluntary depending on the influences and context in which it is made. Voluntariness of consent therefore lies along a continuum and can be measured in degrees depending on the extent to which a decision is voluntary. Feinberg (1986) provides a useful illustration of the different degrees of voluntariness. Along a continuum of voluntariness, 'nonvoluntary' consent would be located at the lower end and 'fully voluntary' at the upper end (Feinberg, 1986) (See Figure 1).

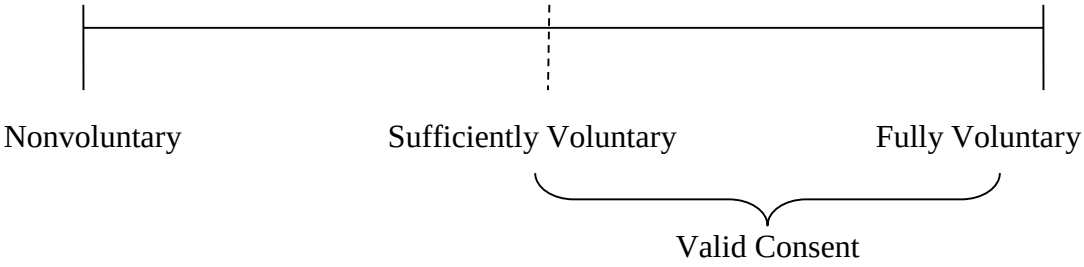


Figure 1. Degrees of voluntariness

According to Feinberg (1986), consent should be considered valid when it is 'sufficiently voluntary'. While the placement of the sufficiently voluntary threshold line may seem somewhat arbitrary, Feinberg (1986) provides three useful 'rules of thumb' to identify where sufficiently voluntary should be placed on the continuum. Firstly, Feinberg (1986) argues that the greater the risk involved in whatever the person is consenting to, the greater degree of voluntariness required. The rationale is to prevent people subjecting themselves to a risk of harm that they have not truly chosen. The severity of the risks/harm and the probability that the risks/harm will occur need to be taken into account when determining what makes consent sufficiently voluntary (Feinberg, 1986). For example, a lower degree of voluntariness would be sufficient for consent to a 10-minute marketing survey conducted in a local supermarket where the only harm is inconvenience. However the degree of voluntariness required for consent to a phase 1 drug trial designed to determine the tolerable toxicity dose of a new drug would need to be significantly higher. Secondly, Feinberg (1986) states that if it is possible that consent may result in irrevocable harm, a greater degree of voluntariness is required than for consent where the harm can be repaired or compensated for. For example, a far higher degree of voluntariness would need to be applied to research enrolment where the possible risk is paralysis as compared to research which poses the risk of transient headaches and dizziness. Lastly, standards of voluntariness depend on other specific circumstances in which a decision is made (Feinberg, 1986). The voluntariness of an action has to be judged in the context in which that action occurs, not against an unrestrictive, hypothetical background. For example, one of the many symptoms of

clinical depression is concentration problems, including trouble focusing or making decisions, qualities generally agreed to be important for making voluntary decisions. However, if a person suffering from depression were to make a decision to start treatment, standards of voluntariness would have to be applied to her exactly as she is, current depression included. Voluntariness of her decision could not be examined from the perspective of a 'normal person in a normal situation' (Feinberg, 1986).

4. Summary

Review of the literature reveals obtaining voluntary consent for research participation to be an ethical imperative. Despite this, there appears to be little consensus regarding what constitutes a voluntary decision to participate in research resulting in a variety of concerns about the voluntariness of consent to research frequently being raised in research ethics literature. In response, regulatory agencies and research ethics committees have implemented a variety of policies and practices to enhance voluntary consent (Appelbaum et al., 2009a). Yet without a valid conceptualisation of voluntariness and an appropriate means of assessing it, it is impossible to determine whether commonly expressed concerns about voluntariness are well founded (Appelbaum et al., 2009a). As such this research aimed to identify a valid way of conceptualising voluntariness and an appropriate means of assessing it.

Chapter 3: Study Aims and Objectives

Given the complexities and discrepancies outlined in Chapter 2, this study aims to identify a valid way of conceptualising voluntariness and an appropriate means of assessing it.

The specific study objectives are to:

1. Conduct a conceptual review and analysis of the voluntariness of consent to research, in order to adapt or develop a valid conceptualisation of voluntariness (Chapter 4).
2. Conduct a review of empirical attempts to assess voluntariness of consent, in order to adapt or develop an instrument to assess voluntariness of consent according to the conceptualisation adopted in Objective 1 (Chapter 5).
3. Pilot the voluntariness assessment measure developed (Chapters 6, 7 and 8).

The aims of the pilot study are to:

1. Determine the perceived voluntariness of research participants' consent.
2. Identify what factors undermine participants' perceived voluntariness of consent.
3. Identify the presence of influences from other people and how these influences are exerted.
4. Identify the presence of controlling (intentional, illegitimate and causal) influences from others and subsequent nonvoluntary participation.
5. Identify what other factors influence participants' consent decision.

Chapter 4: Conceptualising Voluntariness of Consent to Research

The first objective of this study is to conduct a conceptual review and analysis of voluntariness of consent to research in order to identify or develop a valid conceptualisation of voluntariness. While no agreed upon conceptualisation of voluntary consent to research exists (see Chapter 2), several theorists have made substantial progress in attempting to articulate what voluntary consent entails. This chapter critically explores four of the most widely adopted conceptualisations of voluntariness, taking into account the literature reviewed in Chapter 2, before adopting the conceptualisation of voluntariness deemed to be most valid and appropriate for this present study. This conceptual review separates value-neutral and moralised accounts of voluntariness. This distinction is borrowed from Wertheimer (2012); essentially, the voluntariness of a consent decision can be thought of in two ways. First, the voluntariness of a consent decision can be determined based on *a priori* conceptualisations of voluntariness (value-neutral accounts), or, second, the validity of the consent provided can be assessed independently of whether the consent decision can reasonably be described as voluntary or not according to *a priori* definitions (moralised accounts) (Wertheimer, 2012).

1. Value-Neutral Accounts of Voluntariness of Consent to Research

Many maintain that voluntariness is a value-neutral concept whereby a person acts nonvoluntarily if exposed to a controlling influence (cf. Nelson et al., 2011) or if they have no acceptable alternatives (cf. Olsaretti, 1998). In this section the value-neutral accounts of Nelson et al. (2011) and Olsaretti (1998) will be critically reviewed and discussed.

1.1 Freedom from controlling influences

Faden and Beauchamp (1986) argue that the term voluntariness has too many ‘confusing associations’ that would be impossible to clear up in a conceptual analysis of the term. As such they avoid the term entirely by replacing it with a conceptualisation of noncontrol,

the last of the three conditions delineated in their conceptualisation of autonomy (Faden & Beauchamp, 1986) (Chapter 2 – section 1.1). Since then, several authors (cf. Beauchamp and Childress, 2009; Nelson et al., 2011) have adopted and extended Faden and Beauchamp's (1986) 'condition of noncontrol' in order to define the voluntariness of consent. To this end, 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). Faden and Beauchamp (1986), Beauchamp and Childress (2009) and Nelson et al. (2011) maintain that in terms of influences from another person only coercion (when one person intentionally and successfully influences another person by presenting a credible threat of harm so severe that the coercee has no choice but to act in order to avoid the threat of harm) and certain types of manipulation (such as deception) can be controlling and therefore be considered to undermine the voluntariness of consent. Nelson et al. (2011) extend the conditions for voluntary action when they say that for an action to be voluntary two necessary and jointly sufficient conditions need to be present: (a) intentionality and (b) substantial freedom from controlling influence of another person or condition. Controlling conditions refer to a set of constraining situations or contexts (such as poverty) which may or may not undermine voluntariness (Kumuya et al., 2013).

According to this conceptualisation, the first condition of voluntariness is intentionality. Intentional action requires an intention to perform an action, a plan of how the action will be performed and the occurrence of the action (Faden & Beauchamp, 1986). Faden and Beauchamp (1986) further state that an action willed in accordance with a plan is intentional regardless of whether the act itself is wanted or not. Intentionality is a necessary condition for voluntariness. Therefore, an act that is not intentional cannot be voluntary. For example, if a person mistakenly puts sugar on his food instead of salt, he may have intentionally taken a teaspoon of white granules out of a container and sprinkled it on his food but it cannot be said that he intentionally put sugar on his food as he was mistaken about the contents of the container. In this case the action was not intentional and therefore according to Faden and Beauchamp (1986) nonvoluntary. Although intention is argued to be a necessary condition for voluntariness it is not sufficient. In the example of a mugger who says, 'your money or your life', the person

being threatened may be able to make an intentional choice whereby he is able to weigh up the pros and cons of the situation and deliberately decide to hand over his wallet. However, the fact that he made an intentional decision to hand over his wallet does not mean it was voluntary as it was completely controlled by the mugger's threat. Some theories of voluntariness mistakenly conflate intentional action with voluntary action. Graham (2010), for example, assumes that voluntariness is merely the correspondence of a person's will with a person's action and that a decision is voluntary if it is what a person wants from the choices available to them. This flawed conceptualisation of voluntariness neglects the second necessary constituent of voluntariness: control (Nelson et al., 2011). In the 'money or your life' example, Graham (2010) argues that it is possible for a person to voluntarily hand over their wallet. While handing over one's wallet may be intentional it can never be voluntary (according to Nelson et al.'s (2011) conceptualisation) as the mugger almost completely controls the other person thereby eliminating the possibility of a voluntary decision being made.

The second condition of voluntariness identified is control, more specifically, freedom from controlling influences (Faden & Beauchamp, 1986; Nelson et al., 2011). Wall (2001, p. 130) argues that "voluntariness is the degree of control that an agent has over his own behavior". This is not to say that a voluntary choice requires the chooser to control all potentially causal influences. All decisions are made within the context of multiple, often conflicting, social, cultural, political, economic and personal influences. All these influences exert degrees of control; it is only those influences that are substantially controlling that have the potential to negate voluntariness (Nelson et al., 2011).

Whether an influence is substantially controlling or not depends on a 'threshold of irresistibility' and the 'welcomness' of the influence (Faden & Beauchamp, 1986). The welcomness and resistibility of an influence are inherently subjective. They can only be determined subjectively by the person being influenced. Welcomness refers to the extent to which the person being influenced (a) wants to receive (be exposed to) the influence (e.g., payment) and (b) wants to accept the influence in return for a specified action (e.g.,

payment in return for trial participation) (Faden & Beauchamp, 1986). If an influence is welcome, the person being influenced (a) wants to or is happy to be exposed to the influence (e.g., payment) and (b) wants to accept the influence in return for a specified action (e.g., payment in return for trial participation). Bearing in mind that the welcomness of an influence is entirely subjective, an example of a welcome influence may be if person K, a university student, is invited to participate in a Professor's research project. Person K does not find the research requirements objectionable in any way, she is interested in the research topic and she could really use the R50 payment. As such, the influence (payment) is welcomed as person K wants to receive it and wants to accept it in return for research participation. If an influence is unwelcome, on the other hand, the person being influenced (a) does not want to be exposed to the influence (e.g., a threat of harm) or (b) may want to be exposed to the influence (e.g., payment) but does not want to accept the influence in return for a specified action (e.g., payment in return for research participation). An offer of a favourable good such as R150 (influence) may be something a person *wants to receive* but not something they *want to accept in return for research participation* as they judge the burdens of participation outweigh the benefit of the R150 reward. Generally, Faden and Beauchamp (1986) argue that all welcomed influences are 'compatible with substantial noncontrol' and voluntary consent.

In addition to being welcomed or unwelcomed an influence can also be resistible or irresistible (Faden & Beauchamp, 1986). An influence is deemed resistible if a person wants to resist it and is able to do so. An influence is deemed irresistible if a person wants to resist it but cannot. Unwelcome influences reduce voluntariness when they become impossible to resist. It is important to note that irresistible means that a person *cannot* resist it, not that a person chooses not to resist it. A person may decide not to resist an unwelcomed and resistible influence, resulting in a voluntary decision. Even if the influence is just barely resisted it is still possible for the action to be voluntary (Nelson et al., 2011). An example of an unwelcome and irresistible influence provided by Birnbacher (2009) (Chapter 2 – section 2.4.) is of person L who is lost in a desert and is dying from dehydration when she is offered a glass of water in return for a 'disproportionately high sum of money'. The offer of water in return for

disproportionately high payment is unwelcome, as person L wants to receive the water but does not *want* to accept it in return for payment. Person L however agrees as she finds the offer irresistible, she has no meaningful choice if she wishes to avoid dehydration and eventually death.

Whether an influence is controlling or not depends on the extent to which the person being influenced experiences it as welcome and resistible. If an influence is welcomed by the person being influenced, control by others is not an issue and it is compatible with a voluntary informed consent (Faden & Beauchamp, 1986). While unwelcomed influences are only 'compatible with substantial noncontrol' if they can be resisted (Faden & Beauchamp, 1986). If an influence is unwelcomed and irresistible the resultant action will be nonvoluntary. A fully noncontrolled act then means that the action has not been subject to an unwelcomed influence, or that it has been subject to an unwelcomed influence that was resistible (Faden & Beauchamp, 1986). A fully controlled act, on the other hand, means that the actions of a person are "entirely dominated by the will of another" person through an unwelcomed and irresistible influence (Faden & Beauchamp, 1986, p. 258).

1.2 No acceptable alternative

Another value-neutral conceptualisation of voluntariness states that consent cannot be considered voluntary if it is made because of a lack of acceptable alternatives (Olsaretti, 1998). According to Olsaretti (1998) a decision may be deemed 'free' if it is not subject to the influences of other people. A decision however may only be deemed 'voluntary' if an acceptable alternative is available or, in the absence of an acceptable alternative, if a person would have made a given decision had an acceptable alternative been available (Olsaretti, 1998). A decision should therefore be considered nonvoluntary if it is made because no other acceptable alternative is available. According to this conceptualisation, if a desperately ill patient is approached to enroll in an experimental treatment trial, her decision to participate because standard treatments are proving ineffective may be 'free' but not 'voluntary' (according to Olsaretti's (1998) conceptualisation). Alternatives are

deemed unacceptable when they involve a loss of wellbeing (Colburn, 2008). Whether an action is voluntary or not therefore depends on the reasons for which a person acted (Colburn, 2008). When assessing whether an act is voluntary or not, both objective alternatives (do acceptable alternatives exist?) and subjective alternatives (does the person deciding believe that acceptable alternatives exist?) need to be considered. As such, Colburn (2008) concludes that the awareness of alternatives (knowing what alternatives exist) and being well informed about those alternatives (so that their acceptability may be judged) is essential for voluntary choice. Improving a person's awareness of alternatives and ensuring they are well informed about those alternatives will increase their potential to make a voluntary choice (Colburn, 2008). In light of this conceptualisation, Swift (2011, p. 46) suggests that in order to determine whether research participation is voluntary or not, research participants should be asked "whether they feel they have any acceptable alternative other than to say yes to entering a trial when it is offered, and whether they would have declined the trial offer if such an alternative had existed".

Wertheimer (2012) criticises this conceptualisation for being open to too many disputes over details. For example, is a decision nonvoluntary if the decision-maker mistakenly believes there are no acceptable alternatives, or, how unfavourable does an alternative have to be for it to be deemed unacceptable, and is this an objective or subjective judgment (Wertheimer, 2012)? A further criticism is that most research conducted with developing country research participants would not be considered voluntary according to this conceptualisation (Wertheimer, 2012). For example, enrolment in an HIV prevention trial in a developing country context may mean access to a higher standard of care than is available in the local public health clinics. This access to better standards of care would, according to Olsaretti (1998), leave the potential participant with no acceptable alternative to research participation.

2. Moralised Accounts of Voluntariness of Consent to Research

2.1 Legal model of voluntary consent

Appelbaum et al. (2009a) adopt a moralised account of voluntary consent by turning to the legal doctrine of informed consent. Appelbaum et al. (2011) argue that *a priori* approaches to the conceptualisation of voluntariness (cf. Faden & Beauchamp, 1986; Nelson et al., 2011) that begin with an *a priori* principle of voluntariness and delineate the necessary and sufficient conditions of that principle, are of little use to researchers attempting to understand the implications of the requirement that consent must be voluntary to be valid. Appelbaum et al. (2011) argue that a more useful approach is to examine how voluntariness is understood in terms of the law in the context of informed consent.

Appelbaum et al. (2009a) state that for legal purposes a decision "is presumed to be voluntary if no evidence exists that someone else has unduly influenced it or coerced the person deciding" (p. 32). According to the legal definition, consent is presumed voluntary even if it is influenced by the consenter's internal determinations (e.g., values or emotions) or external circumstances (e.g., poverty or illness). Consent is even presumed voluntary, according to the law, if one person has exerted a controlling influence over another or has made other alternatives unacceptable if the first person's actions are legitimate.

Appelbaum et al. (2009a) hypothesise that a decision is nonvoluntary only if it is subject to an influence that is external, intentional, illegitimate and causally linked to the choice of the research participant. Firstly, according to Appelbaum et al.'s (2009a) conceptualisation, for a decision to be nonvoluntary it must be subject to an influence that comes from outside of the person deciding. The influence must be exerted by another person. Internal determinations such as panic or uncertainty may alter a person's ability to make a decision in line with their desires or lead to unwise decisions but they cannot make a choice nonvoluntary (Appelbaum et al., 2009a). In addition to being external, the

influence also has to be intentional. It must result from the intentional action of another person who means to influence a person's decision in a certain way (Appelbaum et al., 2009a). People influence others' decisions all the time, but if it is not that person's intention to influence another person's decision in a certain way, that influence is not sufficient to make the decision nonvoluntary (Appelbaum et al., 2009a). Furthermore, situational constraints such as poverty may influence a person's choice or even limit their range of options but cannot impair the voluntariness of a decision as they do not involve the intentional action of another person. Appelbaum et al. (2009a) however stress that situational constraints can make people more susceptible to intentional influences or make those influences harder to identify. While many people intentionally influence others' decisions, the impact of such external, intentional influences on voluntariness is not problematic unless they are illegitimate (Appelbaum et al., 2009a). That is, the person exerting the influence does not have the right to act in that way (Appelbaum et al., 2009a). Appelbaum et al. (2009a) give the example of how it may be legitimate for a wife to threaten a husband with divorce if he does not get treatment for his drug addiction by enrolling in a research study (the wife is acting within her rights and in doing so is not violating any of her husband's rights). It would however never be legitimate for a physician to threaten a patient with abandonment if he fails to enroll in a research study (because physicians have a nonwaivable fiduciary obligation to their patients). Finally, to invalidate a decision an influence must be causally linked to the person's choice (Appelbaum et al., 2009a). If the external, intentional and illegitimate influence does not actually cause a particular decision to be made, the decision cannot be considered nonvoluntary (Appelbaum et al., 2009a).

Appelbaum et al. (2009a) provide a useful moralised account of voluntariness rooted in the legal doctrine of informed consent. However a potential criticism is that they uncritically adopt the legal definition of voluntary informed consent (Wertheimer, 2012). Appelbaum et al. (2009a) do not explain why the legal model is appropriate for the ethical analysis of voluntariness. Wertheimer's (2012) recent work attempts to explain why this legal model of voluntariness is defensible from an ethical point of view, as discussed below.

2.2 Voluntariness, validity and moral legitimacy

While acknowledging that voluntariness can logically be defined in value-neutral terms, Wertheimer (2012) argues that value-neutral accounts of voluntariness fail to explain when and why nonvoluntariness compromises the validity of consent. Wertheimer (2012) proposes that only a moralised account of voluntariness can explain how a person's consent is nonvoluntary in a way that invalidates their consent.

As a starting point Wertheimer (2012) assumes that for research to be ethical it requires participants to provide valid consent and for consent to be valid it must be voluntary. Wertheimer (2012) refers to this as the *validity requires voluntariness principle*. Furthermore, Wertheimer (2012) distinguishes between different uses of the term voluntariness. First, he identifies $\text{nonvoluntariness}_{\text{descriptive}}$ as being used "simply to convey information about one's choice, situation, or motivation" (Wertheimer, 2012, p. 6). Second, Wertheimer (2012) identifies $\text{nonvoluntariness}_{\text{responsibility}}$ which has moral force and implies that a person should or should not be held responsible/liable for their actions because they were performed nonvoluntarily. Lastly, Wertheimer (2012) uses $\text{nonvoluntariness}_{\text{consent}}$ to imply that a person acts nonvoluntarily in a way that renders their consent invalid. Value-neutral accounts claim that $\text{nonvoluntariness}_{\text{descriptive}}$ always entails $\text{nonvoluntariness}_{\text{responsibility}}$ or $\text{nonvoluntariness}_{\text{consent}}$. Wertheimer (2012) however disagrees and argues that examining the moral legitimacy of a decision reveals that even if a decision is $\text{nonvoluntary}_{\text{descriptive}}$ it can still be $\text{voluntary}_{\text{consent}}$. That is, $\text{nonvoluntariness}_{\text{descriptive}}$ is a necessary but not sufficient condition of $\text{nonvoluntariness}_{\text{consent}}$.

Essentially Wertheimer (2012) argues that the problem with value-neutral accounts of voluntariness is that they are preoccupied with whether a decision can be reasonably described as voluntary ($\text{voluntary}_{\text{descriptive}}$). The issue is not whether the decision can be described as nonvoluntary (they often can) but whether the decision is nonvoluntary in a way that renders consent invalid ($\text{nonvoluntary}_{\text{consent}}$). Wertheimer's (2012) premise is

that there are many situations in which researchers should treat a volunteer's consent as valid (and voluntary) even when that consent could be regarded as nonvoluntary according to value-neutral accounts.

An example provided by Appelbaum et al. (2009a) can be used to illustrate this point. Person M is a drug addict. Person M's wife says she will leave him unless he gets treatment for his drug addiction by enrolling in person N's drug treatment trial. According to Olsaretti's (1998) conceptualisation of voluntariness, (assuming person M does not want his wife to leave him), person M has no acceptable alternative but to enroll in the drug treatment trial. Consent would therefore be nonvoluntary. According to Nelson et al.'s (2011) conceptualisation of voluntariness, person M has been exposed to a controlling influence from his wife. Again, according to this conceptualisation consent would be nonvoluntary. The legal model of voluntariness (cf. Appelbaum et al., 2009a) however regards consent as "nonvoluntary and invalid only if the pressures on the consenter are morally illegitimate" (Wertheimer, 2012, p. 15). In the above example, consent would be considered voluntary and valid according to the legal model, despite the pressure exerted by person M's wife. This is because the law views this pressure as legitimate as person M's wife is acting within her rights as a spouse and not violating any of her husband's rights. The law would even consider consent valid if the researcher knew that person M only consented because of the threat (Wertheimer, 2012).

To substantiate using the legal model for the ethical analysis of voluntariness, Wertheimer (2012) is tasked with explaining how consent should be considered valid despite being made in the presence of no acceptable alternatives or controlling influences, and how such consent can be treated as voluntary.

Wertheimer (2012) draws on both a deontological and a consequentialist argument in order to explain why consent should be considered valid in certain cases despite being nonvoluntary according to value-neutral accounts ($\text{nonvoluntary}_{\text{descriptive}}$). First, from a deontological perspective, a person's positive autonomy is respected by allowing them to authorise interventions on their own behalf but a person's negative autonomy is protected

by ensuring that their authorisation is informed and voluntary to prevent them from authorising interventions to which they do not truly agree (Wertheimer, 2012). Wertheimer (2012) explains that it is impossible to simultaneously enhance respect for both the positive and negative dimensions of autonomy or to get the balance right between the two. Attempts to enhance positive autonomy reveal that a plausible account of autonomy has to operate from within the non-ideal world (a world with poverty and illness etc.) in which people find themselves and in which a person's right to autonomy is defined in relation to other people's right to autonomy (as in the case of person M's wife) (Wertheimer, 2012). Second, from a consequentialist perspective, a person's voluntary consent is seen as necessary to protect that person from unwanted interventions that do not advance their interests and a person's consent is seen as sufficient to authorise interventions in order to advance their interests (Wertheimer, 2012). It is erroneous to view consent as invalid or nontransformative because one has no acceptable alternative (Wertheimer, 2012). For example, if person O were to find himself in a desperate situation where he is stricken by illness or poverty, he would need to be able to authorise interventions that would advance his wellbeing within that situation (Wertheimer, 2012). While it is in a person's interest to be the recipient of legitimate proposals that enhance their wellbeing (such as surgery or employment), it is not in their interest to receive extortionate threats (Wertheimer, 2012). While voluntary consent should be considered valid and transformative in welfare-enhancing propositions it should not be considered binding or transformative in the face of extortionate threats such as a mugger who says 'your money or your life' (Wertheimer, 2012). If the '*validity requires voluntariness principle*' is accepted, claiming that no acceptable alternatives or controlling influences compromise voluntariness would prevent people from entering into welfare-improving transactions (Wertheimer, 2012).

As such, excluding cases in which people are actually coerced by a threat of harm to consent to research, Wertheimer (2012) views most concerns about the voluntariness of consent to research as unfounded. Wertheimer (2012) argues that assumptions as to what constitutes voluntary consent in other areas of life also apply to consent to research participation. If a lack of acceptable alternatives or exertion of controlling influences does

not invalidate consent in other domains of life, it should not be seen to compromise the voluntariness or validity of consent to research. For example, if poverty does not negate consent to employment and serious illness does not void consent to medical treatment then such circumstances, alone, should not be seen to invalidate consent to research (Wertheimer, 2012). Similarly, if offering an incentive in the form of a higher salary to undertake a more demanding or even riskier job does not compromise the voluntariness or validity of a person's consent to employment, there is no reason to believe that incentives in the form of payment or medical treatment may render consent to research nonvoluntary (Wertheimer, 2012). Even controlling influences such as threats made by a third party are not seen to compromise voluntariness if they are legitimate (as in the case of person M above) (Wertheimer, 2012).

Essentially, Wertheimer (2012) argues that no value-neutral account alone can ever appropriately demonstrate that consent in any given situation is voluntary and valid. Nelson et al. (2011) state that "whether an external influence is morally legitimate is conceptually and morally distinct from whether the action taken in response to that influence is voluntary" or not (p. 27). What they mean is that even a legitimate controlling influence such as a policeman threatening a robber, 'surrender or I will shoot' will result in the surrender being nonvoluntary. In response Wertheimer (2012) argues that if such a value-neutral account of voluntariness is adopted then the '*validity requires voluntariness principle*' will have to be discarded and it will need to be determined when and how nonvoluntary actions can still be considered valid. On the other hand, if the '*validity requires voluntariness principle*' is retained "a moralised account of voluntariness in which the voluntariness of a person's consent turns on the legitimacy of the *means* by which their consent is solicited" will have to be adopted (Wertheimer, 2012 p. 27). Whether consent is deemed to be nonvoluntary by value-neutral accounts or voluntary by other accounts, researchers will still be tasked with determining whether such consent should be regarded as valid and this, according to Wertheimer (2012), can only be done by means of a moral analysis.

3. Voluntary Consent as a Legal and Moral Imperative

Miles and Huberman (1994) define a conceptualisation as a framework that "explains, either graphically or in narrative form, the main things to be studied – the key factors, concepts, or variables – and the presumed relationships among them" (p. 18). The purpose of constructing a new conceptualisation of voluntariness is to provide a way of understanding the voluntariness of consent that addresses the gaps in previous conceptualisations.

The value-neutral account of voluntariness advocated by Faden and Beauchamp (1986), Beauchamp and Childress (2009) and Nelson et al. (2011) provides a comprehensive general theory of voluntariness. Moralised accounts of voluntariness (cf. Appelbaum et al., 2009a; Wertheimer, 2012) on the other hand, stress that researchers should only be concerned with voluntariness insofar as it prevents valid informed consent from being obtained. According to moralised accounts, voluntary informed consent should be understood as consent that is free from illegitimate controlling influences of others as it is only such influences that make consent invalid from a legal perspective. Linking voluntariness with the validity of consent is practically useful as it allows researchers to determine when concerns about voluntariness are relevant or not. For this reason, a moralised account of voluntariness will be adopted in this study.

A consequence of adopting such a moralised account of voluntariness is that it renders most concerns about the voluntariness of consent to research expressed by ethicists, researchers and participants themselves (i.e., lack of alternatives) inconsequential. Bull and Lindegger (2011) argue that both Nelson et al.'s (2011) value-neutral account and Appelbaum et al.'s (2009a) moralised account of voluntariness do not pay enough attention to research participant's subjective experience of voluntariness. Internal and contextual conditions may impact participants' subjective perceptions of voluntariness. For example, a desperately ill patient's desire to acquire a potentially effective research intervention may lead to the belief that they have no other choice and that their consent was nonvoluntary. Psychological theory has repeatedly demonstrated the link between

beliefs and perceived behavioural control and behaviour (cf. Ajzen, 2001). Bull and Lindegger (2011) argue that in addition to ensuring that there is no objective evidence of controlling influences from others, "researchers committed to ensuring that participants have made a voluntary consent decision about consenting to research also have a general obligation to assess whether participants themselves consider that they have voluntarily consented to research, and to facilitate voluntary decision-making" (p. 27).

The conceptualisation of voluntariness adopted in this study attempts to take into account both researchers' legal imperative to obtain voluntary and valid informed consent (cf. Appelbaum et al., 2009a; Wertheimer, 2012,) and researchers' moral imperative to ensure that consent is perceived as voluntary by the person providing consent (cf. Bull & Lindegger, 2011).

The conceptualisation of voluntariness described below assumes that the requirements of adequate disclosure of information, capacity to consent and understanding have been met (cf. Barsdorf & Wassenaar, 2005).

3.1 Legal imperative

According to the legal doctrine of informed consent, consent is considered voluntary if it is free from the controlling influences of others (Appelbaum et al., 2009a; General Medical Council, 2010). The majority of ethical guidelines stress that problematic influences from another person are what compromise voluntary consent. For example, the Nuremburg Code (1949) states that voluntary consent should be free from the influences of others as it states "without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion" (p. 1). Likewise, the Belmont Report emphasises that voluntariness requires freedom from "coercion and undue influence" (NBAC, 1979, p. 7). The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guidelines for Good Clinical Practice (ICH GCP) (1996, p. 15) states that voluntary consent requires "that neither the investigator, nor the trial staff, should coerce or unduly influence a

subject to participate or continue to participate in a trial" (Principle 4.8.3). Similarly, Guideline 4 of the Council for International Organizations of Medical Sciences (CIOMS) (2002) International Ethical Guidelines for Biomedical Research Involving Human Subjects stresses that actions of another person such as "coercion, undue influence or inducement, or intimidation" may compromise the voluntariness of consent (p. 32). The US Department of Health and Human Services Regulations for the Protection of Human Research Subjects (45 CFR 46) (The Common Rule) section 46.116 also states that voluntary consent requires freedom from "coercion or undue influence" (p. 7).

For the purposes of this study then consent will be considered voluntary (and subsequently valid) if it is free from controlling influences of others. While this definition of voluntariness is similar to the definitions provided by Beauchamp and Childress (2009), Faden and Beauchamp (1986) and Nelson et al. (2011), elaboration of what makes an influence controlling is significantly different. The conceptualisation described below borrows from and builds on the work of Faden and Beauchamp (1986), Appelbaum et al. (2009a) and Wertheimer (2012).

Every decision is made in the context of competing influences. While all influences affect decision-making, only some control decision-making in a way that constrains voluntariness. The present conceptualisation of voluntariness assumes that all influences fall into the categories of non-controlling influences and potentially controlling influences (see Figure 2).

Non-controlling influences consist of influences such as a person's socio-economic situation, illness, social roles/power differentials, culture/beliefs and internal determinations. Potentially controlling influences, on the other hand, are influences exerted by other people. Only potentially controlling influences have the ability to undermine the voluntariness of consent. This conceptualisation is in line with the legal doctrine of informed consent in which consent is "presumed voluntarary if no evidence exists that someone else has unduly influenced it or coerced the person deciding" (Appelbaum et al., 2009a, p. 30). As such, the circumstances of the potential research

participant (including their pre-existing values, beliefs, psychological state, social role, financial situation and physical wellbeing) will be accepted exactly as they are (cf. Feinberg, 1986). Against those background circumstances it will be determined whether the potential research participant's consent decision was voluntary or whether another person intervened to undermine it (Feinberg, 1986).

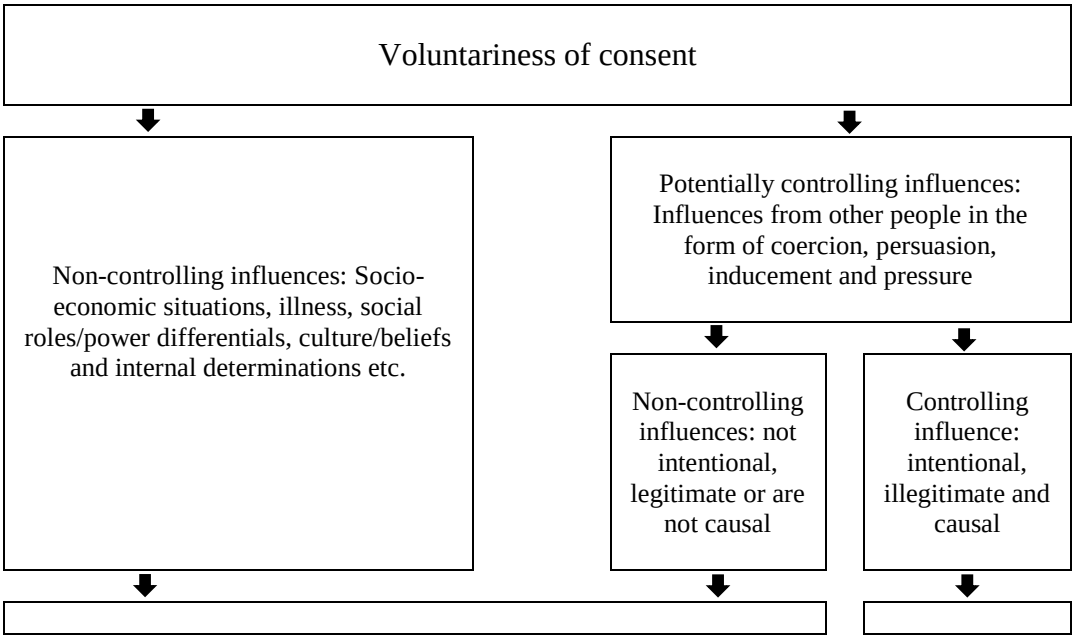
Potentially controlling influences from other people can be exerted through coercion, persuasion, inducement and pressure. For the purpose of this study coercion is understood to occur if one person "intentionally and successfully influences another by presenting a credible threat of unwanted and avoidable harm so severe that the [research participant] is unable to resist acting to avoid it" (Faden & Beauchamp, 1986, p. 261). Persuasion occurs when the persuader 'intentionally and successfully' draws "the [research participant's] attention to reasons for acceptance of the desired perspective" (Faden & Beauchamp, 1986, p. 348). In persuasion the research participant is free to accept or decline the opinion advocated by the persuader. Pressure captures the range of influences (excluding inducements) that fall between the extremes of coercion and persuasion. While inducements are a type of pressure according to this typology, their centrality in debates about voluntariness suggest they deserve special attention and are subsequently allocated a category of their own. An inducement is an undertaking by one person to provide another with a benefit to which they are not otherwise entitled in return for research participation (Appelbaum et al., 2009a).

Whether any of these potentially controlling influences are actually experienced as controlling or not for a particular person can be determined by examining the intentionality, legitimacy and causality of the influence (cf. Appelbaum et al., 2009a). An influence from another person will only be considered controlling if it is intentional, illegitimate and causally linked to the choice of the research participation (Appelbaum et al., 2009a).

For an influence to be intentional the decision-maker must perceive it to result from the deliberate action of another person who means to influence their decision in a certain way

(Appelbaum et al., 2009a). An influence is illegitimate if the person exerting the influence does not have the right to exert that influence or if by exerting that influence they are violating the decision-maker's rights (Appelbaum et al., 2009a; Wertheimer, 2012). Finally, to be controlling, the intentional and illegitimate influence has to actually cause a particular decision to be made (Appelbaum et al., 2009a).

In terms of controlling influences this conceptualisation does not attempt to establish any generalisable rules of thumb. So while it may be possible to generalise that persuasion will never be controlling, that is not the intention. The intention is to provide a means of assessing whether an influence is controlling for a particular decision-maker. What may constitute an illegitimate or causal influence to one person may not be so for the next. This conceptualisation of voluntariness is therefore based on the subjective experience of the decision-maker. Furthermore, Nelson et al. (2011, p. 13) note "that which is voluntary *in fact* is to be distinguished from that which is perceived as voluntary by the person who decides or acts". Potentially controlling influences are not always evident to the decision-maker, and controlling influences are sometimes perceived as non-controlling or vice versa. For example, deception is a controlling influence but as it is unlikely to be visible to the decision-maker it may go undetected. Therefore it is only the decision-maker's perception of potentially controlling influences that can actually be assessed.



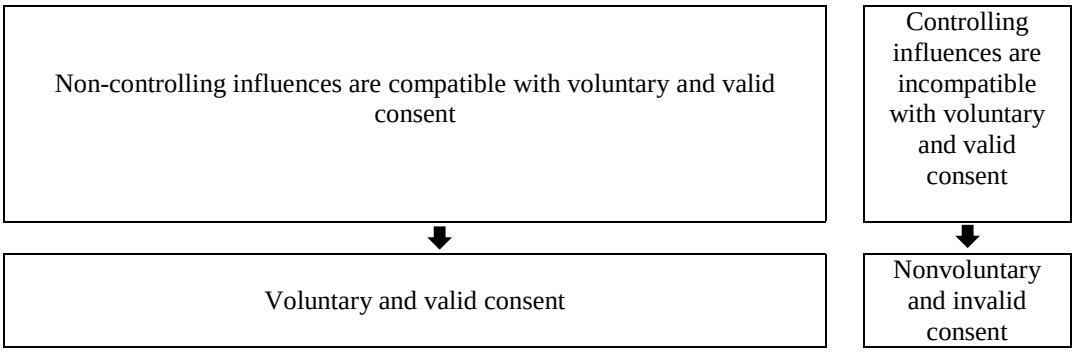


Figure 2. Conceptualisation of voluntariness adopted in this study

The conceptualisation adopted in this study draws on a moralised account of voluntariness based on the legal doctrine of informed consent (cf. Appelbaum et al., 2009a; Wertheimer, 2012). That is, only controlling (intentional, illegitimate and causal) influences from other people have the potential to compromise voluntariness in way that renders consent invalid. The primary concern of this study is therefore to determine whether consent is voluntary and valid according to these criteria. A secondary concern, however, is also to determine whether participants have a subjective experience of voluntariness.

3.2 Moral imperative

In addition to obtaining voluntary consent, the moral imperative states that researchers should also ensure that the participants themselves feel that their consent is voluntary. The participant's personal interpretation of the voluntariness of their consent decision is referred to as *perceived voluntariness*. If consent is nonvoluntary according to the legal doctrine it is invalid. However if consent is not perceived as voluntary it may still be voluntary and valid according to the legal doctrine of informed consent. While only controlling influences are considered important in terms of the validity of consent, in addition to potentially controlling influences of others, non-controlling influences (from conditions) (Figure 2 above) also affect participant's perceived voluntariness. Ideally, research participants should provide voluntary and valid consent (free from intentional, illegitimate and causal influences of others i.e., a controlling influence) and perceive

themselves to have provided voluntary consent. There are however a further three possible scenarios: The second scenario is for a participant to provide nonvoluntary and invalid consent (as a result of exposure to a controlling influence) and perceives their consent to be nonvoluntary. The third scenario is for a participant to provide voluntary and valid consent (free from controlling influences) yet perceive their consent to be nonvoluntary. Consent provided in the absence of acceptable alternatives may be an example of this scenario. Lastly, it is possible for consent to be nonvoluntary and invalid yet perceived as voluntary. Consent provided in the presence of deception may be an example of this last scenario.

4. Summary

It is frequently claimed in research ethics literature that there have been few attempts to conceptualise the voluntariness of consent to research (cf. Agrawal, 2003; Appelbaum et al., 2009a). While no single widely agreed upon conceptualisation exists, several theorists have made substantial contributions to the conceptualisation of voluntariness of consent to research. Conceptualisations of voluntariness can be separated into value-neutral and moralised accounts. Value-neutral conceptualisations maintain that a person acts nonvoluntarily if exposed to a controlling influence (cf. Nelson et al., 2011) or if they have no acceptable alternatives (cf. Olsaretti, 1998). On the other hand, moralised accounts (cf. Appelbaum et al., 2009; Wertheimer, 2012) maintain that the voluntariness of a person's consent depends on the legitimacy of the means by which their consent is obtained. This conceptual review, along with the literature review (Chapter 2), forms the basis of the conceptualisation of voluntariness adopted in this study. This conceptualisation attempted to illustrate the importance of both actual and perceived voluntariness and determine when informed consent to research should be considered nonvoluntary and invalid. Now that an appropriate conceptual framework has hopefully been delineated, the following chapter will review existing empirical voluntariness assessment instruments and outline the development of an instrument to assess voluntariness in terms of the conceptual framework outlined above.

Chapter 5: Measuring Voluntariness of Consent to Research

The second objective of this study is to determine how the voluntariness of consent to research has been assessed in the past and identify whether existing instruments can be used to facilitate the construction of items that assess voluntariness of consent according to the conceptualisation adopted in the previous chapter.

1. Method

In order to identify empirical studies of voluntariness of consent to research a comprehensive search of electronic databases including PubMed, EBSCO Host, SwetWise, PsychINFO and Science Direct was conducted. The search covered English language articles, published in any year up to 2013, describing or using structured instruments designed to systematically collect data on, or assess the voluntariness of, research participants' consent. The search terms 'testing/assessing', 'voluntariness', 'consent' and 'research' were used.

For empirical studies to be included in this review they had to describe or use instruments designed to systematically collect data on or assess the voluntariness of research participants' consent. In addition, the instrument had to be described in sufficient detail to allow review of the content, administration and psychometric properties. Papers describing how voluntariness of consent to research ought to be assessed (cf. Stiles et al., 2011; Swift, 2011) were excluded from the review, as were papers that did not assess voluntariness directly. Many empirical studies, for example, assess voluntariness of consent as a subcategory of understanding (cf. Minnies et al., 2008) thereby merely assessing knowledge that consent is supposed to be voluntary and not whether the participant experienced consent as voluntary or not. Other studies assume high rates of voluntariness when lower rates of consent are present (cf. van der Veer, 2011). Papers assessing related concepts, such as autonomy (cf. Nyika et al., 2009), were also excluded.

The search and selection process yielded 15 papers describing or using different voluntariness assessment instruments. Twelve of the 15 papers included the instrument used or described instruments' content in adequate detail. Authors of the remaining three papers in which the instruments were not published or described in sufficient detail were contacted and agreed to share their voluntariness assessment measures for inclusion in this review.

For each of the 15 papers, information was extracted on the nature of the study (aims, method and findings); administration (administration time, format and sample); psychometric properties of the instrument (reliability, validity, standardisation and norming procedures) and domains assessed (content analysis was used to assign each individual item in each instrument to the domain of voluntariness it attempted to assess). The coding scheme was tabulated and refined until each item for each instrument was assigned to a domain (Bryman, 2004).

2. Results

2.1 Voluntariness studies reviewed

The aims, methods and findings of the 15 studies reviewed are reported below.

2.1.1 Abdool Karim et al. (*1998*)

Abdool Karim, Abdool Karim, Coovadia and Susser (1998) studied the voluntariness of informed consent to HIV testing within a South African perinatal HIV transmission study. A standardised questionnaire using a before and after design was developed and administered to ascertain the degree to which consent to HIV testing was truly informed and voluntary (Abdool Karim et al., 1998). Fifty-six women were enrolled in the evaluation study group who received group counselling on HIV/AIDS and the perinatal HIV transmission study. These women completed a pre- and post-counselling questionnaire. An additional 56 women were enrolled in a sensitisation control group

who only received the post-counselling questionnaire (Abdool Karim et al., 1998). The questionnaire contained four open-ended questions on voluntariness: (1) Did you feel you were compelled to participate in the study? (2) Will care be compromised if you do not participate? (3) Having agreed to participate in the study, do you think that you have the freedom to quit the study at any time? (4) Will the hospital allow you to quit? (Abdool Karim et al., 1998).

The study found that 84% of the study group and 93% of the control group felt compelled to participate in the study (Abdool Karim et al., 1998). Thirty-two percent and 23% of the study and control groups respectively believed that the care they received would be compromised if they did not participate in the study. The majority of participants in the study (93%) and control (88%) groups believed they could withdraw from the study at any time (Abdool Karim et al., 1998). Despite this, only 2% of the study group and no one in the control group thought that the hospital would allow them to leave the study.

2.1.2 Joubert et al. (*2003*)

Joubert, Steinberg, van der Ryst and Chikobvu (2003) studied the voluntariness of consent to HIV testing and subsequent participation of 92 women in a South African clinical trial on the effect of vitamin A on mother to child transmission of HIV. A structured questionnaire was developed to investigate whether consent to HIV testing and clinical trial enrolment was informed and voluntary (Joubert et al., 2003). The instrument assessed voluntariness in terms of the following items: (1) Did you want to participate in the trial? (2) Did you feel forced to take part in the trial? (3) Can you withdraw from the trial at anytime? (4) Do you feel that you will no longer get good medical care when you stop taking part in the trial? (Joubert et al., 2003).

The study found that 98.9% of the 92 participants said that they wanted to participate in the trial and only 3.3% felt forced to participate (Joubert et al., 2003). However, only 24.2% believed that they could withdraw from the study at any time and 92.3% felt that they would no longer receive good medical care if they withdrew from the trial (Joubert

et al., 2003). However, it was in fact likely that if participants withdrew from the study alternative care would not be available because at the time the study was conducted alternative HIV treatment for pregnant women was not widely available (Joubert et al., 2003).

2.1.3 Barsdorf and Wassenaar (*2005*)

In 2005 Barsdorf and Wassenaar assessed racial differences in public perceptions of the voluntariness of medical research participation. One hundred and eleven employees (39 Blacks, 37 Indians and 35 Whites) were sampled from two South African companies (Barsdorf & Wassenaar, 2005). The instrument contained 20 fixed choice questions that elicited respondents' perceptions of voluntariness by assessing participants' perceived freedom to provide or refuse consent.

The authors defined voluntariness as "situation specific experience of willed action with freedom from coercion or control by others in decision-making" (Barsdorf & Wassenaar, 2005, p. 1089). Possible scores of perceived voluntariness ranged from 20–40, with Black respondents ($\overline{x}$ = 34.48) scoring significantly lower than Indian ($\overline{x}$ = 36.67) or White respondents ($\overline{x}$ = 37.77). The authors hypothesised that Black respondents' lower perceived voluntariness was a result of historical disadvantage, vulnerability and knowledge of previous unethical studies being conducted on Black South Africans (Barsdorf & Wassenaar, 2005).

2.1.4 Kass et al. (*2005*)

To explore research participants' motivation, understanding and voluntariness of enrolment in clinical trials, Kass et al. (2005) interviewed a convenience sample of 26 research participants (25 women and 1 man) from six infectious disease randomised control trials in two African countries and the Caribbean. Five open-ended questions in the interview field guide explored voluntariness: (1) Did you consult with anyone before you decided to join this study? (2) Why did you decide to join the study? (3) Do family

and friends know about your participation in this study? Did you tell them about it? Why or why not? How did they react? (4) Do you feel like any person forced you to be in this study? If so, whom? How did they do that? (5) If you want to stop being in this study, do you think that is possible?

All 19 participants who were asked if their participation was voluntary indicated that it was. Eight participants said that no one forced them to participate and/ or that the decision to participate was up to them. Four participants believed that they were unable to withdraw and a further two said that it would be unreasonable to leave the study because of the study benefits. Seventeen of 18 respondents who were asked about their motivation for research enrolment indicated that the opportunity to receive better medical care was the primary incentive for participation (Kass et al., 2005). The authors however acknowledge that this does not necessarily undermine voluntary consent.

2.1.5 Pace et al. (*2005*)

In 2005, Pace and colleagues studied the quality of informed consent in a randomised HIV control trial in Chulalongkorn Hospital, Bangkok, Thailand (Pace et al., 2005). The voluntariness of consent was assessed though 10 survey questions. Elements of voluntariness assessed included: the primary reason participants joined the study, the ease with which participants could have refused enrolment, the pressure participants felt from their circumstances and from other people to join the study, and whether other people helped the participants decide to enroll.

The study found high levels of voluntariness among those studied. Of the 141 participants surveyed, 76% said that it would have been moderately or very easy to refuse enrolment and 71% were aware that they could withdraw from the study at any time. In terms of pressure from others to enroll in the study, 73% felt no pressure from others, 12% felt a small and moderate amount of pressure respectively and only 3% reported a great deal of pressure from others to enroll. Of the 38 respondents who reported feeling pressure from others, that pressure was felt to come from friends (n=21), from family (n=10) and a

personal physician (*n*=3) (Pace et al., 2005). Pressure to enroll was reported by 43 participants due to their health related circumstances. Of these, 10 respondents reported that the trial was the only way for them to access treatment. Neither age, gender, disease progression, access to health care nor previous research experience were found to predict the voluntariness of participation (Pace et al., 2005). The authors conclude that it is possible to obtain voluntary and valid informed consent from developing country research participants.

2.1.6 Marshall et al. (*2006*)

Marshall et al. (2006) conducted the first large-scale cross-cultural study of voluntary participation in genetic epidemiological research on hypertension among 348 US participants and 307 Nigerian participants. A survey instrument was designed to assess a range of topics related to informed consent, including voluntary participation (Marshall et al., 2006). The voluntariness component of the questionnaire assessed whether participants were told participation was voluntary, whether they felt pressure to participate and whether they understood they could withdraw from the study. Married female participants were also asked if they sought permission from their husbands and Nigerian participants were asked if they sought permission from a community leader. In-depth interviews were also conducted with 10% of survey respondents to explore issues in greater detail (Marshall et al., 2006).

The majority of participants (94%) were informed that their participation was voluntary; similarly 99% said that they did not feel pressured to enroll (Marshall et al., 2006). In Nigeria, 67% of participants were told they could withdraw from the study compared to 97% in the US (Marshall et al., 2006). The study also found that no Nigerian participants sought permission from community leaders to join the study but that 47% of Nigerian women sought permission from their husbands to join the study compared to none in the US arm (Marshall et al., 2006).

2.1.7 Agrawal et al. (*2006*)

Agrawal et al. (2006) studied the decision-making process of 163 patients, enrolling in five phase 1 oncology studies across the US. Literature searches and existing instruments were reviewed to develop a survey instrument.Cognitive and behavioural pretesting was conducted before the instrument was finalised. Sixty-one questions assessed eight domains, of which voluntariness was one. The instrument requested information on whether others influenced the participant's decision and whether the participant felt pressure from family, the clinical researchers or their advancing cancer (Agrawal et al., 2006).

The majority (80%) of respondents reported feeling no pressure from family to enroll in the study, while 11% reported a little pressure and 9% reported a moderate or large amount of pressure from family. The authors also found that more educated participants were significantly less likely to feel pressure from family members to participate. Similarly, 87% reported experiencing pressure from a clinical researcher while only 6% and 7% reported feeling little or moderate to a lot of pressure respectively (Agrawal et al., 2006). In contrast 75% of respondents reported experiencing moderate to a lot of pressure to enroll in the study because their cancer was advancing (Agrawal et al., 2006). The authors conclude that the high levels of voluntariness found in this study may be due to the fact that the majority of these participants had high incomes, health insurance and were well educated and as such less vulnerable to social pressures (Agrawal et al., 2006).

2.1.8 Manafa et al. (*2007*)

Manafa et al. (2007) studied the voluntariness of participation and satisfaction with the consent process of 88 respondents participating in an antiretroviral therapy clinical trial in Nigeria. A semi-structured questionnaire was developed and pretested on a sample similar to the respondents.The 60-item instrument contained 10 items on voluntariness. To assess voluntariness, participants were asked to describe how they decided to participate, who and what was involved in their decision, whether others influenced their

decision, their feelings about participation, whether they were hesitant at any point and how the uncertainty was resolved and what motivated them to participate (Manafa et al., 2007). A Likert scale of voluntariness was developed by the researchers to assess and rate participants' descriptions of how they decided to participate and who they consulted (Manafa et al., 2007). Pressure from others and personal feelings of having a choice or no choice about participation were rated (Manafa et al., 2007).

In terms of pressure from others, the authors found that 9.1% of respondents reported extreme pressure from others to participate, 37.5% reported mild pressure, 17% reported strong encouragement and 19.3% reported no pressure or encouragement. Two participants felt threatened by the way they were informed about the trial by study staff. In terms of what the authors call personal pressure to participate, the study found that 55.6% of participants believed they had no other choice, 25% believed that it was wise to participate, 11.4% believed that participation was to their advantage and 8% felt that they were not advantaged by participation (Manafa et al., 2007).

2.1.9 Mangset et al. (*2008*)

Mangset, Forde, Nessa, Berge and Bruun Wyller (2008) administered a semi-structured qualitative interview to 11 stroke patients in two Norwegian hospitals to explore experience with informed consent and their ability to give valid consent. In terms of voluntariness, the instrument assessed whether participants were fully aware that participation was voluntary, the presence of improper pressure, whether family members' opinions were important in participants' consent decisions as well as the effect time pressure and anxiety after a stroke had on voluntary consent.

The authors found that the participants did not understand the concept of voluntariness. However, no participants reported being exposed to improper pressure to participate but time pressure and anxiety after the stroke was found to prevent a voluntary choice from being made (Mangset et al., 2008).

2.1.10 Appelbaum et al. (*2009b*)

In 2009 Appelbaum et al. (2009b) studied the voluntariness of consent to research of 88 participants enrolled in research on substance abuse, cancer, HIV, interventional cardiology and depression in a major university medical centre in the US. Based on a conceptualisation of voluntariness rooted in the law of informed consent and interviews with researchers and participants, the authors developed an instrument to assess participants' motivations for participating and their experiences of offers, pressures and threats. A modified version of the MacArthur Perceived Coercion Scale was also administered in which participants had to indicate whether five statements about the voluntariness of consent were true or false. A voluntariness ladder was also administered which asked participants to rate the voluntariness of consent from 1 – not at all voluntary to 10 – completely voluntary and explain why the particular rating was selected (Appelbaum et al., 2009b).

The study found that the possibility of better care, trust in the researchers and the reputation of the host institution were the most frequently cited motivations for participation. Thirty-five percent of respondents reported the presence of offers, 3% reported pressure and none reported the presence of threats. In addition the majority of respondents who reported the presence of offers rated them as having little influence on their research participation. None of the respondents who reported pressure to participate rated that pressure as having any importance in their decision to participate. The study also found that the majority of participants rated their participation as completely voluntary and did not perceive their decision to have been coerced in any way (Appelbaum et al., 2009b).

2.1.11 Lansimies-Antikainen et al. (*2010*)

Lansimies-Antikainen et al. (2010) studied informed consent to research participation among 1324 research participants in a randomised control trial on exercise and diet in Finland. The population based questionnaire survey contained 44 items, 14 of which

assessed voluntariness and decision-making. Items on voluntariness included awareness of the right to withdraw, freedom from coercion, participants' ability to participate of their own free will, people affecting decision-making and participants' discussions with these people.

Ninety-nine percent of respondents surveyed reported that they enrolled in the study of their own free will and without the presence of coercion. Five percent of participants were not aware of their right to withdraw. The majority of participants (74%) did not discuss their participation with anyone other than the researcher. When asked who or what has the potential to influence their decision to participate, 77% and 25% reported that the researcher and their families respectively can influence participation. Other influences on research participation included: an opportunity to get extra treatments/examinations (82%), willingness to help others (69%) and willingness to please research personnel (10%) (Lansimies-Antikainen et al., 2010).

2.1.12 Dugosh et al. (*2010*)

Dugosh, Festinger, Croft and Marlow (2010) developed the Coercion Assessment Scale (CAS) to measure the coercive pressure that 84 substance abusing criminal offenders experienced with regard to research participation. The 8-item Likert scale assessed participants' agreement with the following statements: *I felt like I was talked into entering the study*; *It was entirely my choice to enter the study*; *I entered the study even though I did not want to*; *I felt that I could not say no to entering the study*; *I thought it would look bad to my case manager/counselor if I did not enter*; *I felt the judge would like it if I entered the study*; *I felt that entering the study would help my court case*; *and I entered the study mainly for financial reasons* (Dugosh et al., 2010).

The study found that the majority of respondents did not feel like they were talked into entering the study (94%) but 96% did not feel that it was entirely their choice to enter the study. However, only 3% entered the study even though they did not want to. The majority of respondents did not feel that they could not say no to entering the study

(82%) and 88% did not think it would look bad to their case manager/counsellor if they did not enter. Over half the respondents felt that the judge would like it if they entered the study (57%) and that entering the study would help their court case (56%). Lastly 38% said to some degree that financial incentives were the main reason for entering the study (Dugosh et al., 2010).

2.1.13 Miller et al. (*2011*) *and Miller and Nelson* (*2012*)

In order to address the need for a valid and reliable instrument to assess the voluntariness of consent Miller et al. (2011) developed the Decision Making Control Instrument (DMCI) to measure the perceived voluntariness of 219 parents enrolling their seriously ill children in research or treatment protocols. After a careful conceptualisation of voluntary consent as intentional and free from controlling influences, the authors generated an experimental item pool from existing instruments and focus group discussions (Miller et al., 2011). The final instrument took the form of a nine-item Likert scale which assessed participants' agreement with the following statements: *I was powerless in the face of this decision*; *Someone took this decision away from me*; *I made this decision*; *I was passive in the face of this decision*; *The decision about the protocol was inappropriately influenced by others*; *I was not in control of this decision*; *Others made this decision against my wishes*; *I was not the one to choose*; *and the decision was up to me*. Most participants scored high on perceived voluntariness (Miller et al., 2011). Lower perceived voluntariness was associated with lower education, male gender, minority status, and a lack of previous experience making a similar decision (Miller & Nelson, 2012).

2.1.14 Kiguba et al. (*2012*)

Kiguba, Kutyabami, Kiwuwa, Katabira and Sewankambo (2012) assessed the quality of informed consent in eight HIV treatment clinical trials and seven HIV and TB related observational studies approved by the School of Medicine Research and Ethics Committee at the College of Health Sciences, Makerere University, Kampala, Uganda. A semi-structured questionnaire was used to collect quantitative data from 600 research

participants (Kiguba et al., 2012). The study found that only 5% of participants surveyed felt pressured to participate but 40.2% believed that refusal to participate would affect their regular medical care (Kiguba et al., 2012). Furthermore 33.7% did not know that they could voluntarily withdraw from the studies (Kiguba et al., 2012).

2.1.15 Horwitz et al. (*2013*)

Horwitz, Roberts and Seal et al. (2013) assessed the voluntariness of 429 participants enrolled in an HIV vaccine trial in Haiti. The voluntariness assessment contained five open-ended questions about "1) the purpose of the study, 2) reasons for volunteering, 3) hopes for study participation, 4) 'bad things' that could happen, and 5) reaction if something in the study made them unhappy" (Horwitz et al., 2013, p.222). Horwitz et al. (2013) described 11% of their sample as making a less than voluntary decision to enroll. The authors identified the following factors as indicating nonvoluntary consent, "1) perceived financial benefit; 2) expectation of an effective HIV vaccine, 3) belief that doctors would never expose participants to risk, and 4) belief that a 'volunteer' is a person who has the willpower to remain in a study" (Horwitz et al., 2013, p.222).

2.2 Administration characteristics

The administration characteristics of each study were assessed in terms of location and sample, format and administration time and timing of administration. These results are summarised in Table 1.

2.2.1 Location and sample

The review found that studies of voluntariness of consent to research appear to be equally distributed between the developed and developing world. Eight studies were conducted in developing countries (Abdool Karim et al., 1998; Barsdorf & Wassenaar, 2005; Horwitz et al., 2013; Joubert et al., 2003; Kass et al., 2005; Kiguba et al., 2012; Manafa et al., 2007; Pace et al., 2005) and six were conducted in developed countries (Agrawal et al.,

2006; Appelbaum et al., 2009; Dugosh et al., 2010; Lansimies-Antikainen et al., 2010; Mangset et al.. 2008; Miller et al. 2011). The study by Marshall et al. (2006) was conducted in both developed and developing countries.

The sample sizes ranged from 11 participants in Mangset et al.'s (2008) qualitative study to 1195 participants in Lansimies-Antikainen et al.'s (2010) population based survey. The mean number of participants sampled was 276.5, the median number of participants was 112 and the mode for all participants sampled was 88. The sample size of the four papers that reported instruments designed to assess voluntariness directly ranged from 88 (Appelbaum et al., 2009; Dugosh et al., 2010) to 429 (Horwitz et al., 2013).

The majority of studies reviewed (n=11) used a single study population which limits the generalisability of the study findings. Only four studies used participants sampled from different types of clinical trials (Appelbaum et al., 2009b; Kass et al., 2005) or similar trials in different countries (Marshall et al., 2006), thereby allowing findings to transcended the research area and geographic region.

Fourteen of the 15 studies assessed voluntariness of consent in the context of actual clinical research participation. Only one study (Barsdorf & Wassenaar, 2005) assessed hypothetical research participation.

2.2.2 Format

Of the 15 papers reviewed only four papers described instruments designed specifically to assess the voluntariness of consent to research (cf. Appelbaum et al., 2009b; Dugosh et al., 2010; Horwitz et al., 2013; Miller et al., 2011). The remaining 11 papers merely assessed voluntariness as part of a broader study of informed consent.

Three studies reviewed used qualitative methodology and in-depth interviews to collect data on voluntariness (Horwitz et al., 2013; Kass et al., 2005; Mangset et al., 2008). The other 12 studies used quantitative methods, two of which made use of a Likert scale

(Dugosh et al., 2010; Miller et al., 2011), the remaining nine made use of a structured questionnaire and one study used both (Appelbaum et al., 2009). Three of the four studies using instruments developed exclusively to assess voluntariness made use of Likert scales (Appelbaum et al., 2009; Dugosh et al., 2010; Miller et al., 2011).

2.2.3 Administration time and timing of administration

The majority of papers (*n*=9) did not report how long the instruments took to administer. The administration time for the remaining six instruments ranged from five minutes (Dugosh et al., 2010) to 60 minutes (Mangset et al., 2008).

Of the 15 studies conducted with actual trial participants, two did not report when the instrument was administered (Abdool Karim et al., 1998; Joubert et al., 2003). Eight studies administered the instrument immediately after consent had been obtained (Agrawal et al., 2006; Appelbaum et al., 2009; Dugosh et al., 2010; Horwitz et al., 2013; Kiguba et al., 2012; Manafa et al., 2007; Miller et al., 2011; Pace et al., 2005) and the remaining four studies administered the instruments once the host study was already underway (Kass et al., 2005; Lansimies-Antikainen et al., 2010; Mangset et al., 2008; Marshall et al., 2006).

Table 1

Administration characteristics

Source	Administration Characteristics				
	Location	Sample	Format	Administration Time	Timing of administration
Abdool Karim et al. (1998)	South Africa	112 women in a perinatal HIV transmission study (56 in the study group and	Structured questionnaire designed to assess whether consent was informed and voluntary,	Not reported	Not reported

		56 in the control group)	containing four open-ended questions on voluntariness		
Joubert et al. (2003)	South Africa	92 women in a clinical trial on the effect of vitamin A on mother-to child transmission of HIV	Structured questionnaire designed to test whether consent was informed and voluntary, containing four closed ended questions on voluntariness	Not reported	Not reported
Barsdorf & Wassenaar (2005)	South Africa	111 employees (39 Blacks, 37 Indians and 35 Whites)	Twenty fixed choice questions elicited respondents' perceptions of voluntariness	10-15 minutes	Not applicable
Kass et al. (2005)	Two African countries and the Caribbean	Convenience sample of 26 research participants (25 women and 1 man) from six infectious disease randomised control trials	Five semi-structured open ended questions in the in depth interview field guide explored voluntariness	30-40 minutes	Once the host study was already underway
Pace et al. (2005)	Thailand	141 participants in a randomised HIV control trial	Survey instrument containing 67 mostly multiple choice questions assessed six domains of informed consent of which four questions assessed voluntariness	33 minutes	Immediately after consent was obtained for the host study
Marshall et al. (2006)	US and Nigeria	348 US participants and 307 Nigerian participants in a genetic epidemiological	A survey instrument designed to assess a range of topics related to informed consent including	Not reported	Once the host study was already underway

		study on hypertension	voluntary participation		
Agrawal et al. (2006)	US	163 patients enrolling in five phase 1 oncology studies	Sixty-one questions assessed 8 domains of patients' decision-making process, of which voluntariness was one	Not reported	Immediately after consent was obtained for the host study
Manafa et al. (2007)	Nigeria	88 respondents participating in an antiretroviral therapy clinical trial	The 60 item semi-structured questionnaire contained ten items on voluntariness	Not reported	Immediately after consent was obtained for the host study
Mangset et al. (2008)	Norway	11 hospitalised stroke patients	Semi-structured qualitative interview	20-60 minutes	Once the host study was already underway
Appelbaum et al. (2009)	US	88 participants in one of five clinical trials on substance abuse, cancer, HIV, interventional cardiology and depression	A structured questionnaire requesting demographic data, motivations for participating and experiences of offers, pressures and threats. The Mac Arthur Perceived Coercion Scale and a Voluntariness Ladder were also administered	30 minutes	Immediately after consent was obtained for the host study
Lansimies-Antikainen et al. (2010)	Finland	1324 participants in a RCT on the effects of regular physical exercise and diet	A population based questionnaire survey containing 44 questions of which 14 assessed voluntariness and decision-making	Not reported	Once the host study was already underway

Dugosh et al. (2010)	US	88 substance abusing criminal offenders enrolled in a RCT of misdemeanour drug court clients	Eight item likert scale	5 minutes	Immediately after consent was obtained for the host study
Miller et al. (2011)	US	219 parents of seriously ill children enrolled in either a research or treatment protocol in a tertiary care paediatric hospital	Nine item likert scale	Not reported	Immediately after consent was obtained for the host study
Kiguba et al. (2012)	Uganda	600 participants in 8 HIV treatment clinical trials and 7 HIV and TB related observational studies	Semi-structured interviewer-administered questionnaire	Not reported	Immediately after consent was obtained for the host study
Horwitz et al. (2013)	Hati	429 participants enrolled in the STEP HIV vaccine trial	Five open ended questions	Not reported	Immediately after consent was obtained for the host study

2.3 Psychometric properties

The psychometric properties of the 15 studies were reviewed. The findings are detailed below and summarised in Table 2.

Of the 12 quantitative studies, only five reported attempts to establish the psychometric properties of the instruments used. For the purposes of this review, failure to report psychometric properties was assumed to be equated with a failure to establish them. Establishing the psychometric properties of an instrument is important to ensure that the measure of a concept is stable and reliable, that the instrument measures what it is designed to measure and to ensure that the interpretation of individuals' scores is

appropriate (Bryman, 2004; Cicchetti, 1994; Urbina, 2004). Psychometric properties to consider when evaluating or selecting an instrument include standardisation and norming procedures, reliability and validity (Cicchetti, 1994).

2.3.1 Standardisation and norming procedures

The standardisation of psychological instruments refers to firstly, the uniformity of administration, scoring and interpretation procedures used (Urbina, 2004). Secondly, it refers to the use of standards for evaluating results (Urbina, 2004). Averages and variability of scores are calculated for a certain group of individuals. These scores become the standard against which the performance of other individuals, to whom the instrument will be administered in the future, is assessed (Urbina, 2004). Norms refer to the average score of a standarisation sample (Cicchetti, 1994). The standardisation of an instrument makes it possible to develop norms for the valid interpretation of the meaning of a given individual's score on the standardised instrument (Cicchetti, 1994). None of the studies reviewed here reported any standardisation or norming procedures. Although the objectivity of the assessment process relies on the standardisation and norming procedures employed (Urbina, 2004), Cicchetti (1994) notes that numerous assessment instruments used in both the behavioural and medical sciences are not standardised on appropriate demographic variables.

2.3.2 Reliability

The second psychometric element evaluated was reliability. Reliability refers to the degree to which a measure of a concept is stable or trustworthy (Bryman, 2004). In terms of psychological assessment, reliability is based on the consistency and accuracy of the results of the assessment process. In order to determine the reliability of an instrument, three aspects of reliability need to be assessed: equivalence, stability and internal consistency.

Equivalence refers to the amount of agreement between two or more instruments that are administered at the same time or, when subjectivity is involved in scoring items, the level of agreement between two or more scorers (Bryman, 2004). Equivalence may be assessed by calculating alternate-form reliability and/or inter-rater reliability. Alternate-form reliability refers to the administration of two or more different forms of the test (with the same purpose but different content) to the same group of individuals to determine the error attributable to variability related to the content of specific items and not the construct measured (Urbina, 2004). Scores from different administrations are correlated to determine an alternate-form reliability coefficient (r_{11}) (Urbina, 2004). Delayed alternate-form reliability can also be calculated when different forms of the instrument are administered at different time intervals (Urbina, 2004). When evaluating alternate-form reliability a very high and positive correlation (0.90 or higher) between various forms of the instrument suggests that content sampling error does not have a major influence on individuals' scores (Urbina, 2004). Scorer or inter-rater reliability refers to the correlation between scores assigned by two or more scorers who independently score the same assessments for the same individuals (Bryman, 2004). When evaluating scorer reliability, a very high and positive correlation (0.90 or higher) suggests that the portion of error accounted for by inter-scorer differences is 10% or less (Urbina, 2004).

Stability is when the same or similar scores are obtained on repeated administration of the instrument to the same group of respondents (Bryman, 2004). Stability is determined by calculating test-retest reliability. Test-retest reliability refers to the correlation between scores obtained from administering the instrument to a group of individuals on two different occasions, separated by a period of time (Howell et al., 2005). Test-retest reliability provides an indication of how likely scores are to vary due to time sampling error (Urbina, 2004). The correlation between the scores on the two administrations produces a test-retest reliability coefficient (r_{tt}). In general when evaluating stability coefficients, below 0.40 is considered poor, 0.40–0.59 is considered fair, 0.60–0.74 is good and over 0.75 is excellent (Cicchetti, 1994).

Lastly, internal consistency refers to the degree of consistency across test items. Internal consistency is evaluated by calculating the instrument's coefficient alpha (α), split-half reliability, inter-item correlation and/or item-total correlation (Howell et al., 2005). When an instrument's coefficient alpha is below 0.70, levels of internal consistency are deemed unacceptable. Internal consistency is considered fair when the coefficient alpha is between 0.70–0.79, good when it is between .80–.98 and excellent when it is above .90 (Cicchetti, 1994). Split-half reliability is calculated by splitting an instrument in two halves and administering it to a group of individuals creating two scores for each individual (Urbina 2004). The correlation between these two scores is the split-half reliability coefficient (r_{hh}) (Urbina, 2004). Inter-item correlation is the comparison of correlations between all pairs of items assessing the same construct by calculating the mean of all paired correlations. Item-total correlation is the average of the total score for each item using the average inter-item correlations (Howell et al., 2005). In general reliability correlations of 0.70 and higher are considered acceptable (Urbina, 2004).

Debate exists over which reliability assessment is most important. Generally test-retest and scorer reliability are considered essential but others argue that the coefficient alpha is preferable as an instrument with high test-retest reliability and low coefficient alpha should not be taken to be reliable (Cicchetti, 1994).

The four studies that reported attempts to assess reliability revealed acceptable levels of internal consistency (Barsdorf & Wassenaar, 2005; Dugosh et al., 2010; Miller et al., 2011) and equivalence (Manafa et al., 2007). None of the studies reviewed however attempted to establish all three aspects of reliability (equivalence, stability and internal consistency). The 20 question voluntariness instrument Barsdorf and Wassenaar (2005) used in the study of public perceptions of perceived voluntariness in hypothetical research participation had an acceptable level of internal consistency (alpha coefficient of .80). The Coercion Assessment Scale developed by Dugosh et al. (2010) had an inter-item correlation ranging between 0.04 and 0.43 and item-total correlations ranging from 0.25–0.61. Their coefficient alpha was 0.66 (Dugosh et al., 2010). According to Cicchetti (1994), when an instrument's coefficient alpha is below 0.70, levels of internal

consistency are deemed unacceptable. The internal consistency for Miller et al.'s (2011) Decision Making Control Instrument was high (0.83) and the item total correlations ranged from 0.34–0.70. In Manafa et al.'s (2007) study of voluntariness, the instrument's inter-rater reliability was determined using Spearman rank correlation. An 81% agreement was obtained for 'pressure from others' and 89% for 'personal feelings of choice'. This indicates that the portion of error accounted for by inter-scorer differences was low. The majority (n=7) of the 11 quantitative studies reviewed did not report attempts to assess the reliability of the instruments used.

2.3.3 Validity

The final psychometric property assessed was validity. Validity refers to whether an instrument measures the construct it is designed to measure (Bryman, 2004). Validity is generally considered the most complex psychometric property to assess. When evaluating an instrument to assess the voluntariness of consent to research both internal and external validity should be considered.

Internal validity can be assessed by determining the content and face validity of an instrument. Content validity refers to the extent to which an instrument fully assesses the construct of interest or the extent to which items are about the construct being measured (Bryman, 2004). The development of a content valid instrument can be attained by deriving content from several sources such as the literature and expert experiences and piloting large pools of items (Cicchetti, 1994). A review of the instrument by several experts for readability, clarity and completeness is a good way to ensure content validity is achieved (Bryman, 2004). Face validity is a component of content validity. Determining face validity is an intuitive process in which reviewers assess whether the instrument appears to measure what it claims to measure (Bryman, 2004).

External validity can be assessed in several ways. Criterion-related validity measures difference as predicted by some criterion such as gender (Bryman, 2004). Concurrent validity refers to the extent to which a new instrument correlates with an existing

instrument developed to measure the same or similar constructs (Cicchetti, 1994). When evaluating concurrent validity, a correlation of 1.00 would indicate that the new instrument is almost identical to the existing one, while a correlation of 0 would call the content validity of the construct being measured into question (Cicchetti, 1994). A rule of thumb for determining an ideal correlation is difficult as much depends on what the new instrument attempts to measure in relation to the existing one (Cicchetti, 1994). Construct validity, on the other hand, is the degree to which an instrument measures the construct that it intends to measure. Determining construct validity requires the researcher to refine their theory throughout the research in order to make prediction about instrument scores in various contexts (Bryman, 2004). Predictive validity is achieved when a measure can be used to predict performance on some future criterion. Discriminant validity is the extent to which the responses to instrument items are performed differentially by specifically selected samples in accordance with hypothesised relationships among the samples selected (Cicchetti, 1994). For an instrument to have discriminant validity it should reveal no relation to unrelated constructs but should be highly correlated to similar measures (convergent validity). Lastly, factorial validity is central to establishing the validity of latent constructs and it requires that convergent and divergent validity be calculated. Convergent validity is determined by comparing an instrument to measures of the same concept developed through different methods (Bryman, 2004).

Four of the 12 quantitative studies reviewed attempted to establish the validity of the instrument used (Barsdorf & Wassenaar, 2005; Dugosh et al., 2010; Lansimies-Antikainen et al., 2010; Miller et al., 2011). Two of the four studies reporting validity only assessed internal validity. The face validity of Barsdorf and Wassenaar's (2005) instrument was established by getting four independent behavioural researchers to review the instrument. Lansimies-Antikainen et al. (2010) obtained their instrument's content validity from the literature and content experts. To determine the discriminant validity of the Coercion Assessment Scale, Dugosh et al. (2010) compared the scores of participants in the 'consent as usual' condition to those of participants in the 'research intermediary' condition. Comparison was not statistically significant but participants in the 'research intermediary' condition had lower scores (Dugosh et al., 2010), providing preliminary

support for the instrument's ability to distinguish between two groups of individuals that 'theoretically' should have experienced different levels of coercion. The preliminary construct validity of Miller et al.'s (2011) Decision Making Control Instrument was tested by examining associations with subscales measuring affect, self-efficacy and trust. The authors concluded that similar correlations with the three subscales supported initial construct validity of the instrument (Miller et al., 2011).

Table 2

Psychometric properties

Source	Psychometric Properties	
	Reliability	Validity
Abdool Karim et al. (1998)	Not reported	Not reported
Joubert et al. (2003)	Not reported	Not reported
Barsdorf and Wassenaar (2005)	The 20 voluntariness questions had acceptable internal reliability (alpha coefficient of 0.80).	The validity of the scale was not formally assessed. However face validity was established by getting four independent behavioural researchers to review the instrument.
Kass et al. (2005)	Not applicable	Not applicable
Pace et al. (2005)	Not reported	Not reported
Marshall et al. (2006)	Not reported	Not reported
Agrawal et al. (2006)	Not reported	Not reported

Manafa et al. (2007)	Inter-rater reliability was determined using Spearman rank correlation, an 81% agreement was obtained for pressure from others and 89% for personal feelings of choice.	Not reported
Mangset et al. (2008)	Not applicable	Not applicable
Appelbaum et al. (2009)	Not reported	Not reported
Lansimies-Antikainen et al. (2010)	Not adequately assessed	Content validity was obtained from the literature and content experts
Dugosh et al. (2010)	Inter-item correlation ranged between .04 and 0.43; Item-total correlations ranged from 0.25-0.61 and the coefficient alpha was 0.66	To determine discriminative validity CAS scores of participants in the consent as usual condition were compared to those of participants in the research intermediary condition. Comparison was not statistically significant by but clients in the research intermediary condition had lower CAS scores
Miller et al. (2011)	Internal consistency for the instrument was high (0.83). Item total correlations ranged from 0.34-0.70.	Preliminary construct validity was tested by examining associations with subscales measuring affect, self-efficacy and trust. The similar correlations with the three subscales supports initial construct validity of the instrument.
Kiguba et al. (2012)	Not reported	Not reported

2.4 Domains assessed

The domains assessed by each instrument were then identified. The construct being measured must be adequately defined so that the domains that constitute it can be identified. This review however found that only six of the 15 studies reviewed attempted

to explicitly define how voluntariness was conceptualised for the purposes of the study. Barsdorf and Wassenaar (2005) define voluntariness as the "situation specific experience of willed action with freedom from coercion or control by others in decision-making" (p. 1089). Despite explicitly stating the definition of voluntariness adopted in their study, Barsdorf and Wassenaar (2005) used questions unrelated to voluntariness (such as beliefs about how researchers choose participants and who respondents feel should be included in research) to get an overall voluntariness rating (cf. Pace & Emanuel, 2005). Pace et al. (2005) define voluntariness as "how freely [participants] made the enrollment decision" (p. 9). Beauchamp and Childress' (2009) definition of voluntariness was adopted by Manafa et al. (2007) whereby "a person acts voluntarily to the degree that he or she wills the action without being under the control of another's influence" (p. 26). Manafa et al. (2007) however fail to distinguish between different sources and types of pressure. That is, the findings fail to explain who the 'others' that exert pressure are and whether pressure constitutes coercion or only subtler forms of pressure. Appelbaum et al. (2009b) define a decision as voluntary when it is free from external, intentional, illegitimate and causal influences and Lansimies-Antikainen et al. (2010) define voluntariness as the "capacity to make a choice freely and in the absence of coercion" (p. 61). Lastly, Miller et al. (2011) state that "for an action to be voluntary it must be intentional and not under a substantial controlling influence" (p. 731), yet their instrument only assesses perceived control of decision-making.

In order for a latent construct such as voluntariness to be measured empirically, it needs to be measured indirectly by identifying and assessing the domains that constitute it. Each item in each of the 15 instruments was coded according to which domain of voluntariness it attempted to assess. Table 3 provides an example of how each instrument was coded and tabulated. The full table generated cannot be included as not all the instruments reviewed are publically available and permission was obtained from the authors to review their instruments but not to quote their specific items.

Table 3

Example of how items were coded into domains of voluntariness

Source	Domains Assessed				
	Forced Participation	Consequences of refusal	Freedom to withdraw	Desire to participate	Informed consent process
Joubert et al. (2003)	Did you feel forced to take part in the trial?	Do you feel that you will no longer get good medical care when you stop taking part in the trial?	Can you withdraw from the trial at any time?	Did you want to participate in the trial?	Were you allowed to ask questions when you decided to take part in the trial?

This large and complicated table of domains of voluntariness was then summarised into Table 4 which delineates the domains assessed and which instruments attempted to assess them. The 15 instruments reviewed assessed 19 domains of voluntariness. It should be noted that these domains were coded inductively from the instruments assessed and do not reflect the authors' conceptualisation of voluntariness. As will be seen, whether some of these domains even constitute voluntariness is debatable.

Four of the 15 instruments reviewed assessed whether participants were informed of the voluntary nature of participation (*n*=2) (cf. Mangset et al., 2008; Marshall et al., 2006) and how this was done during the informed consent process (*n*=2) (cf. Barsdorf & Wassenaar, 2005; Joubert et al., 2003). One instrument assessed participants'knowledge of the study purpose (Horwitz et al., 2013). Three instruments assessed the consequences of refusal (cf. Abdool Karim et al., 1998; Joubert et al., 2003; Kiguba et al., 2012) and seven assessed participants' freedom to withdraw (cf. Abdool Karim et al., 1998; Joubert et al., 2003; Kass et al., 2005; Kiguba et al., 2012; Lansimies-Antikainen et al., 2010; Marshall et al., 2006). Consultation with others regarding participation was assessed by three of the instruments reviewed (cf. Kass et al., 2005; Lansimies-Antikainen et al., 2010; Pace et al., 2005). Seven instruments assessed freedom to choose whether or not to participate (cf. Appelbaum et al., 2009b; Barsdorf & Wassenaar, 2005; Dugosh et al.,

2010; Lansimies-Antikainen et al., 2010; Manafa et al., 2007; Miller et al., 2011; Pace et al., 2005). Freedom to choose is one component of voluntary participation and can be related to the concept of control over the decision-making process, which was assessed by only one instrument (cf. Miller et al., 2011). Only one instrument reviewed assessed desire to participate (cf. Joubert et al., 2003). Five studies assessed motivation to participate (cf. Agrawal et al., 2006; Appelbaum et al., 2009b; Dugosh et al., 2010; Kass et al., 2005; Pace et al., 2005). Six instruments assessed the presence of influences. Influences assessed included: forced participation (*n*=6) (cf. Abdool Karim et al., 1998; Dugosh et al., 2010; Joubert et al., 2003; Kass et al., 2005; Lansimies-Antikainen et al., 2010; Miller et al., 2011), unspecified influences from others (*n*=7) (cf. Agrawal et al., 2006; Appelbaum et al., 2009b; Dugosh et al., 2010; Lansimies-Antikainen et al., 2010; Manafa et al., 2007; Mangset et al., 2008; Miller et al., 2011), unspecified pressure (*n*=3) (cf. Kiguba et al., 2012; Mangset et al., 2008; Marshall et al., 2006), pressure from others (*n*=5) (cf. Agrawal et al., 2006; Appelbaum et al., 2009b; Manafa et al., 2007; Marshall et al., 2006; Pace et al., 2005), pressure from circumstances (*n*=4) (cf. Agrawal et al., 2006; Manafa et al., 2007; Mangset et al. , 2008; Pace et al., 2005) and the presence of threats and offers (*n*=1) (cf. Appelbaum et al., 2009b). Only one instrument assessed the legitimacy of the influence and the importance of the influence in participation (causality) (cf. Appelbaum et al., 2009b). The risks of participation were assessed by Appelbaum et al., 2009b and Horwitz et al., 2013. Horwitz et al. (2013) also assessed the benefits of participation.

Table 4

Domains of voluntariness assessed by instruments reviewed

Domains assessed	Source
Informed of the voluntary nature of participation	Mangset et al., 2008; Marshall et al., 2006
Study purpose	Horwitz et al., 2013
Informed consent process	Barsdorf & Wassenaar, 2005; Joubert et al., 2003; Kiguba et al., 2012

Desire to participate	Joubert et al., 2003
Motivation to participate	Agrawal et al., 2006; Appelbaum et al., 2009; Dugosh et al., 2010; Horwitz et al., 2013; Kass et al., 2005; Pace et al., 2005
Consultation with others	Kass et al., 2005; Lansimies-Antikainen et al., 2010; Pace et al., 2005
Consequences of refusal	Abdool Karim et al., 1998; Joubert et al., 2003; Kiguba et al., 2012
Freedom to withdraw	Abdool Karim et al., 1998; Joubert et al., 2003; Kass et al., 2005; Kiguba et al., 2012; Lansimies-Antikainen et al., 2010; Marshall et al., 2006
Freedom to choose to or not to participate	Appelbaum et al., 2009; Barsdorf & Wassenaar, 2005; Dugosh et al., 2010; Lansimies-Antikainen et al., 2010; Manafa et al., 2007; Miller et al., 2011; Pace et al., 2005
Forced participation	Abdool Karim et al., 1998; Dugosh et al., 2010; Joubert et al., 2003; Kass et al., 2005; Lansimies-Antikainen et al., 2010; Miller et al., 2011
Unspecified influences from others	Agrawal et al., 2006; Appelbaum et al., 2009; Dugosh et al., 2010; Lansimies-Antikainen et al., 2010; Manafa et al., 2007; Mangset et al., 2008; Miller et al., 2011
Pressure:	
a. Unspecified pressure	Kiguba et al., 2012; Mangset et al., 2008; Marshall et al., 2006
b. Pressure from others	Agrawal et al., 2006; Appelbaum et al., 2009; Manafa et al., 2007; Marshall et al., 2006; Pace et al., 2005
c. Pressure from circumstances	Agrawal et al., 2006; Manafa et al., 2007; Mangset et al., 2008; Pace et al., 2005
Threats from others	Appelbaum et al., 2009
Offers from others	Appelbaum et al., 2009
Legitimacy of the influence	Appelbaum et al., 2009
Causality of the influence	Appelbaum et al., 2009
Control	Miller et al., 2011

Risks of participation	Appelbaum et al., 2009; Horwitz et al., 2013
Benefits of participation	Horwitz et al., 2013

3. Discussion

This review provides useful insight into how voluntariness of consent has been assessed to date. The review particularly illustrates ways in which different influences on voluntariness might be identified and measured. In the past, studies of voluntariness have been criticised for focusing largely on research participants from the developing world (cf. Appelbaum et al., 2009b). This review, however, found that studies of voluntariness of consent to research appear to be equally distributed between the developed and developing world. This review also reveals that the majority of studies had small sample sizes and single study populations. This is appropriate given that the primary aims of these studies were to explore the concept of voluntariness, collect preliminary data or pilot instruments and not to make generalisable inferences about a population from a sample. Only one of the studies reviewed used a hypothetical research scenario. This limits the applicability of the findings because what one would do in relation to actual research participation may differ significantly from what they believe they or others may do (cf. Pace & Emanuel, 2005).

The majority of studies used brief quantitative instruments. While this may result in more superficial data being collected it is likely that study staff may favour these over in-depth qualitative measures as they are quick and easy to administer and score and will not delay the consent process. There is also a potential for quantitative instruments to overestimate the measured construct. Previous research on understanding of informed consent, for example, reveals that participants obtain higher scores on quantitative assessment items compared to qualitative assessment items (cf. Lindegger, Milford, Slack, Quayle, Xaba & Vardas, 2006). While qualitative instruments may more accurately reflect the construct being measured (cf. Lindegger et al., 2006), they may be more difficult to administer in terms of time and training of staff and may more easily be administered or scored

incorrectly. As such, when assessing voluntariness of consent it may be advantageous to combine both quantitative and qualitative assessment instruments. Quantitative measure could be administered to all participants and only when concerns about the voluntariness of consent are detected could the qualitative measure be administered to gain an in-depth understanding of how voluntariness was impaired so that remedial action may be taken (Lindegger et al., 2006). Instrument administration time ranged from 5–60 minutes. A shorter administration time may be advantageous in a research context as instruments that are quick to administer may be more easily incorporated into the informed consent process and re-administered throughout studies as participants are re-consented or concerns about voluntariness are raised.

Most studies assessed voluntariness directly after consent was obtained, suggesting that this may be perceived as the optimal administration time. Assessing voluntariness immediately after or as close to the consent decision as possible is advantageous as it removes the risks of other factors (such as trial experiences) altering participants' perceptions of voluntariness. Miller et al. (2011) state that there is a strong possibility that participants' perceptions of voluntariness may change over time and argue that voluntariness assessment instruments should be administered as close to the actual decision as possible. It is possible, for example, that positive trial experiences may encourage participants to take full responsibility for their participation and enhance their perception that participation was voluntary. On the other hand, negative trial experiences may produce feelings of regret and result in participants blaming others for their participation and construe their participation as less than voluntary. Administering the assessment instrument too soon, however, may mean that participants have not had adequate time to reflect on the voluntariness of their consent decision. According to Lansimies-Antikainen et al. (2010), assessing voluntariness a few months after consent has been obtained is optimal as participants are still able to recall the consent process but they have also had experience with the trial and more opportunity to understand and process the implications of voluntary participation.

All existing instruments that assess the voluntariness of consent to research are novel measures that lack well-established validity and reliability. Only five of the 15 studies made preliminary attempts to assess the validity and reliability of the instruments. Failing to establish the reliability of an instrument means that researchers using the instrument to collect data do not know whether the instrument measures the construct in a consistent and accurate manner. Similarly, failing to assess the validity of an instrument means that those administering the instrument have no way of telling whether it measures the construct it is designed to measure (Bryman, 2004).

Furthermore, only six of the 15 studies reviewed attempted to explicitly define how voluntariness was conceptualised for the purposes of the study. Without a clear theoretical underpinning researchers may rely on common sense understandings of voluntariness. This finding reflects the general lack of theory and construct clarity found in the literature on voluntariness of consent. Defining the construct to be measured should be the first step in the development of any new instrument as it guides the generation and selection of items (Miller et al., 2009). Failure to adequately define the construct to be measured prior to instrument development may result in the measurement of domains unrelated to the construct being assessed (voluntariness). Horwitz et al. (2013), for example, state that their finding that 2% of their 429 participants hoped to gain financial benefits or employment after participation potentially indicates compromised voluntariness. Unfortunately, as the authors do not provide any attempt to conceptualise voluntariness it is not evident why or how 'hope to gain financial benefits' undermines voluntariness.

Failure to adequately define voluntariness prior to instrument development may also result in voluntariness of consent being conflated with related constructs such as exploitation, vulnerability, unfortunate circumstances or misunderstandings. While such factors may limit a person's options they do not necessarily undermine voluntariness. Different conceptualisations of factors that impact voluntariness, such as offers and threats, also limit the usefulness of existing measures. This review therefore provides empirical support for Appelbaum et al.'s (2009a) critique that limited conclusions can be

drawn from existing studies of voluntariness as none adopt a shared understanding of voluntariness or use comparable assessment methods.

In addition, many existing voluntariness assessment tools identify the presence of an influence but make no attempt to identify the exact source of the influence or establish the legitimacy of the influence. Failure to identify the exact factor that undermined voluntary consent makes remedial action impossible. Other studies assess participants' knowledge that consent is supposed to be voluntary but fail to determine whether or not it was in fact experienced as voluntary. Furthermore, voluntariness is a latent construct that cannot be measured directly. Voluntariness assessment instruments thus have to measure individuals' self-report of the voluntariness of their consent to research. While necessary, this is not unproblematic as in so far as participants fail to recognise or report problematic influences, the instruments reviewed would not be able to detect them. Lastly, none of the instruments reviewed attempted to assess the voluntariness of potential participants' decision to refuse enrolment. It is conceivable that those who refuse enrolment may have higher levels of voluntariness as they may have been able to resist influences to which they were subjected.

This review reveals the relatively underdeveloped state of empirical research on the voluntariness of consent to research. This is in contrast to the relatively well-developed body of research assessing the 'understanding' component of consent which is much easier to evaluate as it is not a latent construct (Ndebele, Wassenaar, Munalula & Masiye, 2013). Future measures of voluntary consent to research need to be clearly rooted in a theory of voluntariness. Construct clarity should be achieved prior to instrument development. Appropriate psychometric assessment of empirical measures is also required to ensure that reliable and valid measures of voluntary consent to research are developed. While two groups of researchers from the United States have recently taken on this complex task (cf. Appelbaum et al., 2009a; Appelbaum et al., 2009b and Miller et al, 2009; Miller et al, 2011; Nelson et al., 2011), empirical research on the voluntariness of consent to research that adopts the above recommendations is also needed in

developing countries where factors affecting voluntary consent may be markedly different (Nyika et al., 2009).

A review of the literature suggests that this is the first review of empirical measures of voluntary consent. The systematic and standardised nature of the review enhances the validity and reliability of the conclusions reached. The primary limitation of this review is that only published empirical studies of voluntariness of consent to research were reviewed. Grey literature and studies of voluntariness of decision-making in other contexts were therefore excluded. A broader review of empirical studies of voluntariness is needed to establish the generalisability of the findings of this present review.

4. Instrument Development

On the basis of the conceptual review (Chapter 4) and the empirical review (Chapter 5), an instrument to assess the voluntariness of consent to research participation was developed.

The conceptual review and analysis of voluntary informed consent to research (Chapter 4) revealed voluntary consent to consist of a legal and moral imperative. It is a legal imperative that consent be voluntary and valid and a moral imperative that consent be perceived as voluntary by the person providing consent. According to the legal imperative, consent is considered voluntary if it is free from the controlling (intentional, illegitimate and causal) influences of others. According to the moral imperative, research participants also need to have a subjective experience of voluntary consent. If consent is nonvoluntary according to the legal imperative it is invalid. However, if consent is not perceived as voluntary it may still be voluntary and valid according to the legal imperative. Instruments were designed to assess both perceived voluntariness and freedom from controlling (intentional, illegitimate and causal) influences of others.

According to the legal imperative, consent is deemed voluntary and valid if it is free from controlling (intentional, illegitimate and causal) influence of another person. The

following domains will therefore need to be addressed: (1) the presence of influences from other people; (2) the mechanisms through which the influence was exerted; and (3) whether or not the influence was controlling. Several of the studies reviewed assessed these domains. In terms of the presence of influence from other people Agrawal et al. (2006), Appelbaum et al. (2009b), Manafa et al. (2007), Marshall et al. (2006) and Pace et al. (2005) assessed pressure from others and Appelbaum et al. (2009b) assessed threats and offers from others. Appelbaum et al.'s (2009b) instrument however uses the type of influence (e.g., Did anyone threaten you?) as a starting point, it is hypothesised that it may be easier for participants to identify influences if the person exerting the influence is linked to the influence (e.g., Did your partner threaten you?). Only Appelbaum et al. (2009b) attempted to assess the legitimacy of influences. Appelbaum et al. (2009b) assessed legitimacy by asking respondents whether they believed that the influence was fair. Legitimacy concerns the right of a person to act in a certain way and not the perceived fairness of that action (Millum, 2011). As such, it is argued that legitimacy could more appropriately be assessed by asking whether the influencer had the right to act that way or whether the rights of the person being influenced were violated. The South African Revenue Service, for example, has the *right* to coerce the public into paying their taxes through the threat of penalties or legal action even though this action may not be deemed *fair*, as it is only targeted at those registered as taxpayers in the first place. Appelbaum et al. (2009b) assessed causality by getting participants to rate the importance of the influence. It is hypothesised that responses to statements such as 'the influence caused me to participate', ' I would not have participated had the influence not been present' or ' I only participated because of the influence' may be more appropriate phrasing for determining whether the influence actually caused participation or not.

The literature (Chapter 2) and conceptual review (Chapter 4) highlighted the disagreement that exists among experts as to what voluntary consent entails. It is just as likely that voluntariness will have different meanings and implications for different research participants. Assessment of perceived voluntariness then, should include an exploration of what voluntariness means to the research participant and what factors they take into consideration when reflecting on the voluntariness of their consent decision.

While several of the instruments reviewed assess perceived voluntariness, none of the instruments elicit what voluntariness means to the research participant and what they take into consideration when reflecting on the voluntariness of their consent decision. The instruments used by Kass et al. (2005) and Manafa et al. (2007) do however make preliminary attempts to explore participants' own construal of the voluntariness of their participation through open-ended questions. To address this gap, the instrument developed in this study will not only establish participants' perceived voluntariness but also elicit what voluntariness means to the individual participants and what factors they take into consideration when reflecting on the voluntariness of their consent decision.

Stiles et al. (2011) suggests that an assessment of voluntariness should involve the generation of a list of all potential influences relevant to the research population and study context, on the basis of which the researcher "should develop a set of questions to assess the presence and intensity of the impact that these influences" may have on the voluntariness of consent (p. 87). To date, no voluntariness assessment instrument has done this. The instrument developed for this study will attempt to address this gap by systematically exploring all possible influences participants may have been exposed to and the effect these influences had on the voluntariness of the consent decision.

Dugosh et al. (2010) and Miller et al. (2011) have established measures of perceived voluntariness with promising validity and reliability. As the instrument designed by Dugosh et al. (2010) deals specifically with research participants in the criminal justice system, it was not deemed appropriate for use in the present study. The instrument developed by Miller et al. (2011) provides a suitable means with which the convergent validity of a newly-developed measure of voluntariness can be assessed.

4.1 Moral imperative: Assessment of perceived voluntariness

Perceived voluntariness is defined as participant's subjective experience of voluntary consent and is influenced by a multitude of factors such as the participant's background, culture, beliefs, world-view, wellbeing, internal determinations, situational factors,

influences from others and so on. The Voluntariness Narrative Rating Instrument (VNRI) was designed for the present study to assess perceived voluntariness. An existing measure of perceived voluntariness, the Decision Making Control Instrument (DMCI) was included in the battery of instruments to assess the convergent validity of the VNRI.

4.1.1 Voluntariness Narrative Rating Instrument

In order to assess participants' perceived voluntariness of consent, the Voluntariness Narrative Rating Instrument (VNRI) (Appendix 5) was designed to allow participants to describe how they came to enroll in the host research and rate the degree to which they perceive their enrolment as voluntary. To assist the research participants to do this, the VNRI allows the participants to think through what voluntariness means to them by getting the research participants to complete a Nonvoluntary Reference Exercise followed by a Voluntary Reference Exercise. This instrument was adapted from a similar tool developed (but never piloted or used) by Wassenaar (2006) to assess the voluntariness of consent to voluntary HIV counselling and testing (VCT) within a clinical trial.

First, participants are asked to talk about a time in their life when they were forced to make a decision against their will, a decision that they felt was nonvoluntary and rate the voluntariness of that decision using a 10 point scale, with a score of 10 being completely voluntary, a score above 5 being sufficiently voluntary and a score of 1 being completely nonvoluntary [Nonvoluntary Reference Exercise].

Participants are then asked to talk about a time in their life when they made a completely voluntary decision and rate the voluntariness of that decision using the same 10 point scale [Voluntary Reference Exercise].

Once participants have a reference point for a voluntary and nonvoluntary decision from their own personal experience, participants are asked to describe how they came to consent to enroll in the host study [VNRI Narrative]. In addition, participants are asked to share the following elements with the researcher: How they came to be enrolled; why

they decided to participate; how free/voluntary they perceived their participation to be; if any other person influenced their decision; or if any other factor, situation, circumstance influenced their decision to participate. Once the researcher has briefed the participant, as per the above, no further prompts were to be provided. The rationale for this was to allow the participant to tell their story as they wish without the researcher biasing the narrative with prompts which may lead participants to prioritise information they may not otherwise have focused on.

Finally, using their personal nonvoluntary and voluntary ratings as reference points, participants are asked to rate the voluntariness of their participation in the host research using the same 10 point scale [VNRI Rating].

4.1.2 Decision Making Control Instrument

Miller et al.'s (2011) Decision Making Control Instrument (DMCI) (Appendix 6) was included in the instrument battery in order to provide an additional quantitative assessment of perceived voluntariness and to establish the validity of the Voluntariness Narrative Rating Instrument. Although the conceptualisation of voluntariness that underpins the DMCI differs from the conceptualisation of voluntariness adopted in this study (Chapter 4), the DMCI is viewed by the author as being the most valid, reliable and easily administered assessment of perceived voluntariness currently available (Chapter 5). The DMCI ultimately shares the same purpose as the Voluntariness Narrative Rating Instrument – to assess perceived voluntariness of consent. "The DMCI measures the degree to which an individual perceives his or her intentional choice to be voluntary" (Nelson et al., 2011, p. 14). For the purpose of this research a score of 54 will be deemed fully voluntary and a score above 27 will be deemed sufficiently voluntary. Permission to use the DMCI was obtained from the author, Dr Miller (Appendix 1).

4.2 Legal imperative: Freedom from controlling influences of others

The Survey of Influences (Appendix 7) was developed for the present study to measure actual voluntariness or freedom from the controlling influences of others.

4.2.1 Survey of Influences

Construct definition was the first step in the development of the Survey of Influences. Constructs are phenomena that cannot be observed directly (Miller et al., 2009). In order for a construct to be measured it first has to be defined by identifying the elements that constitute it. In this study the construct being measured is voluntariness of consent to research. Construct definition was achieved through a conceptual review and analysis (Chapter 4). Typically, focus groups are used to refine the construct of interest (Bryman, 2004). In this study a conceptual review was used as a proxy for focus group discussions so that the definition of voluntary consent adopted could be based on the conceptualisations of voluntariness developed by experts in the field. The definition of voluntary consent to research was defined in detail in Chapter 4 but will be recapped briefly here. Once the construct of interest has been defined it needs to be operationalised.

The starting point of this study is that it is of primary concern that the legal imperative of obtaining voluntary and valid consent free from the controlling (intentional, illegitimate and causal) influence (cf. Applebaum et al., 2009a) of other people be met. It is of secondary concern that participants also perceive their participation to be voluntary. Furthermore, it was established that perceived voluntariness is not a reliable indicator of actual voluntariness (Chapter 5).

For the purposes of this study consent will be considered voluntary (and subsequently valid) if it is free from controlling influences. All influences fall into the categories of non-controlling influences and potentially controlling influences. Non-controlling influences consist of influences from a person's socio-economic situation, illness, social roles/power differentials, culture/beliefs, internal determinations etc. Potentially

controlling influences on the other hand are influences exerted by other people. Potentially controlling influences from other people can be exerted through coercion, persuasion, inducement and pressure. For the purpose of this study coercion is understood to occur if one person "intentionally and successfully influences another by presenting a credible threat of unwanted and avoidable harm so severe that the [research participant] is unable to resist acting to avoid it" (Faden & Beauchamp, 1986, p. 261). Persuasion occurs when the persuader 'intentionally and successfully' draws "the [research participant's] attention to reasons for acceptance of the desired perspective" (Faden & Beauchamp, 1986, p. 348). In persuasion the research participant is free to accept or decline the opinion advocated by the persuader. Pressure captures the range of influences (excluding inducements) that fall between the extremes of coercion and persuasion. While inducements are a type of pressure according to this typology, their centrality in debates about voluntariness suggests they deserve special attention and are subsequently allocated a category of their own. An inducement is an undertaking by one person to provide another with a benefit to which they are not otherwise entitled in return for research participation (Appelbaum et al., 2009a). Whether any of these potentially controlling influences are actually controlling or not for a particular person can be determined by examining the intentionality, legitimacy and causality of the influence (cf. Appelbaum et al., 2009a). An influence from another person will only be considered controlling if it is intentional, illegitimate and causally linked to the decision of the research participant (Appelbaum et al., 2009a). For an influence to be intentional the decision-maker must perceive it to result from the deliberate action of another person who means to influence their decision in a certain way (Appelbaum et al., 2009a). An influence is illegitimate if the person exerting the influence does not have the right to exert that influence, or if by exerting that influence they are violating the decision-maker's rights (Appelbaum et al., 2009a; Wertheimer, 2012). To be controlling, the intentional and illegitimate influence has to actually cause a particular decision to be made (Appelbaum et al., 2009a). Finally, controlling influences are incompatible with voluntary and valid consent.

Using this conceptual framework each concept was defined and operationalised (linked to specific indicators). Table 5 indicates the definition and operationalisation of each concept.

Table 5

Instrument development

Parent Concept	Concept	Concept Definition	Concept Operationalisation	Further instructions
Non-controlling influences: Influences that are compatible with voluntary and valid consent	Socio-economic conditions	Socio-economic conditions hypothesised to influence research participation in this population were pre-existing illness, limited access to care and treatment and poverty.	I participated because of health reasons/illness I participated because I need health care I participated because I need money	How much did this influence cause you to participate? Would you have participated had this influence not been present?
	Trust	CAPRISA has been operating in the host communities since 2001. Furthermore all host trial participants participated in CAPRISA 004 prior to participating in the host trials. Trust in the research staff was therefore hypothesised to influence participants consent.	I participated because I trust the researchers	How much did this influence cause you to participate? Would you have participated had this influence not been present?
	Internal determin-ations	Internal determination influence all decisions made. Limited access to health care, poverty and social position may leave participants feeling that they have no choice but to participate or that they have to participate to please someone in a position of power.	I participated because I have to please (a) the researchers, (b) my partner, (c) other I participated because I had no other choice I participated because I wanted to	How much did this influence cause you to participate? Would you have participated had this influence not been present?

Potentially controlling influences	Influences exerted by other people have the potential to be controlling	It was hypothesised that the following people may influence participants decision to consent to the host studies: - Partner - Family - Friend - Community leader - Health care provider - Research staff - Employer - Other	Did you talk to X about participation? Did X try to influence you TO participate? Did X try to influence you NOT TO participate? Did X did not try to influence you?	Replace X with: - Partner - Family - Friend - Community leader - Health care provider - Research staff - Employer - Other
Mechanisms through which influences from others are exerted	Coercion	When one person "intentionally and successfully influences another by presenting a credible threat of unwanted and avoidable harm so severe that the [research participant] is unable to resist acting to avoid it" (Faden & Beauchamp, 1986, p. 261).	How did X influence you? - Threat	Replace X with: - Partner - Family - Friend - Community leader - Health care provider - Research staff - Employer - Other
	Persuasion	Persuasion occurs when the persuader 'intentionally and successfully' draws "the [research participant's] attention to reasons for acceptance of the desired perspective" (Faden & Beauchamp, 1986, p. 348).	How did X influence you? - Advice	Replace X with: - Partner - Family - Friend - Community leader - Health care provider - Research staff - Employer - Other
	Pressure	Pressure captures the range of influences (excluding inducements) that fall between the extremes of coercion and persuasion.	How did X influence you? - Pressure - Other	Replace X with: - Partner - Family - Friend - Community leader - Health care provider - Research staff - Employer - Other

	Inducement	An inducement is an undertaking by one person to provide another with a benefit to which they are not otherwise entitled in return for research participation (Appelbaum et al., 2009a).	How did X influence you? - Offer	Replace X with: - Partner - Family - Friend - Community leader - Health care provider - Research staff - Employer - Other
Controlling influences	Intentional-ity	"Deliberate action of another person who intends to influence the potential research participant's consent decision in a certain way" (Appelbaum et al, 2009a, p. 33).	This person was purposefully trying to get me to [not to] participate in this research when they influenced me	1 Strongly agree 2 Agree 3 Neither agree nor disagree 4 Disagree 5 Strongly disagree
	Legitimacy	An influence is illegitimate if the person exerting the influence does not have the right to exert that influence or if by exerting that influence they are violating the decision-maker's rights (Appelbaum et al., 2009a; Wertheimer, 2012).	This person had the right to influence my consent decision in the way they did	1 Strongly agree 2 Agree 3 Neither agree nor disagree 4 Disagree 5 Strongly disagree
			My rights to make a free independent decision about participation were violated when this person influenced me	1 Strongly agree 2 Agree 3 Neither agree nor disagree 4 Disagree 5 Strongly disagree
	Causality	The intentional illegitimate influence from another person has to cause the consent decision to be made (Appelbaum et al., 2009a).	This influence caused me to make the consent decision I did	1 Strongly agree 2 Agree 3 Neither agree nor disagree 4 Disagree 5 Strongly disagree

Development of the Survey of Influences revealed that measuring actual voluntariness (freedom from controlling influences from others) is inherently problematic. First, a research participant has to be aware of the influence exerted by another in order to report it. If participants fail to identify problematic influences from others, any instrument

developed will fail to detect it. Second, whether the influence was intentional or not can only ever be determined by asking the person who exerted the influence in the first place. As this is an unfeasible if not impossible pursuit, assessment of intentionality has to rely on the research participant's perception of whether the other person's influence was intentional or not. Third, illegitimacy also relies on participants' self-report and is an inherently subjective concept. In some cases the law dictates what legitimate and illegitimate behaviour is but even then participants may perceive an action to be illegitimate when it is not. For example, it is legitimate for the South African Revenue Service to penalise people who do not pay their taxes. This however does not mean that any individual person may perceive this penalty as legitimate. Moreover, the legitimacy of actions exerted by one's spouse or family may be entirely subjective and depend on the research participant's culture, beliefs, world-view and so on. The research participant is the only one well placed to determine the causality of the influence on their consent decision. Asking research participants to identify intentional, illegitimate and causal influences from others is therefore inherently subjective. So, as with all self-report measures, what is produced is participants' *perception* of intentional, illegitimate and causal influences from others. Any reasonable attempt to measure actual voluntariness is ultimately a measure of *perceived* freedom from controlling influences.

Does this mean that perceived voluntariness and *perceived* freedom of controlling influences of others are the same and any attempts to assess perceived absence of controlling influences from others should be abandoned? Distinguishing between perceived and actual voluntariness is theoretically useful. Measures of general perceived voluntariness (such as the DMCI) take all influences into consideration. Measures of perceived freedom from controlling influences of others however focus only on the influences that actually have the potential to undermine the voluntariness and subsequent validity of consent and are therefore a more accurate reflection of nonvoluntary consent (even with its limitation of subjectivity) than measures of general perceived voluntariness. Actual voluntariness will therefore be refered to as 'perceived freedom from controlling influences' for the remainder of this dissertation.

4.3 Reliability and validity

Validity refers to whether an instrument measures the construct it is designed to measure (Bryman, 2004). Reliability refers to the degree to which a measure of a concept is stable or trustworthy (Bryman, 2004). During instrument development the following plan for establishing reliability and validity was developed: Once the draft instrument was complete, peer review was to be used to establish the face validity of the instrument. Face validity refers to whether an instrument is subjectively viewed as testing the concept it intends to measure (Howell, 2002). Several other strategies were planned to ensure and test the reliability and validity of the Voluntariness Assessment Instrument during instrument development. First, two coders were to code the VNRI Narratives and inter-coder agreement calculated to ensure the reliability of the thematic coding. Second, the DMCI was included in the battery of instruments to establish the convergent validity of the VNRI. Convergent validity is the extent to which two measures which theoretically should be similar, are in fact similar (Bryman, 2004). Third, the internal consistency of the DMCI wasto be established. Lastly, in order to assess the validity of the Survey of Influences two coders were to code the VNRI Narratives for the presence of controlling (intentional, illegitimate and casual) influences. First, inter-coder agreement was to be calculated to ensure the reliability of this coding. These 'expert assessments' of controlling influences were then to be compared to the controlling influences detected in the Survey of Influences in order to determine the construct validity of the Survey of Influences. Chapter 8, section 7 describes the reliability and validity of the instrument developed and reflects on the implementation of this plan.

4.4 Instrument pre-test

The instrument battery was translated into isiZulu by a professional translation agency and was pre-tested on 15 CAPRISA study participants to determine the appropriateness of the question phrasing, to ensure that the range of response alternatives was sufficient and that there was sufficient variation in responses (De Vaus, 2002). The pre-test also determined whether all items were necessary and established item non-response and

evidence of acquiescence (De Vaus, 2002). Question flow, skip patterns, appropriate length and whether respondents' interest was sustained for the duration of administration were also determined (De Vaus, 2002). On the basis of this pre-test, several minor adjustments were made to the study instrument. The more significant changes to the instrument are discussed below. The original Survey of Influences was formulated to assess how other people influenced participants to participate in the study. The pre-test revealed that participants were more often influenced *not* to participate. To capture this, the instrument was modified to include the possibility that other people tried to influence participants not to participate. The pre-test also revealed that a more colloquial translation of some of words was needed in the isiZulu version of the instrument. During the pre-test the VNRI voluntary and nonvoluntary reference narratives were recorded and transcribed. However, many of the pre-test participants shared sensitive stories about rape or abortion with the researchers as examples of the voluntary/nonvoluntary decisions they had made in the past. While the pre-test confirmed that the reference narratives were a very useful tool to assist participants to understand what voluntariness means for them, collecting data on such traumatic personal incidents was viewed as ethically problematic during a study of voluntary informed consent to research. As a result, while participants were still asked to describe and rate their personal experience of a voluntary and nonvoluntary decision they had made in the past, their narrative description of this decision was not audio recorded and transcribed. Only participants' ratings of the degree of voluntariness of these past decisions were recorded for analysis. That is, the Voluntary and Nonvoluntary Reference Exercises were used solely to assist research participants explore what voluntariness means to them in order to facilitate the description and rating of the perceived voluntariness of their consent to the host trial. Lastly, in the pre-test, participants were only asked in the VNRI Narrative section to think about how they came to enroll in the host study and share this story with the researcher. However, the pre-test revealed that participants provided very brief responses to this. To encourage participants to provide more detailed accounts of their consent decision, the following standardised prompts were added to the final instrument: "Please describe in as much detail as possible: (a) how you came to be enrolled in this study; (b) why you decided to participate; (c) how free you felt about participating in this study; (d) if any other person

influenced your decision; or (e) if any other factor, situation, circumstance influenced your decision to participate."

4.4.1 Protocol deviation

On the 9 October 2013 a protocol deviation was detected. The research protocol stated that the pre-testing of the instrument was to be conducted with CAPRISA 008 and 009 participants. However, due to slow recruitment of these participants the researcher (with the necessary permission from her PhD supervisor and the CAPRISA Principal Investigator) decided to sample pre-test participants from another CAPRISA study. As a result of an unfortunate oversight on the researcher's part the required ethics approval for this technical protocol amendment was not obtained from the UKZN Biomedical Research Ethics Committee. The researcher's PhD supervisor, CAPRISA and the UKZN Biomedical Research Ethics Committee were immediately notified of the protocol deviation. The pre-test data was discarded and a condonation was issued by the UKZN Biomedical Research Ethics Committee (Appendix 2).

5. Summary

Fifteen empirical studies of the voluntariness of consent to research were identified and reviewed. The review found that little attempt has been made to systematically collect data on the reliability and validity of these instruments and no two instruments reviewed were found to be based on a shared conceptualisation of voluntary consent to research. Despite these limitations, several of the instruments reviewed provide a useful indication of how some of the key domains of voluntariness can be assessed. The conceptual and empirical review formed the basis for the development of an instrument to assess perceived voluntariness and freedom from controlling influences of others. The instrument developed attempts to assess both participants' perception of voluntariness as well as their freedom from the intentional, illegitimate and causal influences of others. The following chapter describes the methods employed in the piloting of the instrument that was developed.

Chapter 6: Assessing Voluntariness of Consent to Research: Method

The fourth objective of this study was to pilot the instrument developed to assess voluntary consent to research. In this chapter the study aims and study design are discussed and the research context and study sample are described. The methods of data collection and analysis are presented and the ethical considerations taken into account are explained.

1. Study Aims

The aims of the pilot study were to:

1. Determine the perceived voluntariness of research participants' consent.
2. Identify what factors undermined participants' perceived voluntariness of consent.
3. Identify the presence of influences from other people and how these influences were exerted.
4. Identify the presence of controlling (intentional, illegitimate and causal) influences from others and subsequent nonvoluntary participation.
5. Identify what other factors influenced participants' consent decision.

2. Study Design

This study made use of a cross-sectional research design. The defining elements of a cross-sectional research design are the collection of data from multiple cases at one point in time in order to generate quantifiable data in relation to several variables so that patterns of association can be determined (Bryman, 2004). A cross-sectional design is suitable to this study as this study is primarily descriptive and did not attempt to prove a hypothesis. That is, the study aimed to describe the extent to which research participants provide voluntary consent and to identify factors that may undermine the voluntariness of their consent.

3. Research Context

This study took place within the Centre for the AIDS Programme of Research in South Africa (CAPRISA) (see www.caprisa.org). CAPRISA was established in 2002 under the NIH-funded Comprehensive International Program of Research on AIDS (CIPRA). CAPRISA's mission is to "undertake globally relevant and locally responsive research that increases the understanding of HIV pathogenesis, prevention and epidemiology as well as the links between tuberculosis and AIDS care" (CAPRISA, 2011a). Specifically, CAPRISA conducts research on HIV pathogenesis and vaccines; HIV and TB treatment; microbicides; prevention and epidemiology and the prevention of mother-to-child transmission of HIV (CAPRISA, 2011b). The present study is situated within CAPRISA's microbicide research programme. Young South African women are most vulnerable to HIV infection due to partnering with older men and engagement in multiple concurrent relationships (Sokal, Abdool Karim, Sibeko et al., 2013). Poverty, power differentials and gender-based violence make it difficult for women to negotiate safer sex practices (Sokal et al., 2013). Female controlled innovations to prevent the sexual transmission of HIV in women are clearly desperately needed. Modelling studies demonstrate that even a partially effective microbicide could have a definitive impact on the reduction of HIV transmission (CAPRISA, 2011b). In 2010, the CAPRISA 004 double-blind, randomized placebo-controlled trial demonstrated that tenofovir gel reduced HIV incidence by 39% (95% confidence interval 6 to 60), providing proof-of-concept that an antiretroviral product can prevent sexual transmission of HIV in women (Sokal et al., 2013). Participants for this study were sampled from two active CAPRISA 004 follow up studies, hereafter referred to as 'host studies':

3.1 CAPRISA 008

The CAPRISA 004 tenofovir gel trial demonstrated 39% reduction in HIV infection, with 54% HIV reduction in women who used tenofovir gel consistently, highlighting the importance of gel adherence for effectiveness against HIV (Sokal et al., 2013). The purpose of CAPRISA 008 is to assess the effectiveness of an implementation model which integrates tenofovir gel provision into existing family planning services

(CAPRISA, 2011b). Essentially, CAPRISA 008 examines how well tenofovir gel works and how safe it is when provided through family planning services compared to a clinical trial research setting. Consenting sexually active, HIV-uninfected women aged 18 years and older who previously participated in an antiretroviral prevention study are eligible for participation (CAPRISA, 2011b). Participants are randomized to receive 1% tenofovir gel through either: (1) Public sector family planning services with 2–3 monthly provision and monitoring of 1% tenofovir gel and the use of a Quality Improvement methodology to promote reliable service delivery (intervention arm), or (2) the CAPRISA research clinics with monthly provision and monitoring of 1% tenofovir gel (control arm). CAPRISA 008 participants are provided with the standard package of HIV prevention (this includes the provision of male and female condoms as well as HIV counselling and testing) and reproductive health services (CAPRISA, 2011b). Participants are reimbursed R150 for their enrolment and study exit visit, R100 for each scheduled study visit and R50 for interim study team-initiated visits (NHREC, 2012).

CAPRISA 008 volunteers were informed of the following as per the below extract from the CAPRISA 008 Enrolment Informed Consent, Version 4.0, 11 February 2013:

> "*YOUR PARTICIPATION IS VOLUNTARY*
> *You are being asked to volunteer in the research study named above. In order to be sure that you have sufficient information about this study and your consent is voluntary we are asking you to read* (*or have read to you*) *this consent form in the language of your choice. Should you wish to participate in this study you will need to sign this consent form* (*or make your mark in front of a witness*) *if you agree to participate in this study. We will give you a copy of this form to keep or we can store your copy for you. This consent form might contain some words or ideas or terms that you may not understand or be unsure about its meaning. Please stop me at any time during this process and ask me to explain anything you may not understand.*
> *Before you learn about the study, it is important that you know the following*:
>
> - *Your participation is entirely voluntary.*

- *You may decide not to take part or to withdraw from the study at any time. Your routine medical care at this clinic will not change.*
- *If you decide to not take part in this research study, you can still take part in another research study, if one is available and you meet the study requirements.*"

3.2 CAPRISA 009

The purpose of CAPRISA 009 is to determine whether prophylactic exposure to tenofovir gel alters the therapeutic response to a tenofovir containing antiretroviral regimen (CAPRISA, 2012). The study aims to learn whether using tenofovir gel to prevent HIV infection affects the use of tenofovir to treat subsequent HIV infection when antiretroviral therapy is required. CAPRISA 009 is an open label, two-arm, randomised controlled trial enrolling women who become infected with HIV while participating in or after completion of the CAPRISA 004 and CAPRISA 008 trials (CAPRISA, 2012). The treatment outcomes in women previously exposed to tenofovir gel at the time of HIV acquisition, or when HIV acquisition occured after exposure to tenofovir gel, are randomised to either a tenofovir containing (intervention arm) or a tenofovir-sparing antiretroviral treatment regimen (control arm) (CAPRISA, 2012). CAPRISA 009 participants are reimbursed R150 for each scheduled study visit (NHREC, 2012).

CAPRISA 009 volunteers were informed of the following as per the below extract from the CAPRISA 009 Enrolment Informed Consent, Version 4.0, 30 July 2012:

"*YOUR PARTICIPATION IS VOLUNTARY*

You are being asked to volunteer in the research study named above. In order to be sure that you have sufficient information about this study and your consent is voluntary we are asking you to read (*or have read to you*) *this consent form in the language of your choice. You are being asked to sign this consent form* (*or make your mark in front of a witness*) *if you agree to participate in this study. We will give you a copy of this form to keep or we can store your copy for you. This consent form might contain some words or ideas or terms that you may not*

understand or be unsure about its meaning. Please stop me at any time during this process and ask me to explain anything you may not understand. Before you learn about the study, it is important that you know the following:

- *Your participation is entirely voluntary. You may decide not to participate in the study, but you are still eligible for antiretroviral therapy and you may decide to obtain your HIV care through your own medical provider or the CAPRISA AIDS Treatment Program* (*CAT*).
- *You may decide not to take part or to withdraw from the study at any time. You will not lose the benefits of your routine medical care at this clinic*.
- *If you decide to not take part in this research study, you can still take part in another research study, if one is available and you meet the study requirements*.
- *You can expect to be informed of any new information that may arise, which could affect your decision to remain a part of this study*."

The two host studies are situated in both an urban and rural area of KwaZulu-Natal, South Africa. In the rural community, the control arm of CAPRISA 008 is based at the CAPRISA Vulindlela Clinic. The CAPRISA Vulindlela Clinic is situated in the sub-district of Vulindlela, a rural community in the KwaZulu-Natal midlands, about 150 km north-west of Durban. The CAPRISA 008 intervention arm is based at the Mafakathini Primary Health Care Clinic which provides family planning services and is located adjacent to the CAPRISA Vulindlela Clinic (CAPRISA, 2011a). In the urban community, the control arm of CAPRISA 008 is conducted at the CAPRISA eThekwini Clinic. The CAPRISA eThekwini Clinic is attached to the Prince Cyril Zulu Communicable Disease Centre, a Primary Health Care Clinic of the Durban City Health Department dedicated to the diagnosis and treatment of sexually transmitted diseases and tuberculosis. The Prince Cyril Zulu Communicable Disease Centre and the Lancers Road Primary Health Care Clinic (where the services include antenatal care, family planning, childhood immunisation, STI treatment, minor ailment care, and HIV voluntary counselling and testing services) host the urban intervention arm (CAPRISA, 2011a). CAPRISA 009 is conducted in the CAPRISA Vulindlela and eThekweni Clinics (CAPRISA, 2012).

At the time of data collection for the present study, recruitment and enrolment for the host trials (CAPRISA 008 and 009) were still active. By the end of data collection, 43 of the 120 target participants had been enrolled in CAPRISA 009 and 357 of the 700 target participants had been enrolled in CAPRISA 008.

4. Study Sample

A non-probability sampling method was employed in this study. CAPRISA 008 and 009 participants were invited to participate in this study of voluntariness as they came in for their scheduled host trial visits. The study sample comprised 100 consenting volunteers who at the time of the interview were enrolled in either CAPRISA 008 or 009. This sample size attempted to balance the intensive, time-consuming nature of administering the VNRI as well as the need to obtain a sufficiently large pilot sample to allow meaningful statistical analysis to be conducted.

The following inclusion criteria were employed:

- Participants had to be enrolled in either CAPRISA 008 or 009
- Participants had to be English or isiZulu speaking
- Participants had to be over 18 years of age
- Participants had to provide written informed consent to participate in the study

5. Data Collection

Data was collected over a five-month period from April – August 2013. Participants were informed about the Voluntariness Study by host study staff as they came in for scheduled host study visits. If they were interested in receiving further information about the Voluntariness Study they were referred to the Voluntariness Interviewer after their scheduled host study visit had been completed. The Voluntariness Study information sheet was presented to interested participants. Those wishing to participate were

consented (Appendix 3) and the Voluntariness Assessment Instrument battery was administered.

The battery of instruments was translated into isiZulu for isiZulu speaking participants. Participants had the option of receiving study information, consenting and being interviewed in English or isiZulu. English questionnaires were administered by the researcher and the isiZulu questionnaires were administered by a research assistant.

The research assistant was a PhD student in research ethics, who was adequately qualified to assist with data collection. The research assistant received comprehensive protocol specific and ethics training from the researcher. The researcher was also on site to answer any questions and provide guidance to the research assistant during data collection. Debriefing sessions were conducted between the researcher and research assistant daily.

The following demographic details were collected from all participants. Host trial, race, age, marital status, education, employment status, monthly income, access to health services, time since enrolment and time taken to research a consent decision (Appendix 4). Voluntariness data was collected using the (i) Voluntariness Narrative Rating Instrument (Appendix 5), (ii) Decision Making Control Instrument (Appendix 6) and (iii) Survey of Influences (Appendix 7).

6. Data Analysis

The entire battery of instruments was administered by the researcher or research assistant. Responses were captured on the respective questionnaires and then entered into an excel spreadsheet. Data entry was double checked to ensure accuracy.

The narrative component of the Voluntariness Narrative Rating Instrument was audio recorded and transcribed. In the case of isiZulu participants, isiZulu transcripts were translated into English by the isiZulu speaking research assistant. Translation and

transcription were conducted simultaneously leading to a single English transcript (Hennink, Hutter & Bailey, 2011). The research assistant listened to a segment of recorded isiZulu response, considered an appropriate English translation and wrote it down. Once the entire response had been translated and transcribed in this manner the research assistant listened to the original recorded isiZulu response again and compared it to the English transcript to ensure the appropriate meaning of the response had been captured (Hennink, Hutter & Bailey, 2011).

6.1 Thematic analysis

The transcripts from the narrative component of the Voluntariness Narrative Rating Instrument were analysed using thematic analysis (Ulin, Robinson, Tolley & McNeill, 2002). Thematic analysis is an inductive and iterative process whereby similarities and differences in the data are identified and summarised to corroborate or disconfirm theory. The transcripts were read, re-read and coded. The conceptualisation of voluntariness developed in Chapter 4 provided a set of *a priori* codes with which the data were coded. To this end, data was coded according to whether participants described their participation as voluntary or not and according to the factors influencing participants' consent decision. Additional codes were allowed to inductively emerge as coding progressed. Codes were then organised into themes. Initial transcripts were then re-read to ensure that the codes and themes adequately reflected the meanings conveyed in the transcripts. This strategy closely followed the approach advocated by Ulin et al. (2002).

Ulin et al. (2002) outline five precise analytical steps that should be used in the process of analysis. The first step is reading. This involves 'data immersion', reading and re-reading each set of responses until the researcher is very familiar with the content of the documents. After one has become familiar with the texts, one moves to the second analytic step, coding, in which information is assembled under various codes (labels for assigning units of meaning) in a continuous manner. Codes are then sorted into broader themes. The third step identified by Ulin et al. (2002) is displaying. Once all the information has been combined and themes and codes have been arranged, the researcher

can then examine the themes more closely. Displaying the data enables the researcher to examine the evidence that supports each theme and to illustrate the strength of each theme across all questionnaires. The fourth step is reducing (Ulin et al., 2002). This involves reducing the information to make the most essential concepts and relationships visible. The reduction process usually occurs once all the data is in, and the researcher is familiar with the content. The goal is to get an overall sense of the data and to distinguish overarching and secondary themes. This step involved reading and re-reading the responses, to develop and redefine codes, while noting the detail of themes and ideas. The last step involves interpreting the data, showing how thematic areas relate to one another and how concepts respond to the research question (Ulin et al., 2002).

In order to enhance the validity of the analysis, frequency counts were used to establish the strength of themes. To enhance the reliability of the analysis, the narratives were independently coded by the researcher and research assistant and inter-coder agreement was calculated using Cohen's Kappa. Cohen's kappa is an appropriate technique for estimating paired inter-coder agreement for nominal data (Altman, 1991). Kappa is a coefficient that denotes agreement obtained between two coders beyond that which would be expected to have accrued by chance (Altman, 1991). The data met all the assumptions of Cohen's Kappa (Altman, 1991).

6.2 Statistical analysis

Statistical analysis was primarily conducted for exploratory purposes. Data analysis was conducted with Statistical Package for the Social Sciences (2009, version 18.0). The following statistical techniques were employed:

Frequency counts: Frequency counts were generated for the sample characteristics, VNRI ratings DMCI scores and the Survey of Influences.

Chi-square test of independence: Chi-square tests of independence were used to determine whether there was a significant association between sample characteristics and

VNRI ratings, sample characteristics and potentially controlling influences, VNRI ratings and non-controlling influences, DMCI scores and non-controlling influences, VNRI ratings and potentially controlling influences and DMCI scores and potentially controlling influences. The data met the assumptions of the Chi-square test of independence. The classification of data was exhaustive and mutually exclusive and expected frequencies were not less than five in at least 80% of the categories (Tredoux & Durrheim, 2002).

Chi-square goodness-of-fit test: A Chi-square goodness-of-fit test determines whether the data fits a theoretical distribution (Tredoux & Durrheim, 2002). For each of the three DMCI subscales, three score categories were formed and Chi-square goodness-of-fit tests involving each pair of variables performed. The classification of data was exhaustive and mutually exclusive and expected frequencies were not less than five in at least 80% of the categories (Tredoux & Durrheim, 2002). As such the assumptions of the Chi-square goodness-of-fit test were met.

The Mann-Whitney U-test: The Mann-Whitney U-test test was used to determine whether a difference exists between DMCI scores and the VNRI ratings and the difference in DMCI scores between different sample charateristics. (Tredoux & Durrheim, 2002). The data met the assumption of independence (Tredoux & Durrheim, 2002).

Kruskal-Wallis test: The Kruskal-Wallis test was used to determine whether here was a difference in DMCI scores between different sample charateristics and whether there was a difference between the intentionality, legitimacy and causality of the influence and sample characteristics (Howell, 2002).

Cronbach's coefficient alpha: Cronbach's coefficient alpha is an estimate of the internal consistency of responses to difference items in a scale (Tredoux & Durrheim, 2002). Cronbach's coefficient alpha was used to calculate reliability estimates for the DMCI.

A Repeated Measures Analysis of Variance (*ANOVA*): ANOVA was also performed to test for differences between means for the three DMCI subscale totals (Tredoux & Durrheim, 2002). The data met the assumptions of independence, normality and homoscedasticity (Howell, 2002).

7. Ethical Considerations

7.1 Ethics approval

Ethical approval for the study was obtained from the University of KwaZulu-Natal's (UKZN) Biomedical Research Ethics Committee (Approval number: BE229/11) (Appendix 8).

7.2 Informed consent

Written informed consent was obtained from each study participant prior to data collection (Appendix 3). Participants were informed of the voluntary nature of participation and their freedom to withdraw at any time. Participants were provided with copies of their informed consent forms if they were willing to receive them.

7.3 Risks and benefits

Participants did not benefit directly from participation. Participants may have felt uncomfortable reporting compromised voluntariness or coercive behaviour of the host trial study staff. Participants were assured that their responses were confidential. Participants were free to withdraw from the study at any time and could have refused to answer any questions that they were not comfortable with. If study participants felt that they had been harmed or wronged in any way they were advised to contact the researcher or the University of KwaZulu-Natal's Biomedical Research Ethics Committee.

7.4 Compensation

According to the South African National Health Research Ethics Council (2012) research participants should be reimbursed for time, inconvenience and expenses. Participants in this study did not incur any expenses as the questionnaire was administered during a scheduled host trial visit. Participants who completed the Voluntariness Assessment were reimbursed R50 to compensate for their time. This covered the 60-minute questionnaire administration time and the time participants may have spent waiting to be interviewed. The R50 reimbursement also compensated for the inconvenience of participants having their scheduled host trial visit prolonged by participation in the Voluntariness Assessment.

7.5 Confidentiality

Every effort was made to protect participants' privacy and confidentiality. The signed consent forms were not linked to the study questionnaire. Each participant was assigned a participant code and the questionnaire did not request participants' names or their host trial participant identification number. During transcription of the narrative component the participant's name, if used, was replaced by their participant code. All study data is stored in lockable file cabinets accessible only to the study researcher. Electronic data is stored in password protected files on the researcher's computer and will be destroyed after five years.

8. Summary

This chapter described the research methodology employed in this study. The primary purpose of this study was to pilot the Voluntariness Assessment Instrument developed using a cross-sectional research design with 100 CAPRISA research participants. Specifically this study aims to determine the perceived voluntariness of participation, identify factors that influence participants' consent decision, identify the presence of controlling (intentional, illegitimate and causal) influences from others and assess the

validity and reliability of the pilot instrument. The data collection and analysis process were described and the ethical considerations were outlined. Data was collected over a five-month period by the researcher and a research assistant, data was analysed thematically and statistically. The results are described in the following chapter.

Chapter 7: Assessing Voluntariness of Consent to Research: Results

In this chapter the results of the study are presented. The results of the demographic questionnaire are presented first followed by the results of the Voluntariness Narrative Rating Instrument (VNRI), the Decision Making Control Instrument (DMCI) and then the Survey of Influences (SoI). The results of the three instruments are presented and compared with the sample characteristics. The results of the VNRI ratings and DMCI (perceived voluntariness) are also compared with the factors influencing participants consent decision as identified by the Survey of Influences. Validity and reliability statistics are also presented.

1. Sample Characteristics

Eighty-six of the 100 participants in this study were recruited from CAPRISA 008 and 14 participants were recruited from CAPRISA 009 (see Table 6). The majority of participants were Black (*n*=99). In South Africa, 79.2% of the population are Black Africans (Statistics South Africa, 2012).There were no participants under the age of 21. The majority of participants were between the ages of 21 and 30 years (*n*=58). Thirty-three participants were aged between 31 and 40 years, seven participants were between 41 and 50 years of age and two were over 60 years old. The majority of participants were in a relationship (*n*=79) of which only eight were married. The remaining 21 participants were single. Eighteen participants listed their highest completed level of education as primary school, 72 had completed high school and nine had completed some form of tertiary education. In South Africa, 12.1% of the population have completed some form of tertiary education, 28.4% have completed high school and 2.6% of the population only have a primary school education (Statistics South Africa, 2012). Sixty-eight participants were unemployed and 28 were employed. This is higher than the national South African average unemployment rate of 29.8% (Statistics South Africa, 2012). The majority of participants had no personal monthly income (*n*=52), 17 brought in less than R1,000[1] a month and 30 participants earned between R1,001 and R5,000 per month (total monthly

[1] 1 USD = 10.28 Rand as at 31 August 2013

income includes government grants and subsidies). The income levels for this sample population were less than the national average for Black African headed households which, according to Statistics South Africa (2012), was R5,051 per month. Ninety-eight participants relied on public health services while only two participants said they had access to private health care.

In terms of enrolment in the host trials, three participants had been enrolled in their host trial for less than one month, 45 participants had been enrolled for 1–3 months, one participant had been enrolled between for 3–6 months, 25 participants had been enrolled between 6–12 months ago and 26 participants had enrolled over a year before. When asked how long it took to reach a consent decision the majority of participants said that they reached a consent decision immediately after the informed consent form was discussed with them (*n*=81). Seven participants researched a consent decision in less than 24 hours, eight participants took between 2–7 days to reach a decision and three participants took more than a week to reach a consent decision. The sample characteristics are summarised in Table 6 below.

Table 6

Sample characteristics

	Frequency	Percentage
Host trial		
CAPRISA 008	86	86%
CAPRISA 009	14	14%
Race		
African	99	99%
Coloured	1	1%
Age		
18–21	0	0%
21–30	58	58%
31–40	33	33%

41–50	7	7%
51–60	0	0%
Over 60	2	2%
Marital Status		
Married	8	8%
In a relationship	71	71%
Single	21	21%
Education		
Completed primary school	18	18%
Completed high school	72	72%
Completed tertiary education	9	9%
Missing data	1	1%
Employment Status		
Employed	28	28%
Unemployed	68	68%
Other	4	4%
Monthly Income		
No income	52	52%
Less than R1,000	17	17%
Between R1,001 – R5,000	30	30%
Refused to answer	1	1%
Access to health care services		
Private	2	2%
Public	98	98%
Time since enrolment in host trial		
Less than 1 month	3	3%
1–3 months	45	45%
3–6 months	1	1%
6–12 months	25	25%
Over a year	26	26%

Time to reach a consent decision		
Immediately	81	81%
24 hours	7	7%
2–7 days	8	8%
More than 7 days	3	3%
Missing data	1	1%

2. Voluntariness Narrative Rating Instrument (VNRI)

2.1 VNRI narratives

In this section the results of the thematic analysis of the Voluntariness Narrative Rating Instrument are presented.

2.1.1 Voluntariness of consent

Ninety five of the 100 participants commented on the voluntariness of their consent decision. The overwhelming majority of participants (*n*=93) reported that their consent decision was voluntary and/or free from any influences.

> Participant 21:
> "I felt very free participating in the, the study … No situation or nobody influenced me, because nobody brought me here, eh, I came alone."

> Participant 51:
> "I felt very free to participate because I, I feel at home when I'm here at CAPRISA … I would be lying if I, I say someone or something influenced me. Nobody forced me to take this decision to participate."

Two participants reported that participation was not voluntary by saying that it was not 'free' or 'I didn't feel it was up to me'.

Participant 100:

"I didn't really want to participate but he [boyfriend] told me I should and yes the money helped so I thought why not. Maybe I wasn't forced, um, um, but I didn't feel it was up to me really."

2.1.2 Informed about the voluntariness of participation

Six participants mentioned that they were informed by the research staff that participation was voluntary.

Participant 16:

"They explained here at CAPRISA that there was this particular study and that I was free to participate and stop if I wanted to. They explained to me (although I cannot remember exactly the full details of the story) and I understood."

Participant 49:

"There were people who came to our, um, home and they explained about the gel study that was going to be conducted. They explained all the details including that participation was voluntary, you know, not a compulsory thing."

2.1.3 Consulted others regarding participation

Five participants mentioned that they consulted others about their participation but were not subject to any influences from those they consulted.

Participant 5:

"I did tell my mom and my sisters. And I, eh, talked to them and they didn't mind because even before then, even when I was in the other studies they didn't mind about that."

2.1.4 Influences from others

2.1.4.1 Partner

Three participants said that they were influenced by their partner to participate. Participant 1 was encouraged to participate by her partner. Participant 40 states that she cannot use the gel because her partner will beat her up. Participant 100 says that she was told to participate by her boyfriend.

> Participant 1:
> "Then I phoned him [boyfriend] and I told him that there is this study its 009 … Eh, he wasn't feeling well about the whole thing. So he just said to me, eh, why everything is happening to you? You understand? And I said I don't know and right now I am feeling down. I don't know what decision to take. And he said no it's fine because the way you are you are always talk good about that clinic you must take the right decision and I know they are going to assist you in every way with your health."

> Participant 40:
> "I do not even use their gel. I can't use something I do not trust, eh. How can I use something I don't trust, eh, because I will get home and my boyfriend will beat me up. Eish, I am really afraid to use the gel, I, I throw it away."

> Participant 100:
> "My boyfriend's sister, well I'm single now, but the man I was with before. His sister participates here in the CAPRISA trials. So he said to me, you must also join this study because they take care of you and they also pay you … I didn't really want to participate but he told me I should and yes the money helped so I thought why not. Maybe I wasn't forced, um, um, but I didn't feel it was up to me really."

2.1.4.2 Family

A further two participants said that their families tried to influence their decision.

> Participant 20:
> "Even my parents did not know, but when I told them about my decision they weren't happy that I participate. They said I must not. But I told them, eh, that this is the life I am going to live and it's my decision."

2.1.4.3 Friend

Four participants stated that their friends advised them to join the study.

> Participant 43:
> "My friend told me about the study and she said let's go. Then we came … My friend did not influence me, um, no, but rather she just talked to me nicely and advised me that's why I liked to be part of the study."

2.1.4.4 Research staff

Four participants said that the research staff influenced their decision to participate. Three of these participants said that the research staff encouraged participation while Participant 1 seems to be saying that the research staff told her she had to participate.

> Participant 1:
> "I remember very well, they took my bloods in 004 and then they [research staff] told me that my results have changed so now I am HIV positive and, eish, I was so disappointed. So they told me, no, you need to relax. There is another trial that you have to attend. You have to participate in 009."

> Participant 37:

"There was some CAPRISA people who were assisting us, they were telling and encouraging us to enroll in the study because we could, eh, eh, get help in a lot of things and also that we would be safe (health wise) to prevent diseases because every month you come and get tested, um, we all know that these days there is this disease."

2.1.4.5 Clinic staff

Four participants said that they were referred to the study by staff at a government clinic.

Participant 90:
"I was at the clinic because I had a problem then they told me about a study that was being conducted. After getting help at the clinic, they told me that there is a clinic called CAPRISA that checks for everything including HIV and other reproductive diseases."

2.1.5 Influences from conditions

2.1.5.1 Care and treatment

Forty-six participants mentioned that the care and treatment received during the trial influenced their participation.

Participant 23:
"The reason I participated it's because you get checked for all these diseases for free without any payment. If you have, eh, problem you quickly get assistance, they refer you to other hospitals so [you] can get treatment before you get very sick, um, whilst you still can walk."

Participant 83:

"I decided to take part because sometimes it's not easy as youth to just go and test, but here [at CAPRISA] we get tested regularly, um, and get checked for other diseases for free which is something you don't get at other clinics. You also get encouraged, eh, motivated to live a healthy life because we always test for HIV every month and also get advice to have one partner and to use condoms."

2.1.5.2 Ill health

Twelve participants cited their ill health as influencing their participation.

Participant 17:

"I came to participate at CAPRISA because I was sick. They explained to me that this infection was similar to other diseases like TB, or eh, asthma and that I could also live normally like HIV negative people. The way they treat me here at CAPRISA made me feel free and gave me hope that I could continue living with my life."

2.1.5.3 Payment

Five participants reported participating for the money.

Participant 40:

"I heard from my friend that there was a study and that there was, um, money, I would get money. So I liked to participate because I would get the money. I did not feel free here because I do not even use their gel."

Participant 100:

"They pay you a lot. It's more than you could make a day. I have a nice job but still it's more than I make a day so I thought, why not."

2.1.5.4 HIV prevention

Twenty-six participants claimed to be participating in the hope of preventing HIV infection.

> Participant 66:
> "I decided to participate because of the way they explained about the gel study, eh, that mostly men are the ones that have protection from HIV, we as women are vulnerable because we don't have many things that we can use to prevent infection. So from the study details, um, I realised this gel might be useful in prevention hence I volunteered to be part of the study."

> Participant 76:
> "When they explained that the gel helps prevent HIV I decided to also come to CAPRISA and join because it's a good thing to do. I participated because I cannot trust a man and he might fool you as a woman and eh, eh, end up getting infected."

2.1.5.5 Altruism

Twenty-four participants stated an altruistic motivation for participation.

> Participant 4:
> "I thought it would feel great if I made a difference when the results came back at the end. I, I was there, you know that feeling. That is the only reason I entered. I wouldn't lie. That is the, the only reason why I entered into studies to help others in the future."

> Participant 24:
> "So I was more than interested to join the study, that's how I decided to actually join the study. It's because I'm passionate, everything that has to do with women

empowerment, helping women out there. HIV is, eh, eh, enough you know, I just wanted to do something, to take an initiative to help other people. But at the moment you cannot see the results now, but in the future I know that if they find the study to be a success, I would know in my heart that I did, um, have an input in the study so I would be very happy, that's the reason why I'm in the study to help women not only in South Africa, but the whole world."

2.1.5.6 Trust

Eight participants stated that their trust in the researchers or their positive experience with the research team influenced their participation.

Participant 79:
"I was free to participate although there are some people who were discouraging us from participating by talking bad things about CAPRISA. But I trust the researchers; they are black like us so, so I don't think they will betray and enroll me in a study that would harm me."

2.1.5.7 Distrust

Three participants voiced concern about whether they should trust the researchers.

Participant 25:
"But sometimes I don't know if I should, um, um, be here. Because at times there are certain things that they do hide from us that we don't know. There were some people who were talking saying that, that this gel we are using the people at CAPRISA put AIDS in it."

2.1.5.8 Other benefits of participation

Three participants mentioned that they participate because the study will benefit them without elaborating on the nature of the benefit. Participant 95 stated that receiving food when coming in for study visits motivates her participation.

> Participant 10:
> "I decided to participate because there was somewhere in the flyer where it was stated that it would benefit me."

> Participant 95:
> "And food and drink, you come here and you get food and drink. Ya. That's why I like participation"

2.1.5.9 Misunderstanding

Twenty of the narratives reveal a misunderstanding or overestimation of the effectiveness of the host study product.

> Participant 41:
> "My neighbour told me about the study at CAPRISA and that it is very helpful since it really prevents HIV infection."

> Participant 93:
> "Also the gel we are using had 100% pass I think in 2010 or the previous year. So we are continuing now with the study and it will end up helping other women since as time goes on the gel will be available in clinics for free, like condoms."

2.1.6 Voluntary participation despite the presence of influences

Importantly, the narratives also revealed that participants viewed their participation as voluntary even when they identified the presence of influences.

> Participant 7:
> "My decision to participate in the study was very, um, um, free. At home there was some influence. … I was pregnant so I wanted my child to be protected so, um, I participated and I also told myself that I should participate in the study. The fact that I was sick also made me to participate in the study."

> Participant 46:
> "What made me enroll for the study was that I heard there is a gel to be used by women that will prevent HIV infection. And also if you are part of the study you get tested for STIs and other diseases for free. I decided to, uh, participate because I am unemployed, always at home, I realised that joining the study would benefit me and my health. But I was free in participating. No one or nothing forced me, I took the decision."

2.1.7 Multiple influences

The narratives also revealed that many participants had multiple motivations and influences to participate

> Participant 53:
> "The reason why I came to participate is that I heard that they test and check our health. I then heard that there is a study about a gel to prevent HIV. And also that, eh, there is money. I also decided to participate because its nice being in a study that you know will help one day. There was nobody who influenced or forced me participate, I was the only one who took the decision to participate."

2.1.8 Inter-coder agreement

In order to ensure reliability, the narrative data was analysed by two researchers independently and inter-coder agreement was calculated for the five main themes. The percent agreement and Cohen's Kappa were calculated for the following themes: voluntariness, misunderstanding, HIV prevention, care and treatment and altruism in order to establish inter-coder agreement. High levels of percent agreement were observed (89%–98%). The Kappa value reveals that high levels of agreement were observed for four of the five variables (0.864–0.984). A moderate yet acceptable level of agreement was observed for misunderstanding (0.567). Where disagreement was observed, the lead researcher reviewed the extracts and made a final decision on how the item should be coded. The results of the inter-coder agreement calculations are summarised in Table 7 below.

Table 7

Inter-coder agreement

Codes	Percent Agreement	Cohen's Kappa
Voluntariness	98%	0.864
Misunderstanding	89%	0.567
HIV Prevention	98%	0.948
Care and treatment	95%	0.9
Altruism	96%	0.884

2.2 VNRI ratings

On the basis of their narratives, participants were asked to rate the voluntariness of their participation in the host study on a scale of 1 (nonvoluntary) to 10 (fully voluntary). Eighty-nine participants rated their participation as fully voluntary with a score of 10.

Eleven participants rated their participation as less than fully voluntary. Six participants gave the voluntariness of participation a score of nine, three participants a score of eight and one a score of seven. Only one participant produced a rating (four) in the bottom half of the scale. The low frequency of ratings under 10 necessitated that data be grouped into a fully voluntary category (rating of 10) and a less than fully voluntary category (rating of less than 10) to facilitate statistical analysis. This grouping is summarised in Table 8 and displayed in Figure 3 below.

Table 8

Frequency distribution of VNRI ratings

	Frequency	Percent
Fully voluntary (rating of 10)	89	89%
Less than fully voluntary (rating of less than 10)	11	11%
Total	100	100%

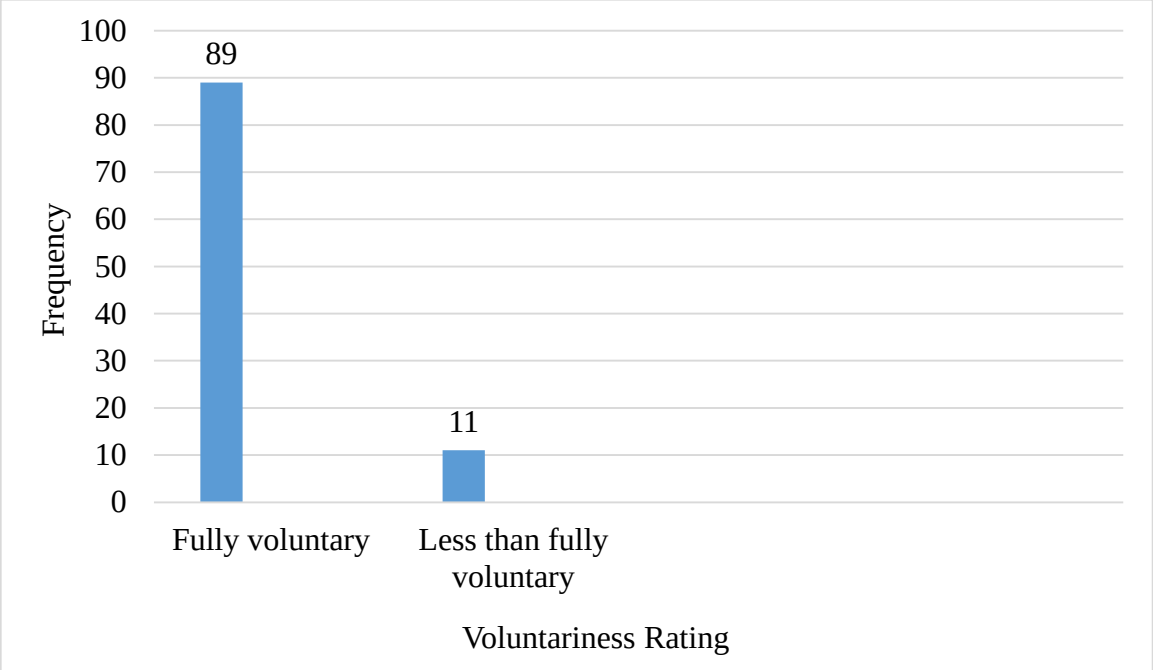


Figure 3. Bar chart of VNRI ratings

2.2.1 Association between VNRI rating and sample characteristics

Chi-square tests of independence were performed to examine the association between participants' voluntariness rating and the sample characteristics (Table 9). The association between voluntariness rating and education was significant (X^2 = 2.75, *df*=1, p=.097, *df*=1, *p*<.1) showing that participants with only a primary school education were more likely to rate their participation as fully voluntary (rating of 10) than participants with high school or tertiary education (Figure 4). The relation between voluntariness rating and time to consent was also significant (X^2 = 6.188, *df*=1, p=.0129, *p*<.05). Participants who took less than 24 hours to reach a consent decision were more likely to rate their participation as fully voluntary (rating of 10) than participants who took more than 24 hours to decide (Figure 5).

Table 9

Cross-tabulation of VNRI rating and sample characteristics

	Host Trial		
Voluntariness Rating	CAPRISA 008	CAPRISA 009	Total
Less than fully voluntary (rating of less than 10)	9	2	11
Fully voluntary (rating of 10)	77	12	89
Total	86	14	100
	Chi-square 0.1795	*p*-value 0.672	

	Age		
Voluntariness Rating	21–30	> 30	Total
Less than fully voluntary (rating of less than 10)	7	4	11
Fully voluntary (rating of 10)	51	38	89

Total	58	42	100
	Chi-square 0.161	*p*-value 0.688	

	Marital Status		
Voluntariness Rating	In a relationship	Single	Total
Less than fully voluntary (rating of less than 10)	7	4	11
Fully voluntary (rating of 10)	72	17	89
Total	79	21	100
	Chi-square 1.759	*p*-value 0.185	

	Employment Status		
Voluntariness Rating	Employed	Unemployed	Total
Less than fully voluntary (rating of less than 10)	2	8	10
Fully voluntary (rating of 10)	26	60	86
Total	28	68	96
	Chi-square 0.454	*p*-value 0.5	

	Education		
Voluntariness Rating	Primary School	High School/Tertiary	Total
Less than fully voluntary (rating of less than 10)	0	11	11
Fully voluntary (rating of 10)	18	70	88
Total	18	81	99
	Chi-square 2.75	*p*-value 0.097*	

	Monthly Income		
Voluntariness Rating	No Income	Income	Total
Less than fully voluntary (rating of less than 10)	6	5	11
Fully voluntary (rating of 10)	46	42	88
Total	52	47	99
	Chi-square 0.02	*p*-value 0.887	

	Time to Consent		
Voluntariness Rating	Less than 24 hours	More than 24 hours	Total
Less than fully voluntary (rating of less than 10)	6	5	11
Fully voluntary (rating of 10)	75	13	88
Total	81	18	99
	Chi-square 6.188	*p*-value 0.0129**	

	Time Since Enrolment			
Voluntariness Rating	Less than 3 months ago	3–12 months ago	Over 1 year ago	Total
Less than fully voluntary (rating of less than 10)	5	3	3	11
Fully voluntary (rating of 10)	43	23	23	89
Total	48	26	26	100
	Chi-square 0.032	*p*-value 0.984		

* Significant at the 10% level of significance.

** Significant at the 5% level of significance

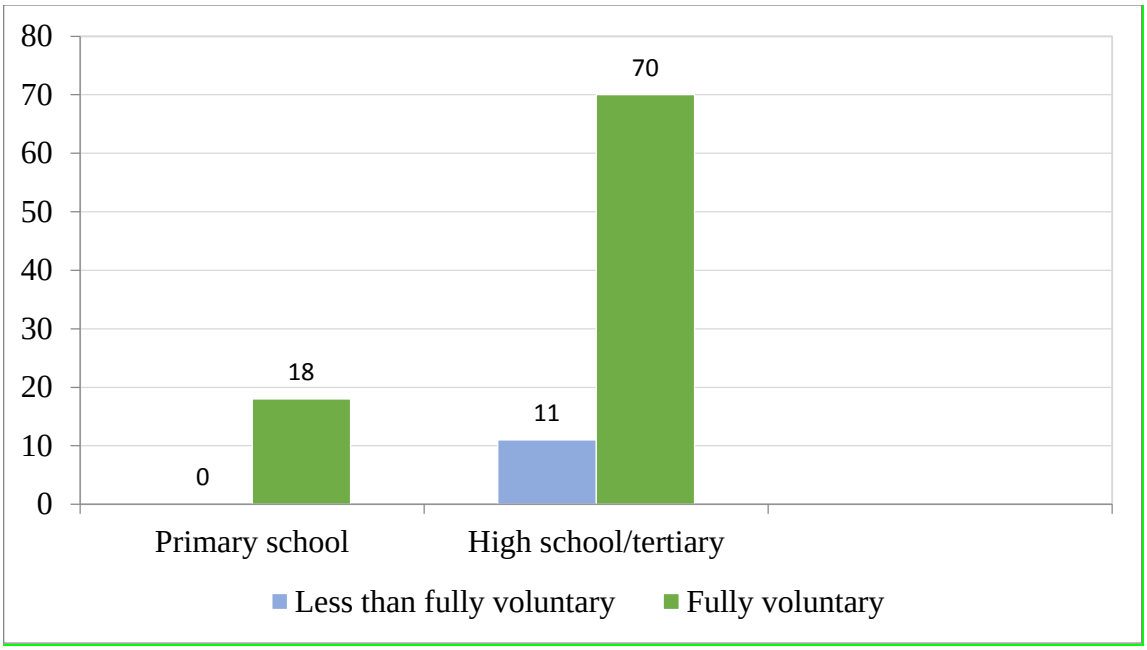


Figure 4. Bar chart of VNRI rating and education

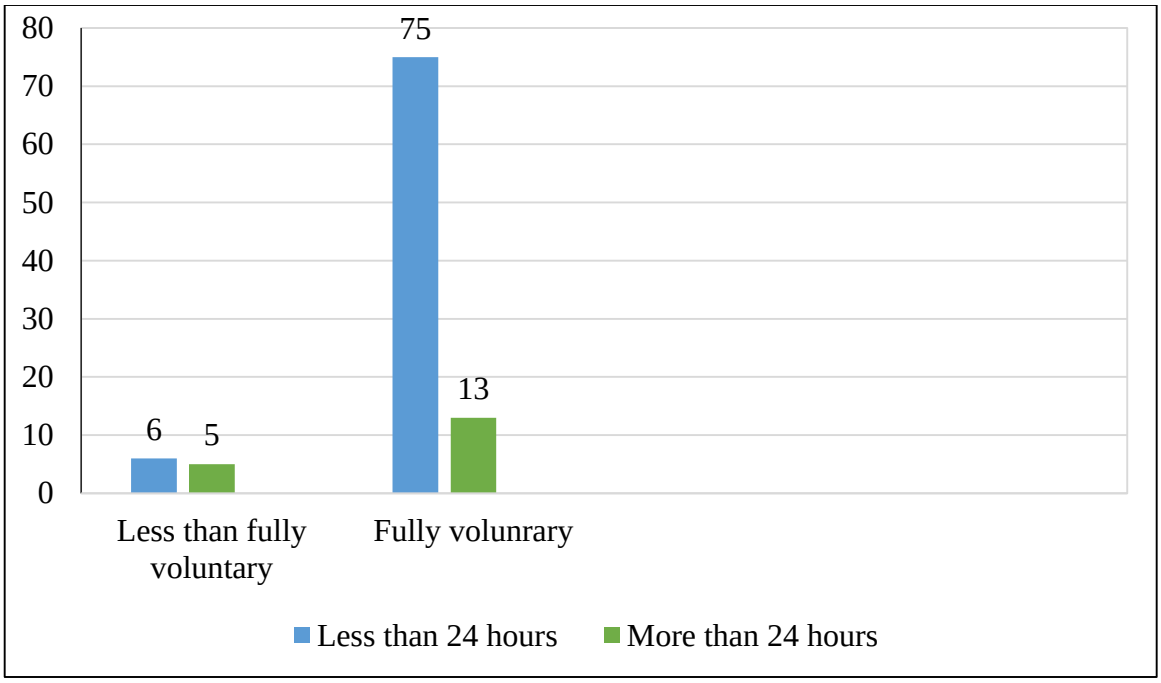


Figure 5. Bar chart of VNRI rating and time to consent

3. Decision Making Control Instrument (DMCI)

3.1 DMCI total scores

Miller et al.'s (2009) Decision Making Control Instrument was administered to all 100 participants. Ninety-six participants disagreed to some extent with the statements, 'I was powerless in the face of the decision' and 'someone took the decision away from me'. Ninety-eight participants disagreed to some extent with the statements, 'I was passive in the face of the decision', 'the decision about the protocol was inappropriately influenced by others', 'others made the decision against my wishes' and 'I was not the one to choose'. Ninety-four participants disagreed to some extent with the statement, 'I was not in control of this decision'. Ninety-eight participants agreed to some extent with the statement, 'I made the decision' and 99 participants agreed to some extent that 'the decision was up to me'. These results are summarised in Table 10 below.

Table 10

Frequency distribution of DMCI items

	Strongly Agree	Agree	Somewhat Agree	*Total Agree*	Somewhat Disagree	Disagree	Strongly Disagree	*Total Disagree*
I was powerless in the face of this decision	2	2	0	*4*	1	25	70	*96*
Someone took this decision away from me	1	3	0	*4*	2	31	63	*96*
I made the decision	68	30	0	*98*	1	1	0	*2*

I was passive in the face of this decision	1	1	0	*2*	2	32	64	*98*
The decision about the protocol was inappropriately influenced by others	0	1	1	*2*	0	31	67	*98*
I was not in control of this decision	1	4	1	*6*	0	37	57	*94*
Others made this decision against my wishes	0	2	0	*2*	1	36	61	*98*
I was not the one to choose	0	2	0	*2*	0	38	60	*98*
The decision was up to me	79	20	0	*99*	0	1	0	*1*

Note. As *N*=100, frequency counts are equal to frequency percent.

The DMCI allows scores between 54 (high perceived voluntariness) and 9 (low perceived voluntariness) to be obtained. The total DMCI scores for this study range from 54–21 (Table 11). Thirty-seven participants scored 54. Twenty-two participants scored between 51 and 53, 21 participants scored between 46 and 50 and 18 participants scored between 41 and 45. Therefore, 80% of respondents obtained a DMCI score above 50, indicating high levels of perceived voluntariness in this study sample. Furthermore in terms of the

DMCI, between 94% and 98% percent of participants disagreed with Likert scale statements indicating nonvoluntary participation (e.g., I was not the one to choose) and over 98% of participants agreed with Likert scale statements indicating voluntary consent (e.g., the decision was up to me), again indicating high levels of perceived voluntariness.

Only two participants scored under 40, with a score of 39 and 21 revealing lower levels of perceived voluntariness. In order to facilitate statistical analysis DMCI scores were grouped as per Table 12 (Figure 6).

Table 11

Frequency distribution of DMCI total scores

DMCI Total Score	Frequency
54	37
53	5
52	12
51	5
50	5
49	6
48	2
47	5
46	3
45	10
44	2
43	3
42	3
39	1
21	1

Table 12

Frequency distribution of grouped DMCI total scores

DMCI Total Score	Frequency
<40	2
41–45	18
46–50	21
51–53	22
54	37
Total	100

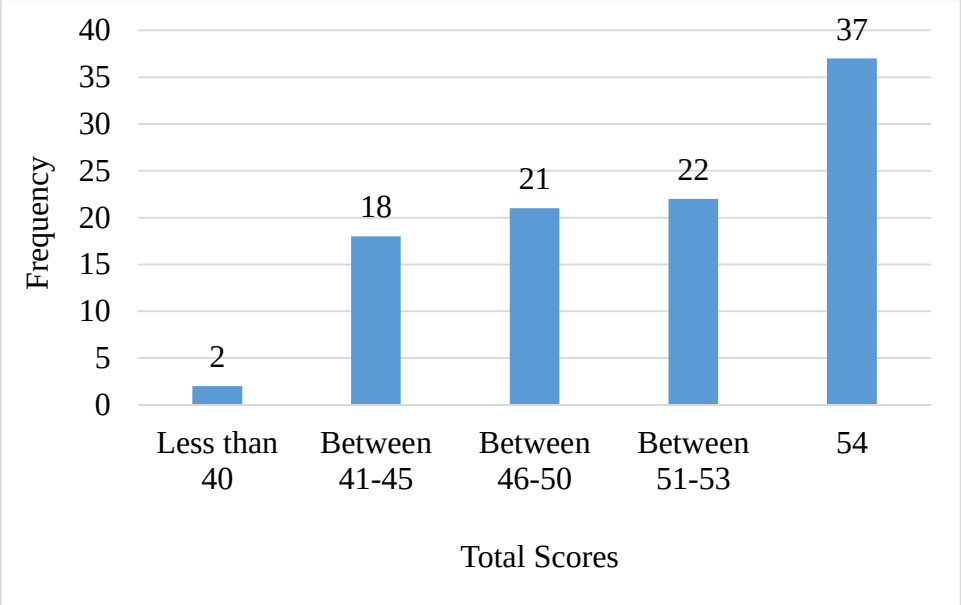


Figure 6. Bar chart of grouped DMCI total scores

3.2 Association between DMCI total scores and sample characteristics

The tables that follow show a summary of results of Mann-Whitney (Table 13) and Kruskal-Wallis tests (Table 14) for DCMI total scores subdivided according to sample characteristics. A significant relationship was only observed between DMCI total scores and monthly income (X^2 = 6.883, *df*=2, *p*=.032, *p*<.05). Participants with no income are

more likely to have a high DMCI total score (indicating high perceived voluntariness) than participants with an income of less than R1,000 per month. The relationship between perceived voluntariness and all other sample characteristics were non-significant (Tables 13 and 14).

Table 13

DMCI total scores compared to sample characteristics – Mann-Whitney

Characteristic	*Z* statistic	*p*-value
Host trial	1.376	0.169
Employed	1.304	0.192
Time to consent	0.578	0.564

Table 14

DMCI total scores compared to sample characteristics – Kruskal-Wallis

Characteristic	Chi-square	*p*-value
Age	1.564	0.458
Marital status	1.849	0.397
Education	1.682	0.431
Monthly income	6.883	0.032**
Time since enrolment	1.995	0.369

** Significant at the 5% level of significance

3.3 DMCI subscale scores

3.3.1 DMCI self-control subscale scores

The self-control subscale was made up of three DMCI items: ‘I made the decision’; ‘The decision was up to me’ and ‘I was not the one to choose’. High scores on this subscale reflect the presence of self-control. Possible scores for this subscale ranged between 18

and 3. Participants' self-control subscale scores in this study ranged between 18 and 6 (Table 15 and Figure 7). Forty-eight participants scored 18, 23 participants scored 17, 13 participants scored 16 and 16 participants scored 15 or less. Only one participant obtained a score in the bottom half of the range of possible scores suggesting that all but one participant in this study experienced perceived self-control.

Table 15

Frequency distribution of grouped DMCI self-control subscale scores

DMCI self-control subscale	Frequency
<=15	16
16	13
17	23
18	48
Total	100

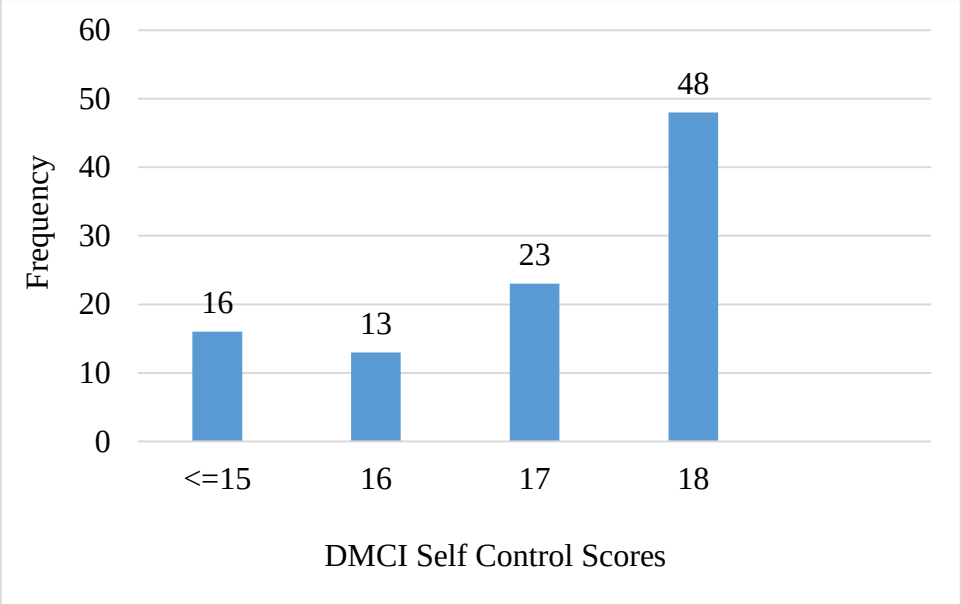


Figure 7. Bar chart of grouped DMCI self-control subscale scores

The tables that follow show a summary of results of Mann-Whitney (Table 16) and Kruskal-Wallis (Table 17) tests for DMCI self-control subscale scores subdivided according to sample characteristics. No significant relationships existed between DMCI self-control subscale scores and any of the sample characteristics indicating that sample characteristics did not affect participants' perceived self-control.

Table 16

DMCI self-control compared to sample characteristics – Mann-Whitney

Characteristic	*Z* statistic	*p*-value
Host trial	0.185	0.853
Employed	1.146	0.252
Time to consent	0.126	0.900

Table 17

DMCI self-control compared to sample characteristics – Kruskal-Wallis

Characteristic	Chi-square	*p*-value
Age	0.898	0.638
Marital status	1.964	0.375
Education	4.436	0.109
Monthly income	4.27	0.118
Time since enrolment	3.975	0.137

3.3.2 DMCI absence of control subscale scores

The absence of control subscale was made up of the following three DMCI items, 'I was powerless in the face of the decision'; 'I was passive in the face of the decision' and 'I was not in control of this decision'. Low scores on this subscale reflect an absence of control. Possible scores for this subscale ranged between 18 and 3 with participants' actual scores in this study ranging between 18 and 4 (Table 18 and Figure 8). Half the

participants scored 18, 11 participants scored 17, 10 participants scored 16 and 29 participants scored 15 or less. Only two participants obtained a score on the bottom half of the range of possible scores indicating that 98% of participants did not demonstrate a perceived absence of control.

Table 18

Frequency distribution of grouped DMCI absence of control subscale scores

DMCI Absence of self-control subscale	Frequency
<=15	29
16	10
17	11
18	50
Total	100

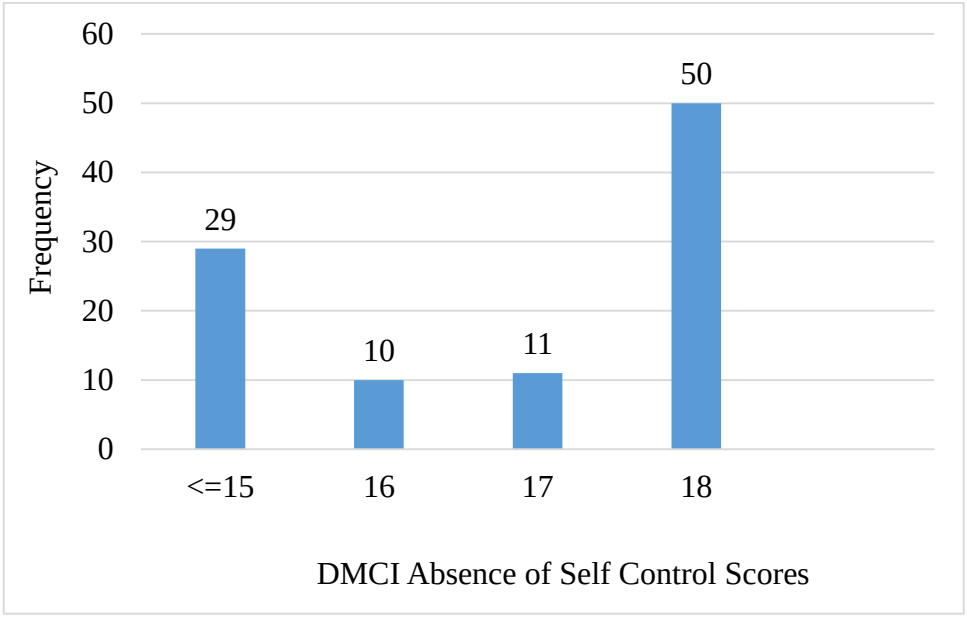


Figure 8. Bar chart of grouped DMCI absence of control subscale scores

The tables that follow show a summary of results of Mann-Whitney (Table 19) and Kruskal-Wallis (Table 20) tests for DMCI absence of control subscale scores subdivided according to sample characteristics. The only significant relationship was observed between DMCI absence of control subscale and monthly income (X^2 = 5.917, *df*=2, *p*=.052, *p*<.1). Participants who earned less than R1,000 were less likely to have a high DMCI absence of control subscale score than participants who earned no income or more than R1,000 per month.

Table 19

DMCI absence of control compared to sample characteristics – Mann-Whitney

Characteristic	*Z* statistic	*p*-value
Host trial	1.288	0.198
Employed	1.202	0.229
Time to consent	0.91	0.363

Table 20

DMCI absence of control compared to sample characteristics – Kruskal-Wallis

Characteristic	Chi-square	p-value
Age	1.993	0.369
Marital status	0.984	0.611
Education	1.474	0.479
Monthly income	5.917	0.052*
Time since enrolment	1.604	0.448

*Significant at the 10% level of significance

3.3.3 DMCI others control subscale scores

The others control subscale was made up of the following three DMCI items, 'Someone took the decision away from me'; 'The decision about the protocol was inappropriately

influenced by others' and 'others made the decision against my wishes'. Low scores on this subscale reflect control by others. Possible scores range between 18 and 6. Participants' scores for the DMCI others control subscale in this study ranged between 18 and 6 (Table 21 and Figure 9). Almost half the participants scored 18 (*n*=49), 15 participants scored 17, eight participants scored 16 and 28 participants scored 15 or less. Only two participants obtained a score on the bottom half of the range of possible scores indicating that 98% of participants' demonstrated perceived freedom from others control.

Table 21

Frequency distribution of grouped DMCI others control subscale scores

DMCI others control subscale	Frequency
<=15	28
16	8
17	15
18	49
Total	100

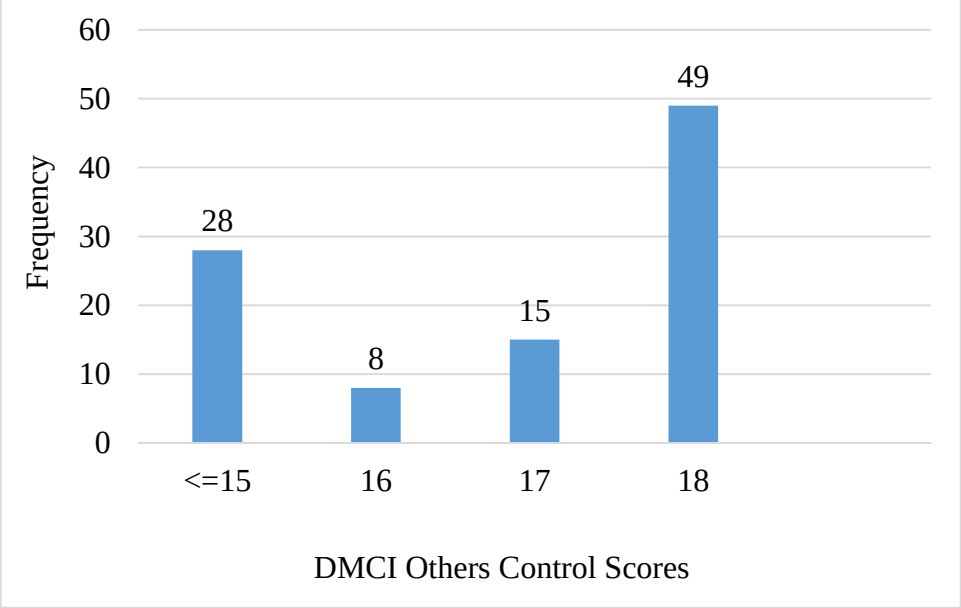


Figure 9. Bar chart of grouped DMCI others control subscale scores

The following tables show a summary of results of Mann-Whitney (Table 22) and Kruskal-Wallis (Table 23) tests for the DMCI others control subscale scores subdivided according to sample characteristics. No significant relationships were observed between the DMCI others control subscale and the sample characteristics indicating that sample characteristics did not affect participants' perceived control from others.

Table 22

DMCI others control compared to sample characteristics – Mann-Whitney

Characteristic	*Z* statistic	*p*-value
Host trial	1.556	0.12
Employed	0.96	0.337
Time to consent	0.845	0.398

Table 23

DMCI others control compared to sample characteristics – Kruskal-Wallis

Characteristic	Chi-square	*p*-value
Age	0.607	0.738
Marital status	2.465	0.292
Education	0.64	0.726
Monthly income	3.733	0.155
Time since enrolment	2.651	0.266

3.3.4 Relationship between scores for DMCI subscales

Spearman's Rank coefficient was used to determine the relationship between the three DMCI subscales (Table 24). There was a moderately strong positive correlation between the self-control subscale and the absence of control subscale (r=.600, p<.05) and a moderately strong positive correlation between the self-control subscale and the others

control subscale (r=.691, p<.05). There was also a moderately strong positive correlation between the others control subscale and the absence of control subscale (r=.799, p<.05). The relationship observed between the three subscales was therefore as expected: As 'self-control' increased, freedom from 'absence of control' and freedom from 'others control' also increased.

Table 24

Relationship between scores for the three DMCI subscales

			Self-control	Absence of control	Others control
Spearman's rho	Self-control	Correlation Coefficient	1.000	.600**	.691**
		Sig. (2-tailed)	.	.000	.000
		N	100	100	100
	Absence of self-control	Correlation Coefficient	.600**	1.000	.799**
		Sig. (2-tailed)	.000	.	.000
		N	100	100	100
	Others control	Correlation Coefficient	.691**	.799**	1.000
		Sig. (2-tailed)	.000	.000	.
		N	100	100	100

** Significant at the 5% level of significance

For each of the three subscales (self-control, absence of control and others control) the three score categories <=15, 16–17 and >=18 were formed (Tables 15, 18 and 21) and Chi-square goodness-of-fit tests involving each pair of variables were performed. In each case the subscale totals are positively associated. The results are summarised in Table 25 below.

Table 25

Associations between subscale variables

Pair	Chi-square	*p*-value	*df*
Self-control and Absence of self-control	52.853	0.000	9
Self-control and Others control	58.222	0.000	9
Others control and Absence of self-control	119.914	0.000	9

The mean total scores for the three subscales were all similar and are shown in Table 29 below.

Table 26

Mean total scores for subscales

DMCI sub-scale	Mean
Self-control subscale	16.94
Absence of self-control subscale	16.49
Others control subscale	16.66

A repeated measures Analysis of Variance (ANOVA) was performed to test for differences between means for the three subscale totals. The hypothesis of equal means was rejected (F=3.481, p=.033). Summaries of the overall test for difference between means (repeated measures ANOVA) and differences between pairs of means (Wilcoxon Signed rank test) are shown in Tables 27 and 28.

Table 27

Results of a repeated measures analysis of variance on subscale totals

Tests of Within-Subjects Effects						
Measure: sum Source		Type III Sum of Squares	*df*	Mean Square	F	Sig.
DMCI	Sphericity Assumed	10.327	2	5.163	3.481	.033**
	Greenhouse-Geisser	10.327	1.690	6.110	3.481	.041**
	Huynh-Feldt	10.327	1.716	6.017	3.481	.040**
	Lower-bound	10.327	1.000	10.327	3.481	.065
Error(DMCI)	Sphericity Assumed	293.673	198	1.483		
	Greenhouse-Geisser	293.673	167.331	1.755		
	Huynh-Feldt	293.673	169.923	1.728		
	Lower-bound	293.673	99.000	2.966		

** Significant at the 5% level of significance

A Wilcoxon signed rank test was performed for the different pairs of subscale variables to determine which of these differ significantly. When applying the Bonferroni correction (multiplying each of the above-mentioned p-values by 3) a significant difference was found between the DMCI self-control and the DMCI absence of control means (Z=-2.373, p=.018, p<.1) suggesting that the self-control subscale mean is greater than the absence of control mean.

Table 28

Wilcoxon signed rank test for differences between subscale total means

Test Statistics[a]			
	dmci_abs - dmci_selfc	dmci_otherC - dmci_selfc	dmci_otherC - dmci_abs
Z	-2.373[b]	-1.990[b]	-.691[c]
Asymp. Sig. (2 tailed)	.018	.047	.489

a. Wilcoxon Signed Ranks Test

b. Based on positive ranks.

c. Based on negative ranks.

3.5 Internal consistency

Internal consistency for the DMCI (.869) and three subscales (.819) was sufficiently high (Table 29) indicating that the DMCI had good internal reliability.

Table 29

Cronbach's alpha for DMCI and DMCI subscales

Items	No of items	alpha
DMCI	9	0.869
DMCI Subscales	3	0.819

4 Survey of Influences

4.1 Influences from other people

4.1.1 Consulted others about participation

The majority of participants (95%) consulted another person about possible research participation. Only five participants did not consult another person about possible research participation. Seventy-three participants spoke to their partner about research participation prior to enrolment. Seventy-one participants spoke to their family and 62 participants spoke to their friends about participation before enrolling. Eighty-two participants reported speaking to a member of the CAPRISA research team prior to enrolment and only two participants spoke about research participation with an external health care provider. None of the participants surveyed spoke to their employer, a colleague or their community leader (Table 30 and Figure 10).

Table 30

Cross-tabulation of people consulted regarding research participation

	Consulted regarding research participation?		Total
	Yes	No	
Partner	73	27	100
Family	71	29	100
Friend	62	38	100
Health Care Provider	2	98	100
CAPRISA Staff	82	18	100
Employer	0	100	100
Colleague	0	100	100
Community Leader	0	100	100

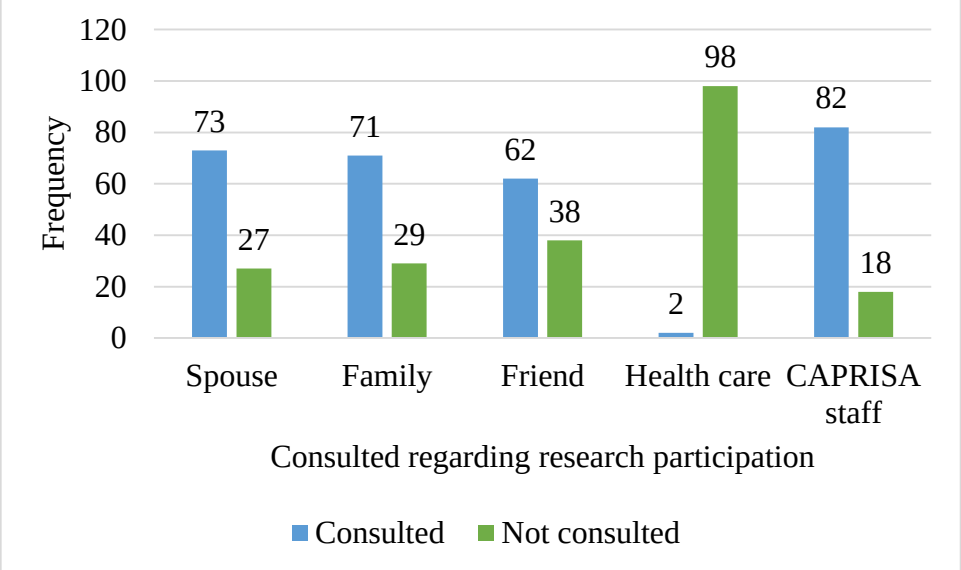


Figure 10. Bar chart of people consulted regarding research participation

4.1.2 Influenced by others

Less than half of the participants sampled (*n*=39) reported being influenced by another person (some of these participants reported being influenced by more than one person). Eleven percent of the 100 participants surveyed reported being exposed to an influence from their partner, 10% from their family, 13% from a friend, 1% from a health care provider and 18% of the whole sample were exposed to an influence from the CAPRISA research staff. That is, the majority of people consulted by participants prior to participation in the host trials did not try to influence the participants' decision about research participation. Of the 73 participants who consulted their partner, 15.1% (*n*=11) reported that their partner tried to influence their consent decision. Of the 71 participants who consulted their family, 14.1% (*n*=10) reported that their family tried to influence their consent decision. Thirteen (20.9%) of the 62 participants who consulted their friends said that their friends tried to influence their consent decision. One of the two participants who consulted their health care provider said that they tried to influence their consent decision. Lastly, of the 82 participants who reported speaking to a CAPRISA staff member, only 21.9% (*n*=18) said that the CAPRISA staff member tried to influence their decision (Table 31 and Figure 11).

Table 31

Cross-tabulation of attempts to influence consent decision

	Attempted to influence consent decision				Total
	Yes		No		
	n	%	n	%	
CAPRISA Staff	18	21.9%	64	78.1%	82
Friend	13	20.9%	49	79.1%	62
Partner	11	15.1%	62	84.9%	73
Family	10	14.1%	61	85.9%	71
Health Care Provider	1	50%	1	50%	2

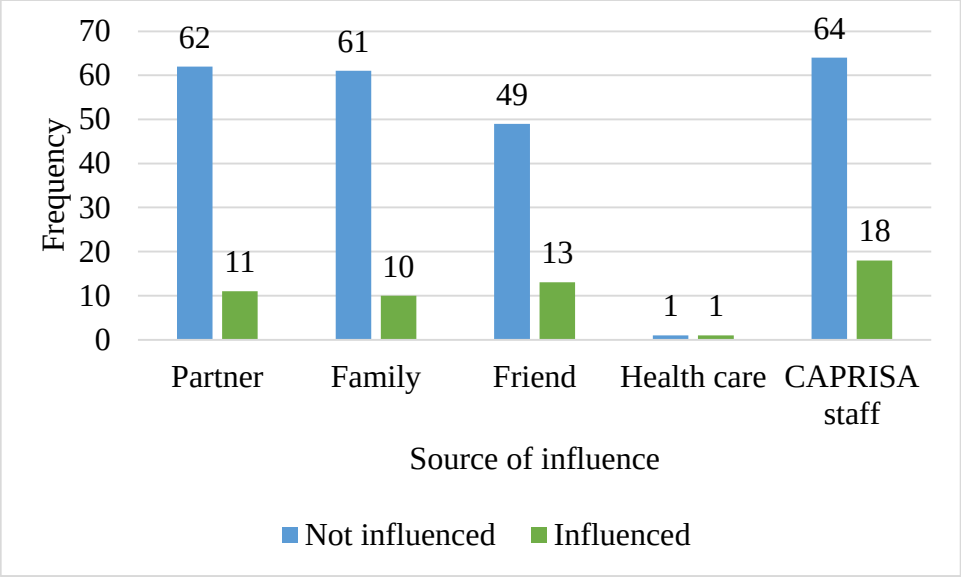


Figure 11. Bar chart of attempts to influence consent decision

Participants reported being both influenced to participate and not to participate (Table 32 and Figure 12). Of the 11 participants who were influenced by their partner, 63.6% (*n*=7) were influenced to participate and 36.4% (*n*=4) were influenced not to participate. Sixty percent (*n*=6) of the 10 participants who reported being influenced by their family said that their family tried to influence them not to participate and 40% (*n*=4) said their family tried to influence them to participate. Eleven of the participants were influenced not to participate by their friend (84.6%) and only two were influenced to participate (15.4%). The one participant who was influenced to participate by their health care provider was influenced to participate. Of the 18 participants who reported that CAPRISA research staff tried to influence their decision 94.4% (*n*=17) said that CAPRISA research staff tried to influence them to participate and only one participant said CAPRISA research staff tried to influence them not to participate.

Table 32

Cross-tabulation of direction of influence

	Direction of influence				Total
	Influenced to participate		Influenced not to participate		
	n	%	*n*	%	
Partner	7	63.6%	4	36.4%	11
Family	4	40%	6	60%	10
Friend	2	15.4%	11	84.6%	13
Health Care Provider	1	100%	0	-	1
CAPRISA Staff	17	94.4%	1	5.6%	18

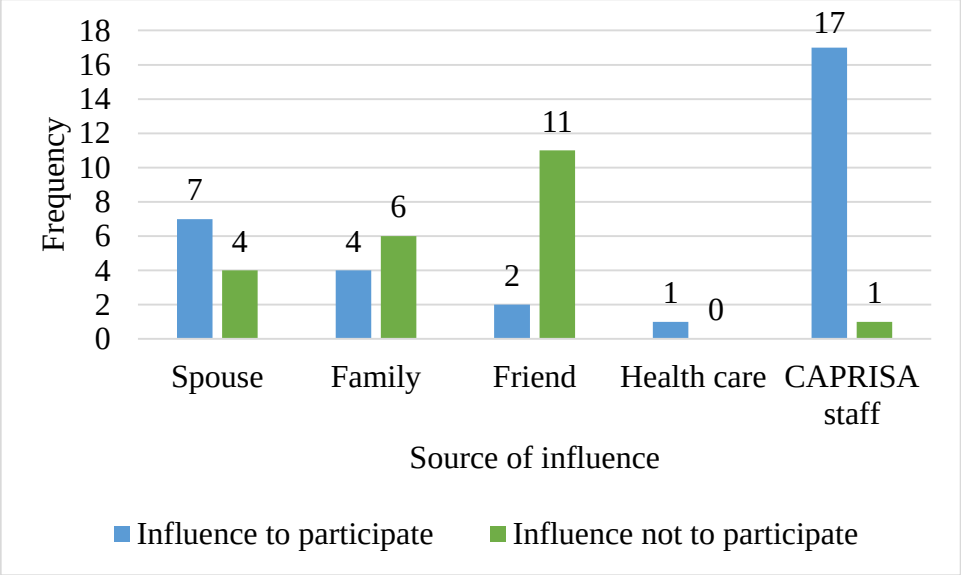


Figure 12. Bar chart of direction of influence

4.1.3 Type of influence

Influences explored in the Survey of Influences were threats, pressure, advice and offers. Participants reported being threatened, pressured and advised by other people (Table 33 and Figure 13). No participants reported the presence of offers. Of the 100 participants, only one participant reported being threatened by their family and two reported being threatened by a friend in attempt to prevent their enrolment in the host research. Two participants reported being pressured by a partner, one participant was pressured to participate and the other was pressured not to participate. Two participants were advised by their partner, three were advised by their family, three were advised by a friend and 11 participants were advised by CAPRISA research staff.

Table 33

Cross-tabulation of type of influence

	Type of influence								Total
	Threat		Pressure		Advice		Other		
	n	%	*n*	%	*n*	%	*n*	%	
Partner	0	-	2	18.2%	2	18.2%	7	63.6%	11
Family	1	10%	0	-	3	30%	6	60%	10
Friend	2	15.4	0	-	3	23.1	8	61.5%	13
Health Care Provider	0	-	0	-	0	-	1	100%	1
CAPRISA Staff	0	-	0	-	11	61.1%	6	33.3%	17*

* Missing data for 1 respondent

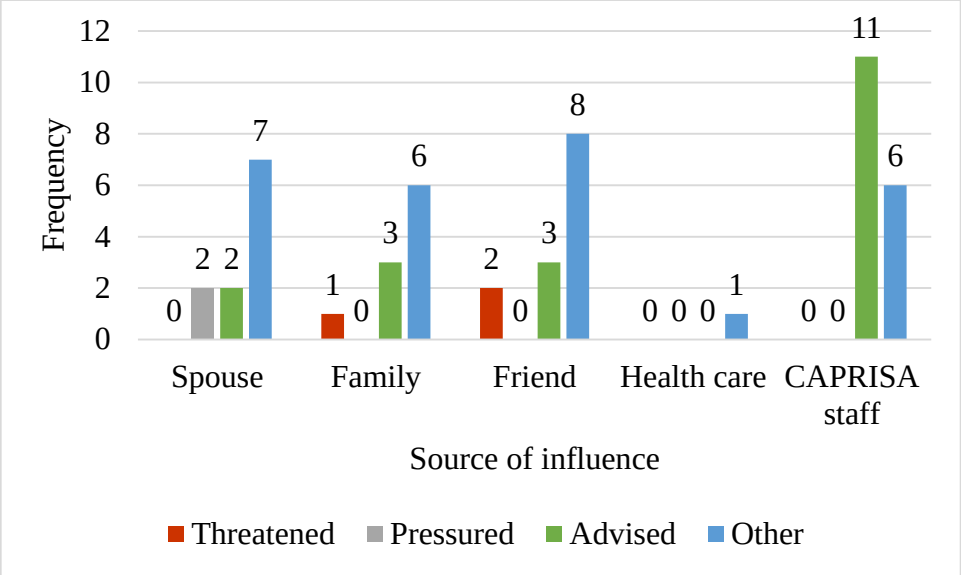


Figure 13. Bar chart of type of influence

4.1.4 Intentionality, legitimacy and causality of influence

The majority of participants perceived influences from other people as intentional and legitimate and not causing them to make the consent decision they did. Only one participant reported perceiving an influence from their partner as controlling and subsequently may have participated nonvoluntarily by indicating an 'agree' response to the intentionality statement, a 'disagree' response to the first legitimacy statement and an 'agree' response to the second legitimacy statement as well as the causality statement.

Of the 11 participants influenced by their partner, seven (63.6%) agreed or strongly agreed that their partner's influence was intentional. In terms of legitimacy, six participants (54.5%) agreed or strongly agreed that their partner had the right to influence their consent decision and four participants (36.4%) agreed that their right to make a free independent consent decision was violated by their partner. Lastly, four (36.4%) participants agreed or strongly agreed that their partner's influence caused them to make the consent decision they did.

Of the 10 participants influenced by their family, six (60%) agreed or strongly agreed that their family's influence was intentional. In terms of legitimacy, five participants (50%) agreed or strongly agreed that their family had the right to influence their consent decision and only one agreed that their right to make a free independent consent decision was violated by their family. Lastly, only one agreed or strongly agreed that their family's influence caused them to make the consent decision they did.

Of the 13 participants influenced by a friend, 11 (84.6%) agreed or strongly agreed that their friends' influence was intentional. In terms of legitimacy, all 13 participants (100%) agreed or strongly agreed that their friends had the right to influence their consent decision and six participants (46.2%) agreed that their right to make a free independent consent decision was violated by their friend. Lastly, only one participant (7.7%) agreed or strongly agreed that their friends' influence caused them to make the consent decision they did.

The one participant who was influenced by their health care provider, disagreed that their influence was intentional, disagreed that the health care provider had the right to influence her decision, that her rights were violated and disagreed that the health care provider's influence caused her to participate.

Of the 17 participants influenced by a member of the CAPRISA research staff, 11 (64.7%) agreed or strongly agreed that the staff member's influence was intentional. In terms of legitimacy, eight participants (47%) agreed or strongly agreed that the staff member had the right to influence their consent decision and only one participant (5.8%) agreed or strongly agreed that their right to make a free independent consent decision was violated by the staff member. Lastly, eight participants (47%) agreed or strongly agreed that the staff member's influence caused them to make the consent decision they did. These findings are summarised in Table 34 below.

Table 34

Intentionality, legitimacy and causality of influence

	Strongly Agree	Agree	Neither Agree or Disagree	Disagree	Strongly Disagree	Total
Intentionality: This person was purposefully trying to influence my consent decision						
Partner	3	4	3	1	0	11
Family	2	4	2	2	0	10
Friend	4	7	1	1	0	13
Health Care Provider	0	0	0	1	0	1
CAPRISA Staff	3	8	2	2	2	17
Legitimacy: This person had the right to influence my consent decision						
Partner	0	6	0	4	1	11
Family	0	5	0	4	1	10
Friend	3	10	0	0	0	13
Health Care Provider	0	0	0	1	0	1
CAPRISA Staff	2	6	3	4	2	17
Legitimacy: This person violated my right to make a free independent consent decision						
Partner	0	4	1	5	1	11
Family	0	1	0	6	3	10
Friend	1	5	0	7	0	13
Health Care Provider	0	0	0	0	1	1
CAPRISA Staff	0	1	1	12	3	17
Causality: This persons influenced caused me to make the consent decision I did						
Partner	1	3	0	5	2	11
Family	1	2	0	7	0	10
Friend	1	0	0	8	4	13
Health Care Provider	0	0	0	0	1	1
CAPRISA Staff	3	5	5	3	1	17

A Kruskal-Wallis test was used to compare intentionality, legitimacy and causality to the person who exerted the influence (Tables 35 and 36). Significant differences between people who influenced participants' consent decision were observed for legitimacy: 'This person had the right to influence my consent decision' (X^2 = 10.984, *df* = 3, *p*=.012, *p*<.05). Participants were more likely to agree that friends have the right to influence their consent decisions. A significant difference was also observed for legitimacy: 'This person violated my right to make a free, independent consent decision' (X^2 = 9.964, *df* = 3, *p*=.019, *p*<.05). Participants were more likely to agree that a partner or friend violated their right to make a free and independent consent decision. Lastly, a significant difference was observed for causality: 'This person caused me to make the consent decision I did' (X^2 = 12.048, *df* = 3, *p*=.007, *p*<.01). Friends had significantly less influence in causing a consent decision to be made than the other groups. CAPRISA staff members had the most influence in causing a consent decision to be made.

Table 35

Kruskal-Wallis tests for comparing intentionality, legitimacy and causality

	Intentionality	Legitimacy: Right to influence	Legitimacy: Rights violated	Causality	Total
Chi-Square	2.094	10.984	9.964	12.048	4.740
df	3	3	3	3	3
Asymp. Sig	.553	.012**	.019**	.007***	.192

** Significant at the 5% level of significance

*** Significant at the 1% level of significance

Table 36

Mean ranks for influences from others[1] and intentionality, legitimacy and causality

	Intentionality	Legitimacy: Right to influence	Legitimacy: Rights violated	Causality	Total
Partner	26.5	22.05	30.45	25	26.5
Family	23.9	20.95	19.2	26.4	18.65
Friend	30.46	36.69	33.35	16.08	31.96
CAPRISA Staff	23.5	23.35	21.5	34	25.44

[1] Due to the fact that there was only one response concerning health care providers, this was excluded from this part of the analysis.

4.2 Influences from conditions

Influences from conditions were also examined (Table 37 and Figure 14). The three main reasons participants enrolled in the host trials were (1) because they wanted to (*n*=97), (2) because they needed health care (*n*=89) and (3) because they trusted the researchers (*n*=84). Ill health influenced just over half of the participants to enrol in the host trials (n=53). Needing money (*n*=13), having no other choice (*n*=12) and pleasing some other person (researcher, partner, someone else) (*n*=12) were less likely to influence participation in the host trials.

Table 37

Influences from conditions

	Influence from conditions		Extent of influence			Participation if influence had not been present	
	Yes	No	A little	A lot	It is the only reason I participated	Yes	No
Wanted to participate	97	3	3	87	7	8	89

Need for health care	89	11	2	76	11	37	52
Trust researchers	84	16	4	77	3	5	78
Illness	53	47	2	37	14	20	33
Need for money	13	87	9	4	0	9	4
Had no choice	12	88	3	6	3	2	10
To please the researchers	5	95	2	3	0	2	3
To please my partner	3	97	0	3	0	2	1
To please someone else	4	96	0	3	1	1	3

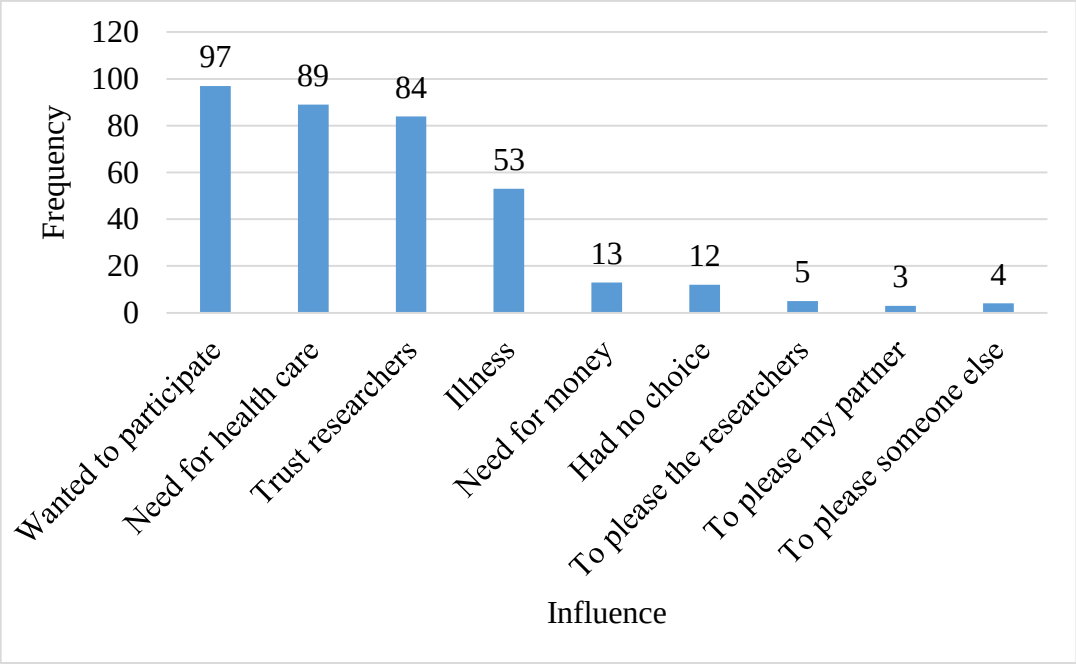


Figure 14. Bar chart of influence from conditions

The importance of each influence was also examined (Table 38 and Figure 15). Of the 97 participants who participated because they wanted to 89.7% (*n*=87) said this influenced their participation 'a lot'. Of the 89 participants who were influenced to participate by the need for health care 85.4% (*n*=76) rated a need for health care as influencing them 'a lot'. Of the 84 participants who mentioned trust in the researcher as influencing their participation 91.7% (*n*=77) said this influenced their participation 'a lot' and of the 53 participants who were influenced to participate by their ill health 69.8% (*n*=37) rated ill health as influencing them 'a lot'.

A Chi-square test (X^2 = 20.269, *df*=6, *p*=.00248) revealed that 'illness' (26.4%) and 'need health care' (12.4%) had significantly higher percentages of 'only reason I participated' responses than 'trust researchers' (3.6%) and 'wanted to' (7.2%).

Table 38

Cross-tabulation of four main influences from conditions and extent of influence

	Extent of Influence						Total
	A Little		A Lot		It is the only reason I participated		
	n	%	*n*	%	*n*	%	
Illness	2	3.8%	37	69.8%	14	26.4%	53
Need health care	2	2.2%	76	85.4%	11	12.4%	89
Trust researchers	4	4.7%	77	91.7%	3	3.6%	84
Wanted to	3	3.1%	87	89.7%	7	7.2%	97

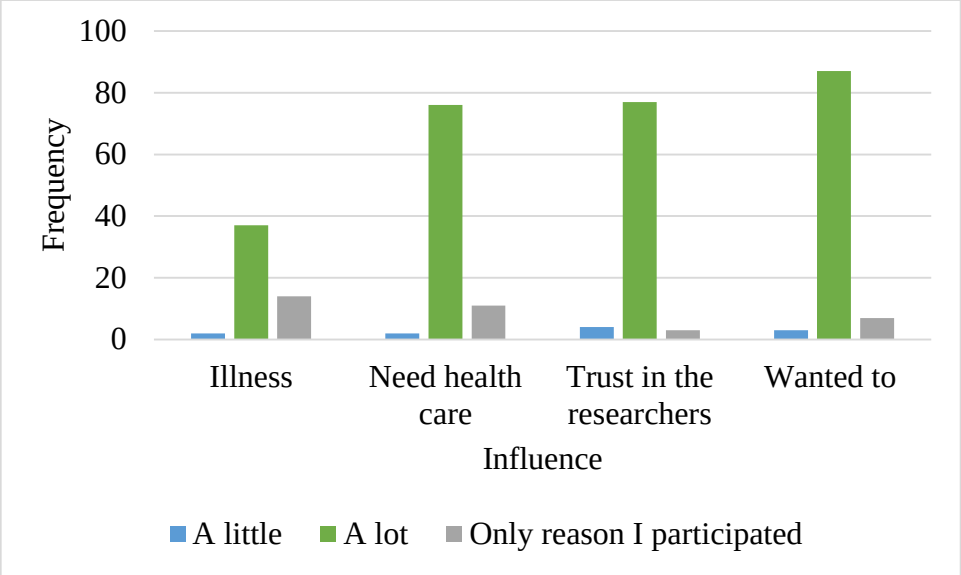


Figure 15. Bar chart of four main influences from conditions and extent of influence

In terms of the four main influences from conditions, the majority of participants said that they would not have participated had these influences not been present (Table 39 and Figure 16). Of the 53 participants citing illness as influencing their participation in the host trials, 62.3% (*n*=33) would not have participated had it not been for their ill health. Fifty-two (58.4%) of the 89 participants who participated in the host trials to receive health care would not have participated had they not needed health care. Of the 83 participants who participated in the host trials because they trusted the researches, 93.9% (*n*=78) would not have participated had this influence not been present. Lastly and importantly, 91.8% (*n*=89) of the 97 participants who participated in the host trials because they wanted to, would not have participated had they not wanted to.

When performing a Chi-square test for this data, illness (37.7%) and free health care (41.6%) had significantly higher percentages of 'yes' responses than trust in the researchers (6%) and wanted to participate (8.2%) (X^2 = 50.977, *df*=3, *p*=.000).

Table 39

Cross-tabulation of participation if influence had not been present for four main influences from conditions

	Participation if influence had not been present				Total
	Yes		No		
	n	%	*n*	%	
Illness	20	37.7%	33	62.3%	53
Need health care	37	41.6%	52	58.4%	89
Trust researchers	5	6.1%	78	93.9%	83
Wanted to	8	8.2%	89	91.8%	97

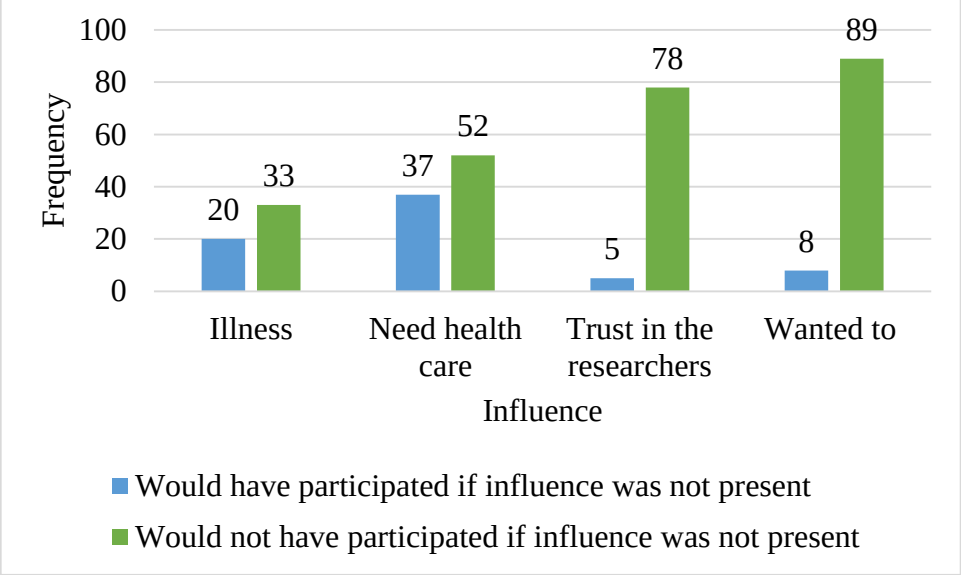


Figure 16. Bar chart of participation if influence had not been present for four main influences from conditions

4.2.1 Relationship between influences from conditions and sample characteristics

Chi-square tests of independence were performed to examine the relation between participants' influences from conditions and the sample characteristics (Table 40).

Table 40

Chi-square statistics of sample characteristics compared to influences from conditions

	Illness	Need Health Care	Need	Please Researcher	Please Partner	Please Someone Else	Trust Researcher	No Other Choice	Wanted To
Host Trial	10.382****	2.012	1.023	0.157	0.96	0.678	0.036	0.081	0.503
Age	10.539***	1.222	0.083	1.182	2.24	3.017	0.909	0.007	2.24
Marital Status	5.775*	1.057	0.869	1.416	0.48	0.374	0.542	3.622	0.48
Employment	1.988	1.868	4.951**	0.376	0.044	1	0.1	3.274*	0.044
Education	0.731	0	1.716	0.527	2.578	1.563	0.289	1.6	0.688
Income	8.81**	3.307	9.792***	6.87**	14.923***	3.256	0.299	7.168***	0.697
Time since enrolment	27.38****	4.796*	1.947	0.304	0.267	0.007	3.429	4.772*	3.351
Time since consent	0.056	0	0.89	0.012	0.477	0.926	2.191	0.427	4.889**

* Significant at the 10% level of significance.

** Significant at the 5% level of significance.

*** Significant at the 1% level of significance.

**** Significant at the 0.1% level of significance.

The Chi-square test revealed a significant relationship between illness and host trial (X^2 = 10.382, *df*=1, *p*=0.00), age (X^2 = 10.539, *df*=2, *p*=0.01), marital status (X^2 = 5.775, *df*=2, p=0.06), income (X^2 = 8.81, *df*=2, *p*=0.01) and time since enrolment (X^2 = 27.38, *df*=2, *p*=0.00) (Table 41). CAPRISA 009 participants were more likely to be influenced to enroll in the host trials by illness than CAPRISA 008 participants. Participants who were older, single and had a higher income were more likely to be influenced to enroll in the host trials by illness. Participants who enrolled more than a year ago were also more likely to be influenced to enroll in the host trials by illness.

Table 41

Cross-tabulation of illness and sample characteristics

	Influenced by Illness		Total[1]
	Yes	No	
Host Trial			
CAPRISA 008	40	46	86
CAPRISA 009	13	1	14
Total	53	47	100
Age			
21–30	25	33	58
31–40	19	14	33
Over 40	9	0	9
Total	53	47	100
Marital Status			
Married	4	4	8
In relationship	33	38	71
Single	16	5	21
Total	53	47	100
Monthly Income			
No income	20	32	52
Less R1,000	11	6	17
Between R1,001–R5,000	21	9	30
Total	52	47	99
Time Since Enrolment			
Less than 3 months	16	32	48
Between 3 months – 1 year	12	14	26
Over 1 year	25	1	26
Total	53	47	100

[1] Frequency counts also represent frequency percentages as *N*=100

A Chi-square test revealed a significant relationship between being influenced to enroll in the host trials by a need for health care and time since enrolment (X^2 = 4.796, *df*=2, *p*=0.08) (Table 42). Participants who enrolled more than a year ago were more likely to be influenced to enroll in the host trials by the need for health care than those who enrolled less than a year ago.

Table 42

Cross-tabulation of a need for health care and sample characteristics

	Influenced by a need for health care		Total[1]
	Yes	No	
Time since enrolment			
Less than 3 months	40	8	48
Between 3 months – 1 year	23	3	26
Over 1 year	26	0	26
Total	89	11	100

[1] Frequency counts also represent frequency percentages as *N*=100

A Chi-square test also revealed a significant relationship between being influenced to enroll in the host trials, a need for money and employment status (X^2 = 4.951, *df*=1, *p*=0.03) and a need for money and monthly income (X^2 = 9.792, *df*=2, *p*=0.013) (Table 43). Participants who were not employed were less likely to be influenced to enroll in the host trials by a need for money and participants with no income were less likely to be influenced to enroll in the host trials by a need for money.

Table 43

Cross-tabulation of a need for money and sample characteristics

	Influenced by a need for money		Total[1]
	Yes	No	
Employment Status			
Employed	7	21	28
Unemployed	6	66	72
Total	13	87	100
Monthly Income			
No income	3	49	52
Less than R1,000	6	11	17
Between R1,001–R5,000	4	26	30
Total	13	86	99

[1] Frequency counts also represent frequency percentages as N=100

A significant relationship was observed between having no choice but to participate and employment status (X^2 = 3.274, df=1, p=0.07), monthly income (X^2 = 7.168, df=2, p=0.03) and time since enrolment (X^2 = 4.772, df=2, p<.1) (Table 44). Participants who were not employed were less likely to participate because they had no other choice. Participants with no income were less likely to participate because they had no other choice. Participants who enrolled less than a year ago were also less likely to participate because they had no other choice.

Table 44

Cross-tabulation of feelings of no other choice and sample characteristics

	Participated because of no other choice		Total[1]
Employment status	Yes	No	

Employed	6	22	28
Unemployed	6	66	72
Total	12	88	100
Monthly Income	Yes	No	
No Income	2	50	52
Less than R1,000	4	13	17
Between R1,001–R5,000	6	24	30
Total	12	87	99
Time since enrolment	Yes	No	
Less than 3 months	5	43	48
Between 3 months – 1 year	1	25	26
Over 1 year	6	20	26
Total	12	88	100

[1] Frequency counts also represent frequency percentages as N=100

A Chi-square test revealed a significant relationship between desire to please the researchers and monthly income (X^2 = 6.87, df=2, p=0.03) and a desire to please one's partner and monthly income (X^2 = 14.923, df=2, p=0.00) (Table 45). However the 'yes' counts are too low to comment. A significant relationship was also observed between wanting to participate and time to consent (X^2 = 4.889, df=1, p=0.03). However, the 'no' counts were too low to comment on.

Table 45

Cross-tabulation of desire to please the researchers, one's partner, wanting to participate and sample characteristics

	Desire to please the researcher		Total[1]
Monthly Income	Yes	No	
No Income	1	51	52

Less than R1,000	3	14	17
Between R1,001–R5,000	1	29	30
Total	5	94	99

	Desire to please one's partner		Total
Monthly Income	Yes	No	
No Income	0	52	52
Less than R1,000	3	14	17
Between R1,001–R5,000	0	30	30
Total	3	96	99

	Wanted to participate		Total
Time to consent	Yes	No	
24 hours or less	80	1	81
More than 24 hours	16	2	18
Total	96	3	99

[1] Frequency counts also represent frequency percentages as *N*=100

5. Comparison between Instruments

5.1 VNRI ratings and DMCI

A Mann-Whitney test showed that there was no significant difference between total DMCI scores for the VNRI voluntariness ratings of less than 10 and VNRI voluntariness ratings of 10 (Z=.644, P=.519) suggesting that the VNRI ratings could not differentiate between high and low DMCI scores (Table 46).

Table 46

DMCI total scores compared to VNRI voluntariness ratings

DMCI total scores	VNRI ratings	Total

	Less than fully voluntary (<10)	Fully voluntary (10)	
<=45	2	18	20
46–50	4	17	21
51–53	1	21	22
54	4	50	54
Total	11	106	117

5.2 VNRI ratings, DMCI and Survey of Influences (others)

A Chi-square test was used to compare influences from a partner, family member, friend or CAPRISA staff member to the VNRI ratings. No significant relationships were observed (Table 47).

Table 47

VNRI ratings compared to influences from others

Influence	Chi-square	*p*-value
Partner	0.55	0.458
Family	0.018	0.894
Friend	0.014	0.906
CAPRISA staff	0.665	0.415

Influences from a partner, family member, friend or CAPRISA staff member were compared to the total DMCI scores using a Chi-square test (Table 48).

Table 48

DMCI total scores compared to influences from others

Influence	Chi-square	*p*-value
Partner	2.744	0.433
Family	1.602	0.659
Friend	3.657	0.301
CAPRISA staff	14.051	0.003*

* Significant at the 0.5% level of significance.

A significant relationship was observed between being influenced by a CAPRISA staff member and DMCI scores (X^2 = 14.051, *df*=3, *p*=.003, p<.005). Participants with low DMCI total scores (<=45) (lower perceived voluntariness) were less likely to be influenced by CAPRISA staff than those with scores above 45 (higher perceived voluntariness) (Table 49).

Table 49

DMCI total scores compared to influences from CAPRISA staff

DMCI total score	Influenced by CAPRISA staff	Not influenced by CAPRISA staff	Total
<=45	11	9	20
46–50	18	3	21
51–53	18	4	22
>=54	35	2	37
Total	82	18	100

5.3 VNRI ratings, DMCI total scores and Survey of Influences (conditions)

Chi-square tests were used to compare influences from conditions to the VNRI ratings and the DMCI total scores (Table 50).

Table 50

VNRI ratings, DMCI total scores and influences from conditions

	VNRI ratings		DMCI total scores	
	Chi-square	*p*-value	Chi-square	*p*-value
Illness	0.561	0.454	3.707	0.295
Need for health care	0.046	0.830	6.771*	0.080
Need for money	0.293	0.588	24.723****	0.000
Please researchers	0.435	0.510	12.581***	0.006
Please partner	0.382	0.537	5.416	0.144
Please someone else	0.834	0.361	8.792**	0.032
Trust researchers	0.439	0.508	0.894	0.827
Had no choice	2.73*	0.099	19.421****	0.000
Wanted to	1.576	0.209	12.371***	0.006

* Significant at the 10% level of significance

** Significant at the 5% level of significance

*** Significant at the 1% level of significance

**** Significant at the 0.1% level of significance

A significant association was observed between VNRI ratings and feelings of having no choice but to participate ($X^2 = 2.73$, $df=1$, $p=.099$, $p<.1$) (Table 51). Participants with a VNRI rating of 10 (fully voluntary) were less likely to feel that they had no choice but to participate than those with a VNRI rating of less than 10 (less than fully voluntary). Participants who perceived their participation as fully voluntary were therefore less likely to feel like they had no choice but to participate.

Table 51

Cross-tabulation of VNRI rating and feelings of no other choice

	Feelings of having no choice		
VNRI rating	Yes	No	Total
Less than fully voluntary (<10)	3	8	11
Fully voluntary (10)	9	80	89
Total	12	88	100

A significant association was observed between DMCI scores and being influenced by the need for health care (X^2 = 6.771, *df*=3, *p*=.080, *p*<.1) (Table 52). Participants with DMCI of 45 or less were less likely to agree that they were influenced by the need for health care than those who scored above 45. Participants with higher levels of voluntariness according to the DMCI were therefore more likely to be influenced by the need for health care.

Table 52

Cross-tabulation of DMCI total scores and the need for health care

DMCI	Need for health care		Total
	Yes	No	
<=45	15	5	20
46–50	19	2	21
51–53	22	0	22
>=54	33	4	37
Total	89	11	100

A significant association was observed between DMCI scores and being influenced by the need for money (X^2 = 24.723, *df*=3, *p*=.000, *p*<.001) (Table 53). Participants with DMCI of 45 or less were less likely to disagree that they were influenced by the need for

money than those who scored above 45. Participants with higher levels of voluntariness according to the DMCI were therefore less likely to be influenced by the need for money.

Table 53

Cross-tabulation of DMCI total scores and the need for money

DMCI	Need for money		Total
	Yes	No	
<=45	9	11	20
46–50	0	21	21
51–53	3	19	22
>=54	1	36	37
Total	13	87	100

A significant association was observed between DMCI scores and being influenced by a need to please the researchers (X^2 = 12.581, *df*=3, *p*=.006, *p*<.01) (Table 54). Participants with DMCI of 45 or less were less likely to disagree that they were influenced by a need to please the researchers than those who scored above 45. Participants with higher levels of voluntariness according to the DMCI were therefore less likely to be influenced by a need to please the researchers.

Table 54

Cross-tabulation of DMCI total scores and a need to please the researchers

DMCI	Please researchers		Total
	Yes	No	
<=45	4	16	20
46–50	1	20	21
51–53	0	22	22
>=54	0	37	37
Total	5	95	100

A significant association was observed between DMCI scores and being influenced by a need to please someone else (X^2 = 8.792, *df*=3, *p*=.0322, *p*<.05) (Table 55). However there were too few 'yes' counts to comment.

Table 55

Cross-tabulation of DMCI total scores and a need to please someone else

DMCI	Please someone else		Total
	Yes	No	
<=45	3	17	20
46–50	1	20	21
51–53	0	22	22
>=54	0	37	37
Total	4	96	100

A significant association was observed between DMCI scores and being influenced by a feeling of having no other choice (X^2 = 19.421, *df*=3, *p*=.000, *p*<.001) (Table 56). Participants with DMCI of 45 or less were less likely to disagree that they were influenced by a feeling of having no other choice than those who scored above 45. Participants with higher levels of voluntariness according to the DMCI were therefore less likely to be influenced by a feeling of having no other choice.

Table 56

Cross-tabulation of DMCI total scores and a feeling of having no other choice

DMCI	Feeling of having no other choice		Total
	Yes	No	
<=45	8	12	20
46–50	1	20	21
51–53	0	22	22

>=54	3	34	37
Total	12	88	100

A significant association was observed between DMCI scores and wanting to participate (X^2 = 12.371, *df*=3, *p*=0.006, *p*<.01) (Table 57). However, there were too few 'no' counts to comment on.

Table 57

Cross-tabulation of DMCI total scores and wanting to participate

DMCI	Wanted to participate		Total
	Yes	No	
<=45	17	3	20
46–50	21	0	21
51–53	22	0	22
>=54	37	0	37
Total	97	3	100

5.4 VNRI narratives and Survey of Influences

The VNRI narratives allowed participants to spontaneously identify factors affecting voluntariness while the Survey of Influences questioned participants about specific influences. The results of the two instruments were compared (Table 58 and Figure 17). The Survey of Influences resulted in more influences being reported in all categories than in the VNRI narratives, except in the case of influence from a health care provider, suggesting that questioning participants about specific influences may be a more valid means of data collection than allowing participants to spontaneously identify influence on their own. The VNRI however identified influences not explored in the Survey of Influences, namely, HIV prevention, altruism, distrust in the researcher and misunderstandings. This suggests that a formal assessment of voluntary consent should incorporate these issues in the future.

Table 58

Comparison between VNRI narratives and Survey of Influences

	Survey of Influences	VNRI Narratives
Influences from others		
Partner	11	3
Family	10	2
Friend	13	4
Health Care Provider	1	4
CAPRISA Staff	18	4
Influences from conditions		
Illness	53	12
Free health care	89	46
Payment	13	5
To please the researchers	5	0
To please my partner	3	0
To please someone else	4	0
Trust researchers	84	8

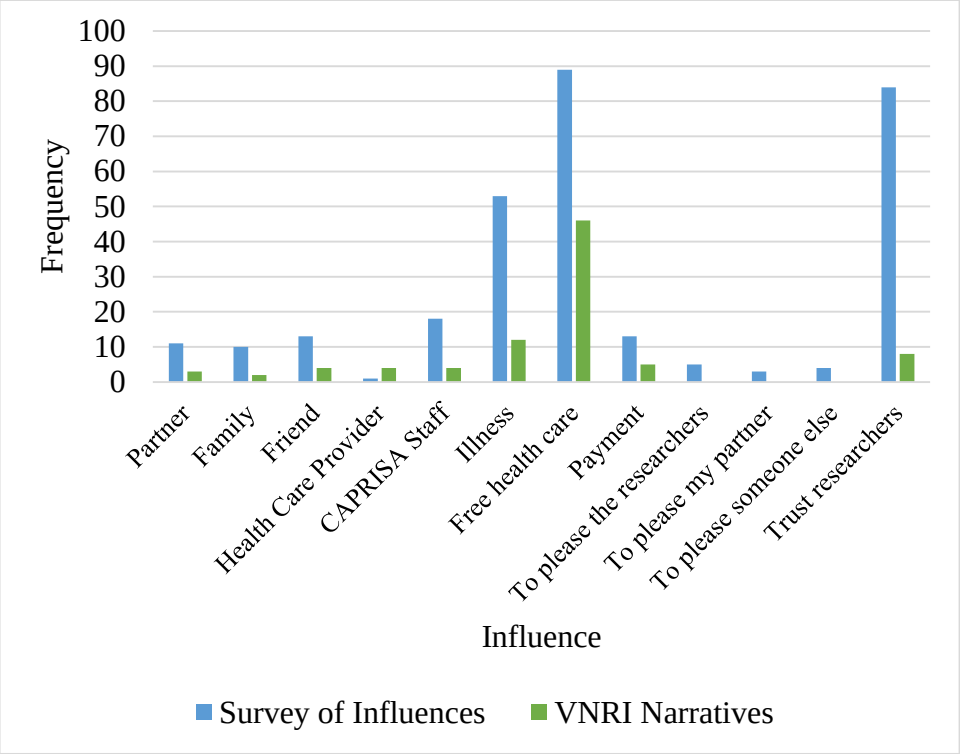


Figure 17. Comparison between VNRI narratives and Survey of Influences

6. Overview of Main Findings in Relation to Pilot Study Objectives

The first aim of this pilot study was to determine the perceived voluntariness of research participants' consent. High levels of perceived voluntariness were documented. The overwhelming majority of participants (*n*=93) reported that they perceived their consent decision as voluntary during their VNRI narratives. Similarly, in the VNRI ratings, 89% of participants rated their participation as fully voluntary with a score of 10. Only one participant produced a rating (four) in the bottom half of the scale. Lastly, the DMCI scores also revealed high levels of perceived voluntariness with 80% of participants scoring above 50 and only one participant obtaining a score (of 21) in the lower half of the range of possible scores.

The second aim of this study was to identify what factors undermined participants' perceived voluntariness of consent. In terms of the VNRI, lower perceived voluntariness was significantly associated with having more than a primary school education

(X^2 = 2.75, *df*=1, *p*=.097, *p*<.1) and taking more than 24 hours to research a consent decision (X^2 = 6.188, *df*=1, *p*=.0129, p<.05). Lower perceived voluntariness was also associated with feelings of having no choice but to participate (X^2 = 2.73, *df*=1, *p*=.099, *p*<.1). In terms of the DMCI, lower perceived voluntariness was significantly associated with earning between R1–R1,000 per month (X^2 = 6.883, *df*=2, *p*=.032, p<.05), not being influenced by a CAPRISA staff member (X^2 = 14.051, *df*=3, *p*=.003, p<.005)and with not needing health care (X^2 = 6.771, *df*=3, *p*=.080, *p*<.1). Lower perceived voluntariness in terms of the DMCI was significantly associated with the need for money (X^2 = 24.723, *df*=3, *p*=.000, *p*<.001), a desire to please the researchers (X^2 = 12.581, *df*=3, *p*=.006, *p*<.01) and feelings of having no choice but to participate (X^2 = 19.421, *df*=3, *p*=.000, *p*<.001).

The third aim of this pilot study was to identify the presence of influences from other people and how these influences were exerted. Partners, family members, friends, health care providers and research staff were identified as influencing participants' consent decisions. Of the 100 participants, only one reported being threatened by their family and two reported being threatened by a friend. All participants threatened were threatened in order to prevent their participation. Two participants reported being pressured by a partner. Only one of whom were pressured to participate in the study. Two participants were advised by their partner, three were advised by their family, three were advised by a friend and 11 participants were advised by the CAPRISA research staff. The pilot study also found that friends had significantly less influence in causing a consent decision to be made than the other groups (X^2 = 12.048, *df*=3, *p*=.007, *p*<.01). CAPRISA staff members had the most influence in causing a consent decision to be made.

The fourth aim of this pilot study was to identify the presence of controlling (intentional, illegitimate and causal) influences from others and subsequent nonvoluntary participation (cf. Appelbaum et al., 2009a). All except one participant perceived influences from other people as intentional and legitimate and not causing them to make the consent decision they did. Subsequently, the majority of influences exerted by others were perceived to be non-controlling by the participants in this study. According to the conceptualisation of

voluntariness adopted in this study, only one participant was subject to a controlling influence and therefore participated nonvoluntarily.

The fifth aim of this pilot study was to identify what other factors influenced participants' consent decision. Illness, a need for health care, a need for money, trust in the researchers, a desire to please another person (partner, researchers, someone else), HIV prevention and altruism were identified as factors influencing research participation. CAPRISA 009 participants were significantly more likely to be influenced to enroll in the host trials by illness than CAPRISA 008 participants (X^2 = 10.382, df=1, p=0.00). Participants who were older (X^2 = 10.539, df=2, p=0.01), single (X^2 = 5.775, df=2, p=0.06) and had a higher income (X^2 = 8.81, df=2, p=0.01) were significantly more likely to be influenced to enroll in the host trials by illness. Participants who enrolled more than a year ago were significantly more likely to be influenced to enroll in the host trials by the need for health care than those who enrolled less than a year ago (X^2 = 4.796, df=2, p=0.08, p<.1). Participants who were not employed (X^2 = 4.951, df=1, p=0.03) and participants with no income (X^2 = 9.792, df=2, p=0.013) were significantly less likely to be influenced to enroll in the host trials by a need for money. Participants who were not employed (X^2 = 3.274, df=1, p=0.07) and participants with no income (X^2 = 7.168, df=2, p=0.03) were significantly less likely to participate because they had no other choice.

7. Summary

The findings of the demographic questionnaire, Voluntariness Narrative Rating Instrument (VNRI), Decision Making Control Instrument (DMCI) and Survey of Influences (SoI) were presented in this chapter. The results for the three instruments were compared to the sample characteristics to determine if any of the sample characteristics were significantly associated with perceived voluntariness or the presence of influences. The VNRI and DMCI were compared to establish the convergent validity of the VNRI. The findings from the VNRI and DMCI were compared to the Survey of Influences to determine if any influences were significantly associated with perceived voluntariness.

Several additional analyses were also conducted. A detailed discussion of these findings is presented in the following chapter.

Chapter 8: Assessing Voluntariness of Consent to Research: Discussion

Obtaining voluntary informed consent prior to enrolment in clinical research is a fundamental ethical requirement. This requirement is given priority in all national and international research ethics codes, guidelines and regulations. The obligation to obtain voluntary informed consent reflects the substantive ethical principle of respect for autonomy. ICH Guideline for Good Clinical Practice, (1996) defines informed consent as "a process by which an individual voluntarily expresses his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the decision to participate (Guideline 1.28, p. 15)". Valid informed consent requires the researcher to provide potential participants with detailed information about what research participation requires, determine that the potential participant understands the disclosed information and ensure the consent provided is voluntary (Beauchamp & Childress, 2009). Disclosure and understanding are therefore prerequisites to voluntary consent, without which a voluntary decision cannot be made. Despite the importance of voluntary informed consent and its underlying principles, both researchers and research ethics committees have difficulties interpreting and promoting voluntary consent to research participation (NBAC, 2001). In order to gain a better understanding of voluntary informed consent to research participation, a pilot study was conducted using a combination of three instruments designed to assess the voluntariness and perceived voluntariness of consent to research (Chapter 5). The VNRI was an existing instrument developed by Wassenaar (2006) adapted for use in this study. The second instrument, the DMCI was developed to assess perceived voluntariness of research participation by Miller et al. (2011). The last instrument, the Survey of Influences, was designed specifically for this study. In this chapter the results of the pilot study (Chapter 7) are discussed in relation to the study aims. First, participants' perceived voluntariness of consent is explored, followed by a discussion of the potentially controlling influences participants were exposed to. The presence of controlling influences and subsequent nonvoluntary participation is then described followed by a discussion of the non-controlling influences that participants were exposed to. Lastly, study limitations are discussed and recommendations are made for future research.

1. Perceived Voluntariness of Research Participants' Consent

The first aim of this pilot study was to determine the perceived voluntariness of research participants' consent. Perceived voluntariness is the research participant's subjective assessment of the voluntariness of their consent decision. Whether a research participant perceives their participation to be voluntary may be different to whether their participation is in fact voluntary according to the legal imperative of valid informed consent.

The conceptual framework adopted in this study (Chapter 4) specifies that only controlling (intentional, illegitimate and causal) influences from other people have the potential to compromise voluntariness in way that renders consent invalid. That is not to say that influences that do not meet these criteria cannot reasonably be experienced by the research participant as compromising the voluntariness of their consent. While researchers' primary concern is to ensure that consent is voluntary and valid (free from controlling influences of others), a secondary concern is to ensure participants also have a subjective experience of voluntariness. It was hypothesised that in addition to potentially controlling influences of others, non-controlling influences also affect participants' perceived voluntariness (Chapter 4).

In this study perceived voluntariness of research participation was assessed in three ways: First, thematic analysis of participants' VNRI narratives provided insight into participants' perceived voluntariness. Second, the VNRI ratings allowed participants to rate their perceived voluntariness along a 10-point scale. Third, the DMCI scores provide a measure of perceived voluntariness based on the extent to which participants agreed or disagreed with nine Likert scale items.

This study documented high levels of perceived voluntariness. The VNRI ratings revealed that 89% of the 100 respondents rated their participation as fully voluntary. Similarly, 80% of respondents obtained a DMCI score above 50, indicating high levels of perceived voluntariness. Furthermore in terms of the DMCI, between 94% and 98%

percent of participants disagreed with Likert scale statements indicating nonvoluntary participation (e.g., 'I was not the one to choose') and over 98% of participants agreed with Likert scale statements indicating voluntary consent (e.g., 'The decision was up to me'). Similarly, the VNRI narratives revealed that of the 95 participants who commented on the voluntariness of their consent decision, 93 reported that their consent decision was voluntary and/or free from any influences.

Only one participant in this study rated their perceived voluntariness on the lower half of the VNRI rating scale with a rating of 4 and obtained a DMCI score of 21, the only score on the lower half of the range of possible DMCI scores. This participant's VNRI narrative reveals: "I didn't really want to participate but he [boyfriend] told me I should and yes the money helped so I thought why not. Maybe I wasn't forced, um, um, but I didn't feel it was up to me really" [Participant 100]. Both pressure from Participant 100's partner and a desire to obtain the financial benefits of research participation appear to undermine her perceived voluntariness as reflected in her low VNRI and DMCI scores.

Considering the vast number of concerns about voluntary consent populated in the ethics literature (Chapter 2), the high levels of perceived voluntariness documented in this study may seem surprising, especially as host study participants may be considered a vulnerable population, many of whom lack access to suitable alternatives to research participation.

The National Bioethics Advisory Commission (2001) identifies several types of vulnerabilities in potential research populations: cognitive/communicative, institutional, deferential, medical, economic and social. Participants in this study may be considered vulnerable according to several of these criteria: First, all except two participants (n=98) in this study relied on government health services. Reliance on government health care may make participants medically vulnerable. South African public health services are plagued by an overwhelming burden of HIV/AIDS-related disease, weak health-systems management and low staff morale resulting in poor health outcomes for those who rely on these services (Harrison, 2009). Second, participants in this study could also be considered economically vulnerable due to the high unemployment rate (68 participants

were unemployed) and low income rate (52 participants had no personal income). Third, the 14 participants sampled from CAPRISA 009 may also be socially vulnerable in terms of the stigma attached to their HIV positive status. Fourth, this study sample comprised female research participants from an African country. There is widespread concern among ethicists that power differentials, patriarchy and African communitarian culture may prevent female research participants from providing voluntary consent (Kamuya, Marsh & Molyneux, 2011; Nyika, Wassenaar & Mamotte, 2009). Lastly, the majority of research participants sampled in this study did not have access to meaningful alternatives to research participation. CAPRISA 008 (the host trial from which 86% of this sample was recruited) represents the only way HIV negative women could access the partially effective tenofovir microbicide gel. Previous research demonstrated a 39% reduction in HIV infection, with 54% HIV reduction in women who used tenofovir gel consistently (Sokal et al., 2013). Host trial participants were sampled from communities with high levels of HIV and a well-documented lack of effective female initiated HIV prevention strategies (CAPRISA, 2011b). This lack of access to acceptable alternatives suggests that participants would feel that their research participation was less than voluntary (Olsaretti, 1998).

Results of this pilot study reveal, however, that not only were high levels of perceived voluntariness documented despite these vulnerabilities, but, in addition, none of these factors were associated with lower perceived voluntariness. The high levels of perceived voluntariness may be accounted for by the fact that the majority of study participants were educated (n=81) and all study participants had participated in previous research. Previous participation in an ARV prevention trial or previous participation in CAPRISA 004 or 008 were inclusion requirements for CAPRISA 008 and 009 respectively (CAPRISA, 2011a; CAPRISA, 2012). Participants were therefore not from a research naïve population, had experience making similar consent decisions in the past and were literate. As such, participants were well equipped to understand the voluntary nature of research participation. However none of these factors were found to be significantly associated with high levels of perceived voluntariness. Similarly, Agrawal et al. (2006) attributed the high levels of voluntariness found in their study to the fact that the majority

of participants had high incomes and were well educated. Miller and Nelson's (2012) recent study of perceived voluntariness found that lower perceived voluntariness was associated with lower education and a lack of previous experience making a similar decision. It is also possible that CAPRISA had excellent community engagement, recruitment and consent procedures in place and that these contributed to the high levels of perceived voluntariness documented in this study (UNAIDS, 2011).

The findings of high levels of perceived voluntariness in this study are largely consistent with findings from previous research conducted in developing and developed countries (cf., Appelbaum et al., 2009b; Kass et al., 2005; Lansimies-Antikainen et al., 2010; Pace et al., 2005). A recent study by Mutenherwa (2012) also documented high levels of perceived voluntariness among vulnerable research participants. Mutenherwa (2012) assessed the perceived voluntariness of the enrolment of Zimbabwean clinic patients in a randomised controlled trial of the impact of a new diagnostic test for tuberculosis. This poor, ill, research population would by traditional accounts (cf. Bosk, 2002; Olsaretti, 1998) be seen to be incapable of making a voluntary decision to participate in research. Yet Mutenherwa's (2012) research found that the majority (98%) of respondents perceived their participation to be voluntary and uncoerced. Such research challenges the commonly held assumption that poverty and illness necessarily undermine voluntary consent. Data from the present study further support this finding.

In contrast, findings from some previous South African studies reveal low levels of perceived voluntariness among research participants (cf. Abdool Karim et al., 1998; Joubert et al., 2003). Previous research on South Africans' perceptions of voluntariness (Barsdorf & Wassenaar, 2005) found that Black respondents, known to have been most disadvantaged by the apartheid regime, scored significantly lower on perceptions of voluntariness than Indian or White respondents. Ninety-nine participants in the present study were Black, 88 of whom rated their participation as fully voluntary, suggesting that lower levels of voluntariness were not as prevalent among Black participants as previously demonstrated by Barsdorf and Wassenaar (2005). The difference in findings may be due to the fact that previous studies (cf. Abdool Karim et al., 1998; Barsdorf &

Wassenaar, 2005; Joubert et al., 2003) were conducted between 1998 and 2005. Researchers' knowledge of research ethics and awareness of the importance of voluntary informed consent has probably improved significantly in that time (Ndebele et al., 2014). Furthermore, Black participants previously disadvantaged by the apartheid regime may be more empowered to make their own decisions now compared to when these previous studies were conducted. The findings from the present study may also simply reflect the excellent informed consent process put in place by CAPRISA.

2. Factors Associated with Lower Perceived Voluntariness

The second aim of this study was to identify what factors undermined participants' perceived voluntariness of consent. Several factors were significantly associated with lower perceived voluntariness. Potential causes of perceived decreased voluntariness were identified by comparing participants' perceived voluntariness (DMCI score and VNRI rating) with the influences identified in the Survey of Influences and sample characteristics. Low perceived voluntariness was not significantly associated with any influences from other people. This is a noteworthy finding as much theoretical work on voluntariness (including the conceptualisation adopted in this study) places influences from others as the primary factor undermining informed consent (cf. Appelbaum et al., 2009a; Feinberg, 1986; Wertheimer, 2012). However, the present finding is most likely a result of the high levels of perceived voluntariness documented among all participants and the low levels of coercion reported. As such, this finding needs to be interpreted with caution and cannot be taken to mean that influences from other people are not taken into consideration when research participants reflect on the voluntariness of their research participation.

Lower perceived voluntariness (VNRI rating of less than 10) was significantly associated with taking more than 24 hours to reach a consent decision. The majority of participants reached a consent decision immediately after the informed consent form was discussed with them (n=81). Participants who took less than 24 hours to reach a consent decision were more likely to perceive participation as fully voluntary than participants who took

more than 24 hours to decide (X^2 = 6.188, *df*=1, p=.0129, *p*<.05). These results may be attributed to the fact that participants who reached a consent decision in less than 24 hours had less time to consult others than those who took more than 24 hours to decide. That is, participants who reached a consent decision within 24 hours may have been more likely to make the decision alone and subsequently perceive their decision as voluntary.

In terms of the VNRI, lower perceived voluntariness (VNRI rating of less than 10) was also significantly associated with having more than a primary school education (X^2 = 2.75, *df*=1, p=.097, *df*=1, *p*<.1). This finding may indicate that better educated participants (those with high school or tertiary education) may have a superior understanding of the voluntariness requirement and be better equipped to critically reflect on the voluntariness of their participation hence perceive their voluntariness as lower than their less educated fellow research participants (those with only a primary school education). This hypothesis is in line with previous studies which have documented higher levels of understanding among college educated research participants (cf., Joffe et al., 2001).

In terms of the DMCI, lower perceived voluntariness (DMCI score of <45) was also significantly associated with not being influenced by a CAPRISA staff member (X^2 = 14.051, *df*=3, *p*=.003, p<.005) and with not needing health care (X^2 = 6.771, *df*=3, *p*=.080, *p*<.1). The finding that lower perceived voluntariness was significantly associated with *not* being influenced by a CAPRISA staff member can be explained by the fact that the majority of participants who were influenced by a CAPRISA staff member described that influence as advice. This suggests that receiving advice regarding research participantion from a member of the research staff may actually increase research participants' perceived voluntariness.

A desperate need for health care is frequently reported to undermine the voluntariness of research participants' consent (Bosk, 2002; Kass et al., 2005). This study however found that lower perceived voluntariness was significantly associated with *not* needing health care. Health care however can be viewed a rational desire (Shapiro & Benatar, 2005). As

such it is possible for individuals to intentionally decide to enter research in order to obtain health care. The significant association between *not* needing health care and lower perceived voluntariness may suggest that those who intentionally participate because they require access to health care may be more likely to perceive this intentional decision as voluntary.

Lower perceived voluntariness (VNRI rating of less than 10; $X^2 = 2.73$, $df=1$, $p=.099$, $p<.1$) and DMCI score of <45; $X^2 = 19.421$, $df=3$, $p=.000$, $p<.001$) was also significantly associated with feelings of having no choice but to participate. A feeling of having no choice but to participate is often seen as synonymous with nonvoluntary participation. Ensuring that participants are appropriately informed of alternatives to research participation is also central to alleviating feelings of having no other choice. This of course is only true insofar as there are in fact meaningful health care alternatives to research participation at a particular research site.

Lower perceived voluntariness (DMCI score of <45) was also significantly associated with the need for money ($X^2 = 24.723$, $df=3$, $p=.000$, $p<.001$) and a desire to please the researchers ($X^2 = 12.581$, $df=3$, $p=.006$, $p<.01$). This suggests that research participants who were motivated to participate in research by a need for money may be less likely to feel that their participation is voluntary. It is for this reason that concern is raised that poverty may make the very offer of research participation an undue inducement (NBAC, 2001). Lower levels of perceived voluntariness however do not provide a substantial basis for arguing that people in need of money should not be allowed to participate in research as this would simply deny potential participants benefits to which they would not otherwise have access (NBAC, 2001). A desire to please the researchers may reflect the power differentials between participants and researchers and participants' reverence for medical professionals. Empowerment of research participants through participatory methods may address these issues and lessen participants' desire to please researchers (UNAIDS, 2011) thereby improving their perceived voluntariness.

Host trial, race, age, marital status, employment, access to private versus public health services, time since enrolment, illness, a desire to please one's partner and trust in the researchers were not significantly associated with lower perceived voluntariness.

It is important to note that in this study 'lower perceived voluntariness' still constitutes 'sufficiently voluntary' in the majority of cases. It was impossible to run comparisons between influences and actual low voluntariness (i.e., VNRI ratings and DMCI scores on the lower half of the range of possible scores) because low voluntariness was only reported by one of the 100 participants (in both the VNRI and DMCI).

Many prominent theories of voluntary action (cf. Appelbaum et al., 2009a; Feinberg, 1986; Wertheimer, 2012) dismiss the impact of contextual constraints and internal determinations on voluntary consent. The conceptualisation of voluntariness adopted in this study agrees with this dismissal. As outlined in Chapter 4 it was assumed that these non-controlling influences may be important in participants' subjective perceptions of voluntary consent. This assumption is supported by the data. It is a moral imperative that participants have high levels of perceived voluntariness even if consent provided in the absence of perceived voluntariness is not necessarily invalid according to the conceptualisation of voluntariness adopted in this study. This conceptualisation postulates that consent should only be considered nonvoluntary and invalid if it is subject to an intentional, illegitimate and causal influence from others (cf. Appelbaum et al., 2009a). The question then is how to ensure that participants have high levels of perceived voluntariness. Feelings of having no other choice and a desire to please the researcher may be mitigated by ensuring that potential participants are well informed of the alternatives to research participation and that researchers are trained to be sensitive to participants' reverence for them and desire to please. It may also be helpful to empower research participants via participatory practices and use recruiters from target populations in order to reduce the power differentials between participants and research staff which may reduce participants' desire to please the researchers (UNAIDS, 2011).

The contextual conditions that give rise to the need for money are more difficult if not impossible to address. Resnik (2002) argues, "there is nothing inherently wrong with conducting research on subjects that suffer from … misfortunes or vulnerabilities, provided, of course, that one does not take unfair advantage of those subjects" (2002, p. 29). Resnik (2002) and Agrawal (2003) maintain that contextual conditions such as the need for money are not related to voluntariness but are of concern because these participants are more susceptible to exploitation (accepting an unfair distribution of the risks and benefits of the research). They further argue that exploitation is prevented by adequate REC review of the risks and benefits of a study (Agrawal, 2003). While this argument is seen to be correct in terms of the legal imperative of voluntariness, this research clearly indicates that such contextual conditions affect perceived voluntariness but not to the extent that participation was experienced as nonvoluntary.

As little can be done by researchers to improve participants' contextual conditions, should participants who perceive their consent to be nonvoluntary when it may in fact be voluntary, according to the legal imperative, be prevented from enrolling in research? Excluding such participants would only further disadvantage poor participants by preventing them from accessing the benefits of research that they desperately require. Rather, these desperate participants should be allowed to participate in research assuming the research is ethical in the first place and participants are not exploited (as determined by an REC) and provided other ethics criteria are satisfied (Emanuel et al., 2004, 2008). The conclusion then is that it is preferable for participants to perceive their consent as voluntary. Researchers also have a moral obligation to increase participants' perceived voluntariness. However, if it is not possible, due to contextual conditions, participants should still be able to enroll as long as their consent is voluntary according to the legal imperative.

While the need for money, feelings of not having a choice and a desire to please the researchers was associated with lower perceived voluntariness, it is important to note that the majority of participants perceived their participation as voluntary despite the presence

of these influences. Limited options are clearly therefore still compatible with perceived voluntariness.

The VNRI narratives allowed participants to spontaneously identify factors affecting perceived voluntariness while the Survey of Influences questioned participants about specific influences. The results of the two instruments were compared. Overall, the Survey of Influences resulted in more influences being reported in all categories than in the VNRI narratives. This suggests that participants do not take all the influences they are exposed to into account when forming their own spontaneous perceptions of voluntariness. Therefore, while it is important for participants to perceive their participation as voluntary, it is possible that their background situation undermines their perception of voluntariness, that they fail to detect and consider possible controlling influences and perceive their participation as voluntary when it is not, or they perceive their participation to be nonvoluntary when there are in fact no controlling influences undermining the voluntariness of their participation. While useful for establishing perceived voluntariness, participants' VNRI ratings and DMCI scores are not sufficient means of establishing perceived freedom from controlling influences (actual voluntariness) and subsequent validity of consent. As a result, additional elements need to be factored in, using the Survey of Influences. That is, the presence of specific influences has to be identified and whether or not they are controlling or not needs to be established.

3. Potentially Controlling Influences

The third aim of this pilot study was to identify the presence of influences from other people and how these influences were exerted. Potentially controlling influences are influences exerted by other people (Chapter 4). The conceptualisation adopted in this study assumes that only external influences from other people have the potential to be controlling and subsequently undermine the voluntariness of a research participant's consent decision. In order to identify the potentially controlling influences on participants' consent decisions, the Survey of Influences explored who influenced

participants' consent decisions, the direction of the influence, the means by which the influence was exerted and whether the influence was experienced as controlling or not.

3.1 Others consulted regarding research participation

In order to identify influences from other people it was first necessary to identify who the participants spoke to about participation before making their consent decision. The Survey of Influences revealed that most participants spoke to another person prior to deciding whether or not to participate. People consulted included the CAPRISA research staff (82%), research participant's partner (73%), family (71%), friends (62%) and a health care provider (2%). None of the participants surveyed spoke to their employer, a colleague or their community leader. Similarly Osamor and Kass reported that 78% of the 100 research participants they surveyed talked to another person before deciding to participate. Fifty-eight participants consulted their spouse, 29 a friend, 23 a family member and 12 consulted a health care provider (Osamor & Kass, 2012). Lansimies-Antikainen et al. (2011) also found that 64% of the 1324 participants in a diet and exercise study discussed enrolment with another person prior to providing consent. Likewise, Manafa et al. (2007) found that 53% of the 88 research participants they studied indicated that another person helped them make their consent decision. These findings suggest that it is common to consult others prior to research participation. This of course does not reduce the voluntariness of consent in any way. While valid informed consent previously consisted of a research participant reaching a consent decision alone, a more inclusive model is now adopted that takes participatory decision-making into account. The Declaration of Helsinki explicitly allows for participatory decision-making (World Medical Association, 2013). Participatory decision-making is also strongly advocated by UNAIDS (2011). Participatory decision-making is when potential research participants reach a decision regarding research participation in consultation with others (e.g., family members or community leaders) (Britz & le Roux-Kemp, 2012). It is ultimately however still up to the potential research participant to make the final voluntary decision (Britz & le Roux-Kemp, 2012).

3.2 Influences from other people

Less than half of the participants sampled (*n*=39) reported being influenced by another person (14 participants reported being influenced by more than one person). Eighteen of these participants said that the influence from another person caused them to participate. The Survey of Influences identified CAPRISA research staff, friends, partners, family, and health care providers as influencing participants' consent decision. While the influences from other people will be discussed here, it is impossible to comment on the effect these influences have on voluntariness unless the type of influences exerted is explored (Chapter 8 – section 3).

3.2.1 CAPRISA research staff

Of the 18 participants who reported that CAPRISA research staff tried to influence their consent decision, 94.4% (*n*=17) said that CAPRISA research staff tried to influence them to participate and one participant said CAPRISA research staff tried to influence them not to participate. Four participants said during their VNRI narrative that the research staff influenced their decision to participate. More participants in this study were influenced by CAPRISA staff members than any other group of people. CAPRISA research staff also had the most significant influence in causing a consent decision to be made. The potential for research staff to influence research participants' consent decision highlights the need for research staff to remain neutral in the presentation of study information to avoid unintentionally pressuring volunteers to participate. Agrawal et al.'s (2006) study of decision-making among phase I oncology research participants similarly found that 7% of the 163 participants reported feeling pressure from research staff. In this study, however, the majority (61%) of the 18 participants influenced by CAPRISA research staff described this influence as 'advice' (Chapter 8 – section 2.3) which is unlikely to compromise consent in any way, but it is clearly a fine distinction between advice and pressure.

3.2.2 Friend

The Survey of Influences revealed that 13% of participants were influenced by a friend. Eleven of the participants were influenced not to participate by their friend (84.6%) and only two were influenced to participate (15.4%). Four participants stated during their VNRI narratives that their friends (all of whom were CAPRISA research participants themselves) advised them to join the study. An unanticipated finding was that friends influenced participation in slightly more cases (n=13) than partners (n=11) or family (n=10). Participants in this study were significantly more likely to agree that friends have the right to influence their consent decisions (X^2 = 10.984, df = 3, p=.012, p<.05) compared to other people. The study however found that friends actually had significantly less influence in causing a consent decision to be made than the other groups (X^2 = 12.048, df = 3, p=.007, p<.01) than other groups. So while friends have the most right to influence participation they had the least effect on the consent decision. This suggests that the role friends play in consent decisions may have been overlooked in the past. The only previous study to document friends' influence on research participation was Pace et al.'s (2005) study of voluntary consent among 141 Thai research participants. The study found that 15% of participants felt pressure from a friend to join the study (Pace et al., 2005). The influence of friends may warrant further investigation in future studies.

3.2.3 Partner

The Survey of Influences revealed that 11% of the 100 participants surveyed reported being exposed to an influence from their partner. Seven of these participants were influenced to participate and four were influenced not to participate by their partner. Only three participants mentioned in their VNRI narratives that they were influenced by their partner to participate.

Participant 100:

"My boyfriend's sister, well I'm single now, but the man I was with before. His sister participates here in the CAPRISA trials. So he said to me, you must also join this study because they take care of you and they also pay you … I didn't really want to participate but he told me I should and yes the money helped so I thought why not. Maybe I wasn't forced, um, um, but I didn't feel it was up to me really."

Appelbaum et al. (2009a) claim that influence from one's spouse would generally not be considered an illegitimate influence because widely accepted social norms dictate that spouses have substantial freedom to influence each other's behaviour. This study however found that participants were significantly more likely to agree that a partner violated their right to make a free and independent consent decision ($X^2 = 9.964$, $df = 3$, $p=.019$, $p<.05$). This does not necessarily contradict Appelbaum et al.'s (2009a) claim because of the 79 participants in a relationship, only eight participants in this study were actually married to their partner. This suggests that while spouses may legitimately influence their partners' decisions, this legitimacy may not necessarily extend to partners who are unmarried. Social and gender norms affect the role partners play in decision-making (Molyneux et al., 2013). In Africa it may be difficult for women to make important decisions without consulting their partner (Nyika et al., 2009; Osamor & Kass, 2012). Participatory decision-making among partners may be voluntary, however, it is also possible that a woman may feel that she has to pass decision-making to her partner (Molyneux et al., 2013) or that she has to go along with her partner's recommendation.

3.2.4 Family

Family may play a central role in research participants' consent decision in non-Western settings (Marshall et al., 2006). The Survey of Influences revealed that 10% of the 100 participants surveyed reported being exposed to an influence from their family. Seven of these participants were influenced to participate and four were influenced not to participate by their family. Five (50%) of the 10 participants influenced by family

members in this study agreed that their family had the right to influence their consent decision. Pressure from one's family to join a research study has been documented at comparable rates by Agrawal et al. (2006) and Pace et al. (2005). Two participants said in their VNRI narratives that their families tried to influence their decision.

> Participant 20:
> "Even my parents did not know, but when I told them about my decision they weren't happy that I participate. They said I must not. But I told them, eh, that this is the life I am going to live and it's my decision."

Participant 20's ability to resist her family's influence contrasts with results of Munro and Arber's (2011) study into the influence families have on women's participation in breast cancer clinical trials. The authors found that family members' opinions were the most important influence on women's consent decision, in some cases even more important than the women's own desire to consent (Munro & Arber, 2011).

3.2.5 Health care provider

The Survey of Influences revealed that one participant was influenced to participate by their health care provider. The VNRI narratives revealed that four participants were referred to the study by staff at a government clinic. In Pace et al.'s (2005) study of voluntary consent among 141 Thai research participants, 2% felt pressure from their personal physician to join the study. Patients may interpret referral to a clinical trial as their health care provider's recommendation that they participate and may subsequently not realise they are free to refuse (Bosk, 2002). This was not the case in this study as the four participants who said in their VNRI narrative that they were referred by a health care provider, all had high levels of perceived voluntariness according to their DMCI scores and VNRI ratings.

3.2.6 Community leaders

International ethical guidelines highlight the important role community leaders have in research participants' decision-making (Chapter 3). Previous research however has not provided empirical support for this. Marshall et al. (2006), for example, state that although it was hypothesised that community leaders play a central role in research participants' consent decision in non-Western settings, their study on voluntary consent to genetic research found that none of the Nigerian research participants sought permission from community leaders prior to joining the study. The present study similarly found that none of the participants sampled even spoke to their community leader about research participation. Community leaders are an important gate keeper to communities (UNAIDS, 2011). Obtaining community leaders' permission for research to be carried out in their communities is good ethical research practice (UNAIDS, 2011). It however appears that individual participants were unlikely to personally consult their community leaders prior to research participation. The reported lack of consultation with community leaders by CAPRISA participants may be accounted for by the fact that CAPRISA is a well-established research organisation that has been operating in the community for several years. For this reason participants may feel that the research already has their community leaders' approval and, as such, participants may not feel the need to consult with community leaders personally. An alternate explanation is that Western bioethicists find it morally satisfying to respect this practice which in fact enjoys very little real observance in rural settings.

The majority of participants in this study consulted others about research participation yet few of these participants were actually influenced to participate by those they consulted. In order to establish whether an influence from another person is controlling, the mechanisms through which that influence was exerted first need to be established.

3.3 Types of influences

As the influences from other people have been identified and discussed above, the mechanisms these people employed to influence a participant's consent decision will now be explored. Both 'who' influenced a decision and 'how' it was influenced are important in determining whether an influence is controlling or not (Chapter 8 – section 4). The following types of influences were assessed in the Survey of Influences:

3.3.1 Coercion

For the purpose of this study coercion is understood to occur if one person "intentionally and successfully influences another by presenting a credible threat of unwanted and avoidable harm so severe that the [research participant] is unable to resist acting to avoid it" (Faden & Beauchamp, 1986, p. 261). Coercion was explored in the Survey of Influences by identifying the presence of perceived threats from others. There are two sources of coercion: Coercion from researchers and coercion from third parties. The case of coercion from researchers is relatively clear cut. Researchers do not have the right to coerce people to participate in their studies and multiple safeguards are put in place by research ethics committees to prevent this from happening. This may explain why the study did not identify any threats from CAPRISA staff. Furthermore, researchers often do not have the means to successfully exert a threat on a research participant. One exception is if a patient's health care provider is also the researcher they may threaten to stop providing care unless the patient enrolls. Coercion by a third party occurs when someone outside the research study coerces a person to participate. Of the 39 participants influenced by another person, only one participant reported being threatened by a family member and two reported being threatened by a friend. These three participants were all threatened in order to prevent their participation in the research and they all ended up participating despite the precence of the threat revealing that coercion did infact not occur.

As in this study, past research has consistently found coercion in research to be rare (Klitzman, 2012). In Appelbaum et al.'s (2009b) study of the voluntariness of consent to research of 88 US research participants, no participants reported the presence of threats. The study also found that the majority of participants did not perceive their decision to have been coerced in any way (Appelbaum et al., 2009b). Similarly, Lansimies-Antikainen et al.'s (2010) study of informed consent in a randomised controlled trial on exercise and diet in Finland found that 99% of the 1324 respondents surveyed reported that they enrolled in the study without coercion. These combined findings lend support to Emanuel et al.'s (2005) hypothesis that the risk of coercion in research is severely inflated.

3.3.2 Persuasion

Persuasion was explored by identifying advice from others. Persuasion is when the persuader 'intentionally and successfully' draws "the persuadee's attention to reasons for acceptance of the desired perspective" (Faden & Beauchamp, 1986, p. 348). The persuadee is free to accept or decline the perspective advocated by the persuader. The Survey of Influences revealed advice to be the most common form of influence (*n*=19). Two participants were advised by their partner, three were advised by their family, a further three were advised by a friend and 11 participants were advised by CAPRISA research staff. Of those reporting influences from other people during the VNRI narratives, this influence was most often advice or encouragement from friends (4%), research staff (3%), family (2%) and partners (2%).

> Participant 43:
> "My friend told me about the study and she said let's go. Then we came … My friend did not influence me, um, no, but rather she just talked to me nicely and advised me, that's why I liked to be part of the study."

Similarly, Appelbaum et al. (2009b) found that 26% of the 88 people they surveyed were motivated to participate in research as a result of advice from other people and 37% were

motivated by advice from a doctor or nurse. Moreover, VNRI narratives revealed that four participants were referred to the study by clinic staff.

> Participant 90:
> "I was at the clinic because I had a problem then they told me about a study that was being conducted. After getting help at the clinic, they told me that there is a clinic called CAPRISA that checks for everything including HIV and other reproductive diseases."

Although advice from others is not considered to compromise voluntary consent, research participants may feel that they cannot say no professionals' advice or recommendation that they join a study (Kass et al., 2005). Applebaum et al. (2009b) also found that when advice from a doctor or nurse played an important role in decision-making, participants had a higher perceived coercion score.

3.3.3 Inducements

An inducement is an undertaking by one person to provide another with a benefit to which they are not otherwise entitled in return for research participation (Appelbaum et al., 2009a). Offers from others are one of the most frequently cited influences on voluntary research participation. Surprisingly, the Survey of Influences found that no participants reported being offered anything to participate in the host trials. This may indicate that research participants in this study did not perceive the payment or care and treatment they received as part of the host trial as an offer made by the researchers in return for participation. It is possible that research participants perceived payment and care and treatment to be a given component of the host trial. Five participants did however identify payment as an influence during their VNRI narratives.

> Participant 100:
> "They pay you a lot. It's more than you could make a day. I have a nice job but still it's more than I make a day so I thought, why not."

There is widespread concern in ethics literature that payment for research participation promotes irrational decision-making and may subsequently compromise voluntary consent (Kitzman, 2012; Koen et al., 2008). The South African National Health Research Ethics Council (2013) has generated guidelines for the ethical payment of research participants. Several empirical studies have examined the effects of inducements on research participation. For example, Dugosh et al. (2010) found that 38% of 84 substance-abusing criminal offenders surveyed reported that financial incentives were the main reason they joined the study. Conversely, Osamor and Kass (2012) found that only two of 100 research participants they surveyed reported participating for monetary compensation. Horwitz et al. (2013) studied the voluntariness of consent of 492 volunteers in an HIV vaccine trial in Haïti and found that 4% of the volunteers admitted volunteering for the perceived financial benefit. The authors describe this as a warning sign for nonvoluntary consent (Horwitz et al., 2013). Appelbaum et al. (2009b) found that 35% of the 88 research participants they surveyed reported the presence of offers but that the majority of these respondents rated the offers as having little influence on their decision to enroll in the research. Similarly, Bentley and Thacker's (2004) study of the effects of payment on potential participants' risk evaluations and willingness to participate in research found that monetary payment had positive effects on respondents' willingness to participate in research, regardless of the level of risk. However, higher monetary payments did not appear to blind respondents to the risks of a study (Bentley & Thacker, 2004). The findings from this study are in line with those from previous studies which suggest that the concern that incentives are a constraint on voluntariness has been exaggerated (Appelbaum et al., 2009b).

3.3.4 Pressure

Pressure from others is frequently assessed in studies of voluntariness but rarely, if ever, defined. For the purposes of this study pressure was assumed to capture the range of influences (excluding inducements) that fall between the extremes of coercion and persuasion. In an attempt to capture this range of influences, pressure was assessed in this study by allowing participants to classify influences from others as 'pressure' or 'other'.

Low levels of pressure from others to participate were identified in this and previous studies. Only two participants reported being pressured (both by a partner) according to the Survey of Influences. One of these participants was pressured to participate and one pressured not to participate. The VNRI narratives revealed that two participants were told by research staff (*n*=1) and a partner (*n*=1) that they had to participate. Being instructed or told to participate in research has not been specifically discussed in the research ethics literature but is considered a type of pressure in this study as in the absence of a threat it does not constitute coercion. Comparable findings have been demonstrated elsewhere. Marshall et al. (2006) found that 99% of their US participants and 97% of their Nigerian participants did not feel pressured to participate in the genetic research they were enrolled in. Of the 598 Ugandan research participants surveyed by Kiguba et al. (2012) 95% did not feel pressured to participate. Appelbaum et al. (2009b) found that only 3% of the 88 participants they surveyed reported the presence of pressure. In Pace et al.'s (2005) study of voluntary consent among 141 Thai research participants, 73% felt no pressure from others to join the study while 7% felt pressure from family. Agrawal et al.'s (2006) study of decision-making among phase I oncology research participants found that 7% and 9% of the 163 participants reported feeling pressure from research staff and family respectively.

Over half of the participants in this study who identified another person to have influenced their consent decision, classified that influence as 'other' (*n*=28). This means the influence did not fit into the other available categories of 'threat', 'advice', 'offer' or 'pressure'. A limitation of this study is that participants were not asked to elaborate on this 'other' category. It is possible that participants often feel influenced to (or not to) participate in a research study by those who are just concerned about their wellbeing, hence the inability to categorise the influence.

> Participant 1:
> "Then I phoned him [boyfriend] and I told him that there is this study its 009 … Eh, he wasn't feeling well about the whole thing. So he just said to me, eh, why everything is happening to you? You understand? And I said I don't know and

> right now I am feeling down. I don't know what decision to take. And he said no it's fine because the way you are you are always talk good about that clinic you must take the right decision and I know they are going to assist you in every way with your health."

Participant 1 then went on to categorise this influence from her boyfriend as 'other' in the Survey of Influences. The high number of influences classified as 'other' may however lend support to inclusion of a 'catch all' category of 'pressure' in this study's conceptual framework.

'Persuasion' and 'other' were found to be the most common mechanisms through which influences were exerted. Very low levels of threats and pressure were detected and participants did not report the presence of offers. Now that the sources of influence and mechanisms through which the influences were exerted have been explored, it is possible to examine which of these potentially controlling influences undermine voluntariness according to the conceptualisation of voluntary consent adopted in this study. This will be done below (Chapter 8 – section 3).

4. Controlling Influences

The fourth aim of this pilot study was to identify the presence of controlling (intentional, illegitimate and causal) influences from others and subsequent nonvoluntary participation. According to the conceptualisation of voluntariness adopted in this study, assessing the intentionality, legitimacy and causality of an influence (cf. Appelbaum et al., 2009a) will determine whether a potentially controlling influence (i.e., an influence from another person) was controlling or not and whether the subsequent consent decision was voluntary or not. The intentionality, legitimacy and causality of the influences identified in this study will first be discussed separately. They will then be examined together to assess whether any influences can be classified as controlling according to this framework.

4.1 Intentionality

It may or may not be the intention of the person exerting the influence to influence a participant's consent decision in one way or another. Only intentional influences have the ability to control a participant's consent decision. According to Appelbaum et al. (2009a) an intentional influence results from the planned action of another person who aims to influence the potential participant's consent decision. However, it is impossible to determine from the research participant whether another person's influence was intentional or not. What is focused on instead is whether the research participant *perceived* the influence as intentional. The majority of participants who reported influences from others viewed this influence as intentional. Intentional influences were recorded as an 'agree' or 'strongly agree' response to the intentionality statement ['it was this person's intention to influence my consent decision'] in the Survey of Influences. Intentional influences were identified among seven (63.6%) of the 11 participants influenced by their partner, six (60%) of the 10 participants influenced by their family, 11 (84.6%) of the 13 influenced by their friends and 11 (64.7%) of the 17 participants influenced by a member of the CAPRISA research staff. The majority of participants in this study who reported being influenced by another person viewed this influence as intentional. The conceptualisation of voluntariness proposed by Appelbaum et al. (2009a) and adapted in this study adopts a 'simple view' when distinguishing between intentional and unintentional action. That is, an action only becomes intentional when the person performing it had the intention to perform it (Adams, 1986; McCann, 1986). Faden and Beauchamp (1986) also emphasise the importance of intentionality in both their definition of coercive and persuasive influences. For example, coercion occurs when one person "*intentionally* and successfully influences another by presenting a credible threat of unwanted and avoidable harm so severe that the [research participant] is unable to resist acting to avoid it" (Faden & Beauchamp, 1986, p. 261). Persuasion occurs when the persuader '*intentionally* and successfully' draws "the [research participant's] attention to reasons for acceptance of the desired perspective" (Faden & Beauchamp, 1986, p. 348). However, intentionality of the influence has not previously been assessed in studies of voluntariness of consent. Intentionality alone reveals nothing about the voluntariness of

the consent decision. Intentionality needs to be considered in relation to the legitimacy and causality of the influence.

4.2 Legitimacy

The conceptualisation adopted in this study assumes that an intentional influence from another person only has the potential to compromise voluntariness if it is illegitimate, that is, the person exerting the influence does not have the right to influence the participant's consent decision and/or if the research participant's right to make a free independent decision was violated by the person exerting the influence. An illegitimate influence was reflected in a 'disagree/strongly disagree' response to the statement "this person had the right to influence my consent decision" and an 'agree/strongly agree' response to the statement "my right to make a free independent consent decision was violated when this person influenced me". Six participants (54.5%) agreed that their partner had the right to influence their consent decision. Five participants (50%) agreed that their family had the right to influence their consent decision. All 13 participants (100%) agreed that their friends had the right to influence their consent decision. Eight participants (47%) agreed that a staff member had the right to influence their consent decision. The one participant who was influenced by their health care provider, disagreed that the health care provider had the right to influence her decision. Four participants (36.4%) agreed that their right to make a free independent consent decision was violated by their partner. Only one agreed that it was violated by her family. Six participants (46.2%) agreed that their right to make a free independent consent decision was violated by their friend. The one participant who was influenced by their health care provider, disagreed that her rights were violated. Only one participant (5.8%) agreed that their right to make a free independent consent decision was violated by the staff member. The majority of participants in this study who were exposed to an influence therefore perceived the influence to be legitimate. That is, they did not perceive the influence to violate their right to make a voluntary decision. While only Appelbaum et al. (2009a) and Wertheimer (2012) consider legitimacy in relation to voluntary consent, much work on coercion in general takes legitimacy into consideration. Haksar (1976), Lamond (2001), Oberdiek (1976) and Wertheimer (1987), for example,

agree that some influences are coercive yet justifiable by other considerations. Like legitimate influences, justified coercion is licensed by certain social conventions and as such does not undermine individual freedom (Carr, 1988). Legitimacy has only been assessed previously by Appelbaum et al. (2009b) in relation to voluntary research participation. Intentional and illegitimate influences only result in a controlling influence if they *cause* a consent decision to be made. Causality is considered further below.

4.3 Causality

Lastly, for an influence to be controlling, in addition to being intentional and illegitimate, it has to cause the participant to make a particular consent decision. A causal influence was indicated by an 'agree/strongly agree' response to the statement, "this influence caused me to participate". Only four (36.4%) participants agreed that their partner's influence caused them to make the consent decision they did. One participant agreed that their family's influence caused them to make the consent decision they did. Only one participant (7.7%) agreed that their friend's influence caused them to make the consent decision they did. Eight participants (47%) agreed that their friend's influence caused them to make the consent decision they did. The majority of participants therefore did not perceive the influences exerted by other people to cause them to make the consent decision they did. If another person exerts an intentional, illegitimate influence on a potential research participant, the influence may be wrong but if a consent decision is not a consequence of the influence, the decision is not rendered nonvoluntary (Appelbaum et al., 2009a). The importance of causality is also highlighted by Faden and Beauchamp (1986) when they emphasise that coercion only occurs if the coercer 'successfully' gets the coercee to comply with the threat or the persuader 'successfully' gets the persuadee to adopt a desired perspective.

4.4 Nonvoluntary and invalid consent

The majority of participants perceived influences from other people as intentional and legitimate and not causing them to make the consent decision they did. Subsequently, the majority of influences exerted by others were perceived to be non-controlling by the

participants in this study. This finding is consistent with high levels of perceived voluntariness observed in the VNRI ratings and the DMCI. However, as explained in Chapter 4 although desirable, correspondence between actual (perceived freedom from controlling influences) and perceived voluntariness is not a given. In fact only one participant reported perceiving an influence from their partner as controlling by indicating an 'agree' response to the intentionality statement, a 'disagree' response to the first legitimacy statement and an 'agree' response to the second legitimacy statement as well as the causality statement.

The conceptualisation of voluntariness on which this empirical study is based (Chapter 4) assumes that consent to research can only be considered nonvoluntary and invalid if it is made as a result of exposure to a controlling (intentional, illegitimate and causal) influence exerted by another person. Ninety-nine percent of participants enrolled in this study therefore provided voluntary and valid consent. The high levels of voluntary and valid consent documented in this study may suggest one of two things, assuming that the conceptualisation of voluntariness adopted is valid and the assessment method is appropriate. First, it may suggest that when conceptualised correctly (cf. Appelbaum et al., 2009a; Wertheimer, 2012) nonvoluntary research participation is far less of a concern than many commentators suggest. Second, it may suggest that nonvoluntary consent is prevented by the high ethical standards of the host research unit (CAPRISA). More research is needed to provide support for this conceptualisation and assessment method. If such support is obtained, further research needs to determine whether nonvoluntary participation is as much of a problem as commentators suggest or if the findings of high levels of voluntary and valid consent found here are similar in other research populations in other countries. If high levels of voluntariness are not documented in future studies in which this study's conceptualisation and assessment methods are adopted then CAPRISA's research practices should be carefully investigated to establish what elements enhanced participants' voluntary consent.

5. Non-Controlling Influences

The fifth aim of this pilot study was to identify what other factors influenced participants' consent decision. Several non-controlling influences were explored in the Survey of Influences. These included influences from ill health, socio-economic conditions (a need for health care and money), trust in the researchers and internal determinations of wanting to participate, feelings of having no other choice and a desire to please another person. Several other non-controlling influences inductively emerged from the VNRI narratives. These included altruism, distrust and misunderstandings. In this study several of these non-controlling influences were significantly associated with lower perceived voluntariness. Non-controlling influences are influences on a consent decision that are conceptualised as compatible with voluntary and valid consent.

5.1 Ill health

Ill health influenced just over half of the participants to enroll in the host trials (*n*=53) according to the Survey of Influences. In addition to the 14 HIV positive participants sampled from CAPRISA 009, it is likely that many participants were referred to CAPRISA after receiving treatment at a primary health care clinic for sexually transmitted diseases and it may be this to which they are referring when they talk of 'illness'. Twenty-six percent of respondents mentioned ill health as an influence in the VNRI narratives.

Of the 53 participants who were influenced to participate by their ill health, 69.8% (*n*=37) rated ill health as influencing them 'a lot' and 62.3% (*n*=33) would not have participated had it not been for their ill health. As CAPRISA 009 participants are HIV positive they were significantly more likely to be influenced by illness than CAPRISA 008 participants (X^2 = 10.382, *df*=1, *p*=0.00), as were participants who were older (X^2 = 10.539, *df*=2, *p*=0.01), single (X^2 = 5.775, *df*=2, p=0.06), had higher incomes (X^2 = 8.81, *df*=2, *p*=0.01) and had been enrolled for more than a year (X^2 = 27.38, *df*=2, *p*=0.00). Previous studies in both the developed and developing world have documented similar findings. Agrawal

et al. (2006) found that 75% of the 163 research participants they studied felt pressure to participate because of their cancer. Osamor and Kass (2012) found that 67 of 100 research participants participated to learn more about their illness.

As a non-controlling influence, illness cannot undermine voluntary consent in a way that renders consent invalid. Illness is often claimed (cf. Bosk, 2002; Nelson & Merz, 2002) to leave participants feeling that are less able to make a voluntary decision (perceived voluntariness). Several participants indicated in the VNRI Narratives that research participation gives them hope. Bosk (2002), however, claims that the belief that research reflects participants' best hope for cure or relief negatively impacts the voluntariness of their consent decision.

> Participant 17:
> "I came to participate at CAPRISA because I was sick. They explained to me that this infection was similar to other diseases like TB, or eh, asthma and that I could also live normally like HIV negative people. The way they treat me here at CAPRISA made me feel free and gave me hope that I could continue living with my life."

The key study finding regarding ill health was that ill health was not significantly associated with lower perceived voluntariness. This finding does not support the concern raised in the ethics literature that ill health negatively impacts participants' perceived voluntariness of consent. As Nelson and Merz (2002) suggest, illness may not undermine voluntariness but ill participants may be susceptible to "unrealistic enticements and manipulation of hope" (p. 72). Such 'unrealistic enticements and manipulation of hope' however require intervention of another person and, in this study, would have been detected when participants were asked about offers or pressures from others as discussed in section 3 above.

5.2 Socio-economic conditions

Socio-economic conditions explored in the Survey of Influences were the need for health care and money.

5.2.1 The need for health care

The need for health care influenced 89% of participants to enroll in the host trials. Seventy-six (85.45%) of these participants rated the need for health care as influencing their decision 'a lot' and 58.4% (n=52) of the 89 participants who participated because they needed health care would not have participated had this influence not been present. Only 11 of these 89 participants said that the need for health care was the only reason they participated. Participants who enrolled more than a year ago were significantly more likely to be influenced to enroll in the host trials by the need for health care than those who enrolled less than a year ago (X^2 = 4.796, df=2, p=0.08, p<.1). The VNRI narratives revealed that 46 participants were influenced by their need for health care.

> Participant 83:
> "I decided to take part because sometimes it's not easy as youth to just go and test [for HIV], but here [at CAPRISA] we get tested regularly, um, and get checked for other diseases for free which is something you don't get at other clinics. You also get encouraged, eh, motivated to live a healthy life because we always test for HIV every month and also get advice to have one partner and to use condoms."

The finding that the majority of participants (n=89) were influenced by the need for health care and that 52 of those participants would not have participated had they not needed health care may indicate an inadequacy with the South African public health care system on which 98% of the participants in this study reportedly rely. In theory South African public health care should provide comparable services to those received in the host trials at no cost (Abdool Karim et al., 2011). However, "under-developed health

facilities, overworked staff and drug shortages are a reality that impact access to and quality of health services for indigent populations" in South Africa (Abdool Karim et al., 2011, p. 6).

Previous studies in both the developed and developing world have documented similar findings. Appelbaum et al. (2009) found that of the 88 participants surveyed in their study of voluntariness of consent to research, 80% were motivated by the possibility of getting better care, 59% were motivated to participate by access to treatment they could not get elsewhere and 52% were motivated by the availability of free care. Kass et al. (2005) also found that the chance to receive better medical care was a major motivator for research participation. Pace et al., (2005) found that of the 141 participants surveyed in a randomised HIV treatment controlled trial in Thailand, 43% reported feeling pressure to participate due to their health-related circumstances. Of these, 10 respondents reported that the trial was the only way for them to access treatment (Pace et al., 2005). Lastly, Osamor and Kass (2012) found that 30 of 100 research participants participated to get medical care.

The VNRI narratives revealed that a further 26 participants were influenced to participate by potential HIV prevention.

> Participant 66:
> "I decided to participate because of the way they explained about the gel study, eh, that mostly men are the ones that have protection from HIV, we as women are vulnerable because we don't have many things that we can use to prevent infection. So from the study details, um, I realised this gel might be useful in prevention hence I volunteered to be part of the study."

HIV prevention is a well-documented motivator for HIV prevention trial participation (cf. Dhalla & Poole, 2011; Dhalla & Poole, 2014). Bartholow et al. (1997) suggest that this is a result of the high perceived risk of HIV acquisition in the populations sampled for HIV prevention trials. HIV prevention as a motivation for research participation in HIV

prevention trials poses slightly different problems for voluntary consent than the more general motivation of a need for health care. If research participants hope to obtain HIV prevention as a part of the trial's standard of care packages then this is similar to their desire to obtain health care from the trial in general (as discussed above). HIV prevention as a motivation may become problematic when participants hope to prevent HIV by using the study product. Participants need to clearly understand that the trial product is experimental and may or may not provide protection from HIV. This understanding is essential to making a voluntary decision regarding research participation. The 26 participants who described HIV prevention as influencing their participation were all clear about this. For example, Participant 66 said, "… this gel might be useful in [HIV] prevention". Section 5.6 below details the problems posed for voluntariness when participants believe that the study product does in fact provide protection from HIV. According to the conceptualisation adopted in this study (Chapter 4), the need for health care is seen as a non-controlling influence which cannot undermine voluntariness. However, as many critics (cf. Nelson & Merz, 2002; Sears, 2005) suggest, the need for health care may undermine participants' perceived voluntariness. This study however did not find a significant association between the need for health care and lower perceived voluntariness. Interestingly, lower perceived voluntariness was significantly associated with *not* needing health care ($X^2 = 6.771$, $df=3$, $p=.080$, $p<.1$). A desperate need for health care is frequently reported to undermine the voluntariness of research participants' consent (Bosk, 2002; Kass et al., 2005). As discussed in section 2 above, health care is described by Shapiro and Benatar (2005) as a rational desire. As a rational desire, individuals may intentionally and rationally decide to enter research in order to obtain access to better health care. The significant association between *not* needing health care and lower perceived voluntariness may suggest that those participating to obtain health care made a rational and intentional decision regarding their participation which they therefore view as voluntary.

5.2.2 The need for money

The majority of participants in this study were unemployed with no personal income. It is therefore surprising that only 13 of the 100 participants said that they participated because they needed the money and none of these participants said that the need for money was the only reason they participated. Participants who were not employed (X^2 = 4.951, *df*=1, *p*=0.03) and participants with no income (X^2 = 9.792, *df*=2, *p*=0.013) were however significantly less likely to be influenced by the need for money. Social desirability may explain this counter-intuitive finding (Bryman, 2004). Participants who are unemployed and/or have no personal monthly income may not want to appear as though they are only participating in order to earn money. This finding is inconsistent with a study of co-enrolment in CAPRISA 004. Abdool Karim et al. (2011) found that some co-enrolled CAPRISA 004 participants who had little or no income, stated that they were influenced by the payment of R150 per study visit.

Socio-economic conditions may influence how participants perceive the voluntariness of their consent decision. In this study, lower perceived voluntariness (DMCI score of <45) was significantly associated with the need for money (X^2 = 24.723, *df*=3, *p*=.000, *p*<.001). This suggests that research participants who were motivated to participate in research by a need for money may be less likely to feel that their participation is voluntary. It is for this reason that concern is raised that socio-economic conditions may make the very offer of research participation an undue inducement (NBAC, 2001). Difficult or desperate background conditions such as poverty are frequently cited as having the potential to undermine voluntary decision-making (Barsdorf & Wassenaar, 2005; Kass et al., 2005). It is argued that offering payment in return for research participation to participants from impoverished communities leaves the potential participant with no meaningful choice but to enroll in the research (Olsaretti, 1998). Contextual vulnerabilities, according to Sears (2005), can cause a person to misinterpret the purpose of research to fit in with their own needs and priorities.

The National Bioethics Advisory Commission (2001) acknowledges that it is difficult to determine when the offer of research participation becomes an undue inducement. The Belmont Report states that "undue influence … occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance" (National Commission, 1979, p. 14). Arguing that the need for money documented in this study renders the offer of research participation an undue inducement would require proving that offering financial compensation that research participants would not otherwise receive is unwarranted and inappropriate (NBAC, 2001). The NBAC (2001) argues that it cannot be reasonably claimed that people in need of money should not be allowed to participate in research thereby denying them benefits to which they would not otherwise have access to. The NBAC (2001) further argues that the provision of financial compensation may comprise an inducement for research participation but it cannot be claimed to be undue and as such does not necessarily diminish the voluntariness of research participants' consent in a way that renders it invalid. Hence the careful work on reimbursement of trial participants done by Koen et al., (2008) endorsed by the South African National Health Research Ethics Council Guidelines (2012).

Wertheimer and Miller (2007) argue that the difference between an inducement and an undue inducement is not related to the inducement itself but the potential research participants' response to the inducement. An inducement is only undue, according to Wertheimer and Miller (2007), if it distorts the potential research participants' judgment and leads to irrational decision-making. Similarly, according to Appelbaum et al. (2009a), offers are acceptable insofar as they expand a person's options without limiting their choice. A person who chooses research participation in order to receive financial reimbursements may be in desperate circumstances and may have no other feasible alternatives, but Feinberg (1986), argues that it cannot be claimed that such a choice is not voluntary. Choosing the most reasonable option out of a range of unfavourable options when a person is forced to by unfortunate circumstances by no means undermines the voluntariness of the consent provided. Similarly, Faden and Beauchamp (1986) argue that a person may be constrained by circumstances, without any feasible alternatives but they can still carefully deliberate about their situation and reach a voluntary decision.

Similarly, Emanuel et al. (2005) argue that there are four necessary conditions that need to be met for an inducement to be undue. First, a desirable good has to be offered in return for a specified action. Second, the offered good must be excessive so that it cannot be resisted. Third, the offer has to result in a person making a poor judgment in relation to the specified action. Finally, the person's poor judgment must result in a high probability that they will experience serious harm that threatens their interests. Although the reasonableness of risks is subjective, Emanuel et al. (2005) argue that undue inducements apply only when risks are undoubtedly unreasonable. Emanuel et al. (2005) argue that providing offers such as payment or medical care that are beneficial, wanted and reasonable as part of an 'otherwise ethical research study' cannot constitute an undue inducement and as such cannot undermine the voluntariness of consent. While unfortunate circumstances may make certain offers irresistible, they only become undue inducements when a "person's unfortunate circumstances and compromised judgment are combined with accepting a seriously unfavourable risk-benefit ratio that threatens fundamental interests" (Emanuel et al., 2005, p. 338). They go on to argue that undue inducements are therefore prevented by appropriate REC review that ensures that studies have acceptable risk-benefit ratios.

Although feeling pressured to participate in order to obtain the financial benefits is a "psychologically powerful" motivator (Agrawal et al., 2006, p. 4482) and may affect participants' perception of the voluntariness of their consent decision as evidenced by this study, it is not considered a controlling influence that can undermine consent according to this study's conceptualisation. The conceptualisation of voluntariness adopted in this study takes research participants' background, including the socio-economic conditions to which they are exposed, as a given. It is against this background that researchers need to determine whether controlling (intentional, illegitimate and causal) influences have been exerted by others to undermine the voluntariness and validity of consent.

However, the NBAC (2001) recommends that undue inducements be examined on a case-by-case basis. This was done in the present study. Concern is raised in the ethics literature

that inducements may lead potential participants to be dishonest about information that may lead to their exclusion from the study (Koen et al., 2008) as was the case with Participant 40:

> Participant 40:
> "I heard from my friend that there was a study and that there was, um, money, I would get money. So I liked to participate because I would get the money. I did not feel free here because I do not even use their gel. I can't use something I do not trust, eh. How can I use something I don't trust, eh, because I will get home and boyfriend will beat me up. Eish, I am really afraid to use the gel, I, I throw it away."

According to the conceptualisation of voluntariness adopted in this study, participant 40 had been exposed to an intentional and causal influence (offer of money) but this influence is legitimate, as CAPRISA is mandated by the Medicines Control Council to reimburse trial participants with a predetermined amount of money (Koen et al., 2008).

In terms of perceived voluntariness, Participant 40 states "I *liked* to participate because I would get the money." The use of the word *liked* suggests that participating was something she wanted to do. However, she goes on to state that "I did not feel free here because I do not even use their gel". Furthermore, Participant 40 rated the voluntariness of her participation as a 7 (out of a possible 10) on the VNRI rating and obtained a DMCI score of 42 (out of a possible 54). While these scores indicate that she perceived her participation as less than fully voluntary, neither score was in the lower half of the voluntariness continuum, indicating that her consent was perceived as sufficiently voluntary.

Participant 40 therefore perceived her participation as sufficiently voluntary and there is no evidence of a controlling influence of another person. In terms of voluntariness then, the consent provided is valid.

Emanuel et al. (2005) state that while unfortunate circumstances may make certain offers irresistible, they only become undue inducements when a "person's unfortunate circumstances and compromised judgment are combined with accepting a seriously unfavourable risk-benefit ratio that threatens fundamental interests" (p. 338). In the case of Participant 40, the unfavourable risk-benefit ratio is not related to the research itself but to her decision to participate for money (benefit) despite the fact that she is afraid that her boyfriend will beat her up if he found out that she was participating (risk). Her consent then is ethically problematic and is likely to be invalid for several *other* reasons. Participant 40 is putting her personal safety at risk by participating without her partner's knowledge and she is jeopardising the validity of the host trial by not using the study product. Participant 40's intentional decision not to use the study product is consistent with substantial adherence problems reported in microbicide gel studies (Woodsong et al., 2013). Agrawal (2003) highlights the importance of correctly classifying ethical concerns so that appropriate safeguards and remedial actions can be effected. It could be argued that because perceived and actual voluntariness (perceived freedom from controlling influences) are not compromised, this issue does not warrant further discussion here. In practice, however, if other ethical issues are identified during the assessment of voluntary consent, they too require appropriate remedial action.

5.3 Trust

"Trust is a dynamic aspect of interpersonal relationships that involves the complex and interwoven perspectives of the truster, the one trusted, and the object of one's trust" (De Melo-Martín & Ho, 2008, p. 202). People participate in research because they trust the research enterprise in general and the research organisation and researchers in particular (Lansimies-Antikainen et al., 2011). CAPRISA has been operating in the host communities, with community leaders' support, since 2000 and the majority of participants participated in CAPRISA 004 prior to participating in the host trials (CAPRISA, 2011a). Trust in the research staff was therefore conceptualised to influence participants' consent and was examined in the Survey of Influences.

In this study, 83 participants were influenced by trust in the researchers. Of these participants, 91.7% (*n*=77) said trust in the researcher influenced their participation 'a lot' and 93.9% (*n*=78) would not have participated had this influence not been present. These findings suggest that trust in the researchers is a necessary prerequisite for research participation. However, only 3.6% of the 83 participants who participated because they trusted the researchers said it was the only reason they participated. In the VNRI narratives, eight participants stated that their trust in the researchers or their positive experience with the research team influenced their participation. Appelbaum et al. (2009b) found that trust in the researchers and the reputation of the host institution were the most frequently cited motivations for research participation. Furthermore, four fifths of the 707 active participants in the All Babies in Southeast Sweden Study identified trust in the researcher as an important factor in their decision to participate (Helgesson, Hansson, Ludvigsson & Swartling, 2009). A lack of trust was not identified to be an important factor for those who decided not to participate or who opted out (Helgesson et al., 2009). Similarly, Mangset et al. (2008) found that five of the 11 stroke patients they interviewed revealed that trust in the researcher to keep them safe and provide them with the best available treatment was the reason they enrolled.

Potential research participants need to trust that the necessary study information will be disclosed to them and that conditions such as confidentiality and freedom to withdraw will be met by the researchers. However, trust can negatively impact participants' understanding of study information, ability to differentiate between research and treatment and their assessment of the risk and benefits of research (Molyneux et al., 2005). Trust can be problematic when it is based on a therapeutic misconception (a belief that the research intervention is administered for the participants' benefit and is likely to be successful) (Molyneux et al., 2005). Molyneux et al. (2005) warn that trust also becomes problematic when research participants simply place their trust in the researchers rather than "make 'rational' choices based on the information given" (p. 1464). There is concern then, that trust may override participants' desire to provide informed and truly voluntary consent (Bosk, 2002).

Participant 79:

"I was free to participate although there are some people who were discouraging us from participating by talking bad things about CAPRISA. But I trust the researchers; they are black like us so, so I don't think they will betray and enroll me in a study that would harm me."

This extract reveals that trust in the researchers may cause participants to overlook the risks associated with the research, even though the potential risks of participation are clearly outlined in the consent form. Researchers have a responsibility not to exploit the trust research participants place in them. While trust may lead participants to ignore risks or provide grounds for exploitation, it does not necessarily undermine voluntary consent, Mandava and Millum (2012) however argue that trust is only problematic when it is unwarranted and is illegitimately used to induce someone to make decisions they would not otherwise make. While trust may impact a participant's perceived voluntariness, trust in the researcher is not a potentially controlling influence and therefore cannot undermine the voluntariness and validity of consent.

In contrast, three participants voiced concern about whether they should trust the researchers during their VNRI narratives.

Participant 25:

"But sometimes I don't know if I should, um, um, be here. Because at times there are certain things that they do hide from us that we don't know. There were some people who were talking saying that, that this gel we are using the people at CAPRISA put AIDS in it."

Participant 40:

"I do not even use their gel … I can't use something I do not trust, eh. How can I use something I don't trust, eh."

Mistrust may, to an extent, lead to a more critical appraisal of the research by participants, however, it may also be detrimental to researchers if it perpetuates negative opinions of the research or hampers recruitment (Molyneux et al., 2005). When mistrust exists, such as the case of Participant 25, researchers should attempt to dispel rumours, reduce concerns and build trust among participants (Molyneux et al., 2005).

5.4 Internal determinations

Internal determinations influence all decisions made. Limited access to health care, poverty and social position may leave participants feeling that they have no choice but to participate or that they have to participate to please someone in a position of power. The internal determinations assessed in the Survey of Influences included, wanting to participate, feelings of having no other choice and a desire to please another person.

5.4.1 Wanting to participate

The overwhelming majority participants enrolled in the host trials because they wanted to (*n*=97). Of these participants 89.7% (*n*=87) said 'wanting to participate' influenced their participation 'a lot'. Furthermore, 91.8% (*n*=89) of the 97 participants said they would not have participated had they not wanted to. Likewise, Joubert et al. (2003) found that 98.9% of the 96 participants they surveyed wanted to participate in a South African study of the effect of vitamin A on mother-to-child transmission of HIV.

Wanting to participate shows that the decision to participate was in line with the participants' will or desires. According to some conceptualisations, voluntariness is simply the correspondence of one's will with one's action (cf. Graham, 2010). Wanting to participate would, according to these conceptualisations, be an appropriate indication of perceived voluntariness. This study, however, did not find wanting to participate to be significantly associated with high perceived voluntariness.

5.4.2 No other choice

Twelve participants said that they participated because they had no other choice, 10 of whom said they would not have participated if these feelings of having no other choice had not been present. These findings are lower than Manafa et al.'s (2007) findings that 55.6% of the 88 Nigerian research participants they studied indicated they had no other choice but to join the research study. In this study, participants with higher perceived voluntariness according to both the VNRI ratings ($X^2 = 2.73$, $df=1$, $p=.099$, $p<.1$) and the DMCI scores ($X^2 = 19.421$, $df=3$, $p=.000$, $p<.001$) were significantly less likely to be influenced by a feeling of having no other choice. It follows that participants who felt they had no other choice are less likely to perceive their consent as voluntary. Some authors associate feelings of no other choice or a perceived lack of alternatives with nonvoluntary consent (cf. Olsaretti, 1998). The effect 'feelings of no other choice' have on perceived voluntariness is different to there effect on actual voluntariness (perceived freedom from controlling influences). Feelings of having 'no other choice' may undermine perceived voluntariness but do not undermine actual voluntary consent. Consent provided by a participant who believes they have no other choice is still voluntary and valid as long as it is not subject to the controlling influence of another person.

Many ethical guidance documents stress the importance of researchers providing participants with information about alternatives to research participation (cf. CIOMS, 2002). Consideration of the alternatives to research participation is an important part of making an informed decision (Resnki, Patrone & Peddada, 2010). Ensuring that participants are appropriately informed of alternatives to research participation is also central to alleviating feelings of having no other choice. This of course is only true insofar as there are in fact meaningful alternatives to research participation. The CAPRISA 008 (the host trial from which 86% of this sample was recruited) consent information sheet identifies 'other research studies that are testing ways to prevent HIV infection' as an alternative. This host study however represents the only way HIV negative women (who had participated in a previous ARV prevention trial) can access the

partially effective tenofovir microbicide gel. Previous research demonstrated a 39% reduction in HIV infection, with 54% HIV reduction in women who used tenofovir gel consistently (Sokal et al., 2013). Host trial participants were sampled from communities with high incidence and prevalence rates of HIV and a well-documented lack of effective female initiated HIV prevention strategies (Sokal et al., 2013). This lack of access to acceptable alternatives may leave participants feeling their participation is less than voluntary (Olsaretti, 1998). The CAPRISA 009 consent from states that "instead of being in this study you have the choice of: Participation in the CAPRISA AIDS Treatment programme, treatment with ART through the South African national rollout program or no treatment. Antiretroviral medications, laboratory tests to monitor the effectiveness of these medications, and quality medical care for HIV/AIDS may or may not be available to you outside the study. The clinic staff will discuss with you other treatment choices in your area and the risks and the benefits of all the choices" (CAPRISA, 2012). Alternatives to research participation in CAPRISA 009 may then appear to be a less appropriate and feasible option, leaving participants feeling that they have no other choice.

5.4.3 Desire to please others

The first code of ethics published for the behavioural sciences in 1952 stated that researchers should obtain informed consent that does not exploit participants' sense of obligation or desire to please (Faden & Beuchamp, 1986). Twelve participants reported participating to please another person (researcher n=5, partner n=3, someone else n=4). Participating to please another person was not raised by any of the participants during the VNRI narratives. Participants with higher levels of perceived voluntariness according to the DMCI were significantly less likely to be influenced by a need to please the researchers (X^2 = 12.581, df=3, p=.006, p<.01). Feelings of needing to please the researcher may therefore undermine perceived voluntariness. Only two previous studies explored the need to please other people. None of the participants studied by Osamor and Kass (2012) participated to please the researcher or doctor. In contrast, Dugosh et al. (2010) found that over half (n=57%) of the 84 substance-abusing criminal offenders they

surveyed participated in research to please the judge. A desire to please the researcher may be mitigated by training researchers to be sensitive to participants' reverence for them and desire to please. It may also be helpful to empower research participants via participatory practices and by using recruiters from target populations in order to reduce the power differentials between participants and research staff which may reduce participants' desire to please the researchers (UNAIDS, 2011).

5.5 Altruism

Genuinely altruistic behaviour is motivated by a concern for others, the need to help others for their own sake (Jansen, 2009). Jansen (2009) explains how altruistic motivations are of ethical significance to research participation. First, it is argued that altruistic motivations justify exposing research participants to increased risk of harm. That is, people should be able to assume higher risks of serious harm to advance medical causes they care about just as they may be willing assume a high level of risk to attain a personal goal (such as climbing Mount Everest) (Jansen, 2009). Second, it is argued that altruistic motivations for research participation protect participants from exploitation. That is, when a research participant has altruistic motivations, they share the same interests as the researcher. These participants then cannot be used unfairly to advance interests that are not their own (Jansen, 2009) Lastly, Jansen (2009) argues that showing that research participants volunteered altruistically may reduce concerns that they did not understand the nature and purpose of the trial or that their participation was not voluntary. The VNRI narratives revealed altruism (*n*=24) to be a primary influence on research participation. Unfortunately, altruism was not systematically explored in the Survey of Influences. Altruism played an important role in host trial participation as it enabled women to take an active role in the fight against HIV/AIDS.

> Participant 24:
> "So I was more than interested to join the study, that's how I decided to actually join the study. It's because I'm passionate, um, with, um, everything that has to do with women empowerment, helping women out there. HIV is enough, you know,

> I just wanted to do something, to take an initiative. To help other people. But at the moment you cannot see the results now, but in the future I know that if, eh, they find the study to be a success, I would know in my heart that I did, eh, have an input in the study. So I would be very happy. Ja, that's the reason why I'm in the study to help women, um, not only in South Africa, but the whole world."

Mangset et al. (2008) similarly found that seven of the 11 stroke patients they studied consented to clinical trial enrollment because they believed in the importance of the research and felt a duty to participate. Lansimies-Antikainen et al. (2010) found that 29% of the 1324 participants enrolled in an exercise and diet intervention study enrolled in order to help others now and in the future. DeCosta, D'Souza and Krishnan (2004) also found that altruism was the biggest motivator for research participation in community-based trials in India. A study by Kost et al. (2011) identified altruism as the primary motivation for research participation in a sample of 85 research participants. In Appelbaum et al.'s (2009b) study of voluntary consent to research among 88 research participants enrolled in clinical research, 73% were motivated to enroll by a desire to help others suffering from the same condition. Appelbaum et al. (2009b) also found that higher scores on the Perceived Coercion Scale were associated with the importance of altruism in participants' decisions. The authors argued that those who feel they need to help others may perceive themselves as less free to refuse research participation (Appelbaum et al., 2009b). Appelbaum et al. (2009b) suggest that this may be worthy of further investigation as altruism is consistently regarded as the least problematic influence on research participation.

5.6 Misunderstanding

Misunderstanding is an interesting finding not considered carefully in the conceptualisation of voluntariness. While it appears to be a non-controlling influence, as will be explained, it is possible for the misunderstanding to result from actions of another person. In this case misunderstanding could be considered a potentially controlling influence.

A fifth of the narratives (20%) revealed a misunderstanding of the effectiveness of the study product. The study product, 1% tenofovir gel, was found to have a 39% protective effect in a previous CAPRISA phase IIb, double-blind, randomized, placebo-controlled trial (CAPRISA, 2011). However, participants' narratives revealed that some participants believed that the study product actually prevents HIV infection (as opposed to having a partial protective effect).

> Participant 41:
> "My neighbour told me about the study at CAPRISA and that it is very helpful since it really prevents HIV infection."

> Participant 93:
> "The gel we are using had 100% pass I think in 2010 or the previous year. So we are continuing now with the study and it will end up helping other women since as time goes on the gel will be available in clinics for free, like condoms."

Such misunderstandings have also been documented in previous research. Woodsong, Alleman, Musara et al., (2012) recently investigated 66 women and 40 of their male partner's motivations to join an HIV prevention vaginal microbicide trial in Malawi and Zimbabwe. The authors found evidence of the 'preventive misconception' in 29% of women and 20% of men. 'Preventive misconception' is defined as "the overestimate in probability or level of personal protection that is afforded by being enrolled in a trial of a preventive intervention" (Simon, Lavori & Sugarman, 2007, p. 371). Similarly, Horwitz et al. (2013) studied the voluntariness of consent of 492 volunteers in an HIV vaccine trial in Haïti and found that 2% of the volunteers admitted volunteering in the belief that they were receiving an effective HIV vaccine. The authors describe this as a "red flag response suggesting involuntary consent" (Horwitz et al., 2013, p. 222). Lastly, Mangset et al. (2008) found that many of the participants they studied perceived the request for their participation in research as a 'recommendation' and they believed they would receive the best treatment available.

Misunderstanding clearly has implications for informed consent but does it undermine voluntary/valid consent? Misunderstanding the effectiveness of the study product is thought to result from either (1) inadequate disclosure on the part of the researchers, (2) misunderstanding on the participants' part or (3) 'false beliefs' (Feinberg, 1986) / therapeutic optimism (Horng & Grady, 2003).

Full disclosure of information is a fundamental prerequisite of valid informed consent. A research participant cannot be expected to make a decision if they have not been provided with all the information pertinent to that decision. The Declaration of Helsinki states that research volunteers should understand the information provided before deciding whether or not to participate (Britz & le Roux-Kemp, 2012; World Medical Association, 2013). A research participant cannot be expected to make a decision if they do not understand the information they have been provided with. Cahana and Hurst (2008) maintain that at a minimum a participant should understand all the information that could lead an 'average or reasonable' person to refuse participation. Horng and Grady (2003) distinguish between two types of misunderstandings that can occur in clinical research: therapeutic misconception and therapeutic misestimation. Therapeutic misconception occurs when research participants believe that aspects of a research study are designed for their personal benefit (Appelbaum, Roth, Lidz et al., 1987). Horng and Grady (2003) argue that therapeutic misconception is ethically problematic as understanding the nature of research is critical to voluntary research participation. Therapeutic misestimation on the other hand refers to research participants who underestimate the research risks and/or overestimate the research benefits (Horng & Grady, 2003). According to Horng and Grady (2003), therapeutic misestimation is not ethically problematic if the misestimation of benefits or risks are small, or are not the main motivation for participation. In the present study, misunderstanding is of particular concern in the CAPRISA 008 trial as overestimating the protective benefit of the study product may result in increased risky sexual behavior and subsequent possible increased chances of HIV acquisition.

Feinberg (1986) argues that even when appropriate information is provided and the participant appears to understand, mistaken beliefs or mistaken expectations of the future

may still occur. For example, the researcher may explain to a participant that the study product was only found to provide moderate protection against HIV acquisition and the participant may fully understand that. Despite understanding this information, participants may be very optimistic and honestly believe that they will certainly (as opposed to might) be one of people for whom the product successfully prevents HIV acquisition. Horng and Grady (2003) term this false belief 'therapeutic optimism' and define it as the research participant's hope for the best personal outcome. The authors claim that it is not ethically problematic as hope does not compromise the autonomy of a decision (Horng & Grady, 2003). According to Jansen (2006) therapeutic optimism is when a research participant understands the disclosed information but misapplies it to themselves (Jansen, 2006). Jansen (2006) argues that therapeutic optimism is more than just 'hope'. Hopeful people emphasise the positive, they do not believe that they are more likely to have positive results than others (Jansen, 2006). Jansen (2006) explains that therapeutic optimism is a result of cognitive or motivational misrepresentations that impede decision-making. Egocentric tendencies have also been used to explain therapeutic optimism. A research participant may believe that there will be less negative consequences of research participation for themselves than for others by focusing on their own risk-reducing factors but ignoring equally relevant risk-reducing factors of others (Jansen, 2006). Jansen (2006) correctly perceives therapeutic optimism as ethically problematic as it can lead participants to make decisions that contravene their interests (Jansen, 2006). A research participant, for example, who as a result of therapeutic optimism believed that the study product would prevent her from getting HIV, may fail to utilise other HIV prevention strategies and may land up acquiring HIV. Therapeutic optimism is therefore of ethical concern in this study as it may result in participants inadvertently exposing themselves to the risk of serious harm.

As participants' narratives do not reveal anything about the source of the misunderstanding it is difficult to comment on the subsequent voluntariness of participation. If misunderstanding results from deception or intentional inadequate disclosure on the part of the researcher there is a possibility that it will meet the criteria of an intentional, illegitimate and causal and subsequently controlling influence from

another person and undermine voluntary consent. However, both host studies are conducted by experienced researchers, in collaboration with host communities and closely monitored by functional ethics and regulatory oversight committees, therefore the chances of misunderstanding resulting from inadequate disclosure or deception are assumed to be slim. It is thus more likely that misunderstandings result from the participants' therapeutic misconception or therapeutic misestimation. In this case misunderstanding is unlikely to compromise the voluntariness of consent. All sources of misunderstanding are likely to remain undetected by the participant therefore not influencing their perceived voluntariness either. Misunderstanding may not compromise the voluntariness of consent but it is ethically problematic for other reasons, primarily because participants, believing they are being given an effective HIV prevention product, may engage in increased risky sexual behaviours (Cassell, Halperin, Shelton & Stanton, 2006). An education campaign directed at CAPRISA 008 trial participants which emphasises the partial effectiveness of the study product may be an appropriate form of remedial action in this situation. It may even be necessary to re-consent participants once they properly understand what they are consenting to.

Several non-controlling influences were identified in this study. While non-controlling influences cannot undermine the actual voluntariness of consent (perceived freedom from controlling influences), this study found the need for health care and money and a desire to please the researchers to undermine the perceived voluntariness of consent. Altruism and misunderstanding were identified as important influences on perceived voluntariness, not originally considered in this study's conceptualisation of voluntariness.

6. The Decision Making Control Instrument (DMCI)

The DMCI (Miller et al., 2011) was primarily included in this study to allow the convergent validity of the VNRI to be established. However, this study also presented an opportunity to pilot the DMCI in a developing country context. Miller et al. (2011) suggested that future research could use the DMCI to explore potential causes of decreased perceived voluntariness by combining the DMCI with 'an empirical

assessment of the external conditions' under which the consent decision was made. This study assessed the association between research participants' DMCI scores and the factors influencing participants' consent decision (as determined by the Survey of Influences). Miller et al. (2011) also suggested that future research should test the DMCI with populations vulnerable as a result of economic disadvantage and lack of access to health care. As discussed in Chapter 8, section 1, participants sampled in this study are developing country participants with low personal income and a reliance on inadequate public health care.

The DMCI was used by Miller and Nelson (2012) to assess the perceived voluntariness of 184 parents of children with cancer who had recently made a decision about enrolling their child in a treatment or research protocol. The authors found lower perceived voluntariness to be significantly associated with lower education, male gender (fathers), 'nonwhite' parents (minority status) and a lack of previous experience with similar decisions (Miller & Nelson, 2012). The present study was conducted with African female participants all of whom had previously participated in research. The only external factor identified by Miller and Nelson (2012) as reducing perceived voluntariness that was also examined in this study was lower education. The present study however did not find lower education to be significantly associated with lower perceived voluntariness as determined by the DMCI. In this study a significant relationship was observed between DMCI scores and the need for money (X^2 = 24.723, df=3, p=.000, p<.001), a desire to please the researchers (X^2 = 12.581, df=3, p=.006, p<.01) and feelings of having no choice but to participate (X^2 = 19.421, df=3, p=.000, p<.001). This suggests that the need for money, a desire to please the researcher and feelings of having no choice undermine participants' perception of voluntariness.

7. Reliability and Validity

The last aim of this study was to establish the reliability and validity of the Voluntariness Assessment Instrument. Reliability refers to the degree to which a measure of a concept is stable or trustworthy (Bryman, 2004). Validity refers to whether an instrument measures

the construct it is designed to measure (Bryman, 2004). Several strategies were implemented to maximise the reliability and validity of the instrument. Furthermore, inter-coder reliability, internal consistency and convergent validity were determined where appropriate. Peer review was used to determine the face validity of the instrument. An ethics expert reviewed the Voluntariness Assessment Instrument and found that it appeared to assess the concept (voluntariness) that it was designed to measure (Bryman, 2004).

In terms of the VNRI narrative component (the participants' description of how they came to enroll), various strategies were implemented to enhance the reliability and validity of qualitative research. In relation to qualitative research, validity is defined by Hammersley (1990) as the "extent to which an account accurately represents the social phenomena to which it refers" (p. 57). The biggest threat to validity in qualitative research is anecdotalisim. Anecdotalisim occurs when qualitative findings reflect a few 'well-chosen examples' instead of being based on a critical analysis of the entire data set (Silverman, 2005). Frequency counts were used to demonstrate the strength of themes across the entire data set and combat anecdotalisim. Reliability in qualitative research refers to the consistency with which data are assigned to the same codes by different researchers (Hammersley, 1990). In order to ensure reliability, the narrative data was analysed by two researchers and inter-coder agreement was calculated for the six main themes. The percent agreement and Cohen's Kappa were calculated for the five main themes in order to establish inter-coder agreement. High levels of percent agreement were observed (89%–98%). As percent agreement often overestimates inter-coder agreement, Cohen's Kappa was also calculated. A value of 1.0 represents perfect agreement. A value of .0 represents no agreement. High levels of agreement were observed for four of the five variables (.864–.984). According to Altman (1991) a *K* value of above .81 shows a very good agreement. A moderate yet acceptable level of agreement was observed for misunderstanding (.567) (Altman, 1991). The reliability and validity of the VNRI narrative component were therefore considered acceptable.

The reliability and validity of the VNRI rating component (the participants' rating of the perceived voluntariness of their consent decision along a 10-point scale) was enhanced by the inclusion of voluntary and nonvoluntary reference narratives and ratings. First, participants were asked to talk about a time in their life when they were forced to make a decision against their will, a decision that they felt was nonvoluntary and rate the voluntariness of that decision using a 10-point scale. With a score of 10 being completely voluntary and a score of 1 being completely nonvoluntary [Nonvoluntary Reference Exercise]. Participants were then asked to talk about a time in their life when they made a completely voluntary decision and rate the voluntariness of that decision using the same 10-point scale [Voluntary Reference Exercise]. Once participants have a reference point for a voluntary and nonvoluntary decision from their own personal experience, participants were asked to describe how they came to consent to the host study [VNRI Narrative]. Finally, using their personal nonvoluntary and voluntary ratings as reference points, participants were asked to rate the voluntariness of their participation in the host research using the same 10-point scale [VNRI Rating]. The inclusion of the two reference narratives enabled participants to critically consider what a voluntary and nonvoluntary decision meant to them. The reference narrative also allowed the researcher to verify that participants assigned low ratings to their nonvoluntary reference narrative and high ratings to their voluntary reference narrative. This ensured that appropriate ratings would later be assigned to the narrative of their consent decision, that is, low ratings would reflect perceived nonvoluntariness and high ratings would reflect perceived voluntariness.

The convergent validity of the VNRI rating component was tested by administering an existing measure of perceived voluntariness (the DMCI) to participants after the VNRI ratings had been completed. However, the correlation between the results of the two instruments could not be calculated as the assumptions for Spearman's Rank Order Correlation were not met (the relationship between the two variables were non-monotonic). However, a Mann-Whitney test was conducted to determine the difference between total DMCI scores for VNRI ratings of less than 10 and VNRI ratings of 10. The test revealed that VNRI ratings could not differentiate between high and low DMCI scores (Z=.644, p=.519). While this method of assessing convergent validity was the only

method available due to the nature of the data, it is methodologically flawed and therefore does not provide a good indication of the validity of the VNRI rating component. The methodological flaw lies in the low frequency of low (less than 10) VNRI scores. To have accurately compared the DMCI and VNRI findings, the scores from both instruments should have been split into scores on the top half of the distribution and scores on the lower half of the distribution and then compared. However, the low frequency of VNRI scores under 10 necessitated dividing VNRI scores into those of 10 and those of under 10. The VNRI scores under 10 still represent a voluntary decision as the majority of scores under 10 ranged between seven and nine. Essentially then, the Mann-Whitney test showing that the VNRI ratings could not differentiate between high and low DMCI scores (Z=.644, p=.519) is not necessarily a result of the VNRI being invalid so much as it is likely to be a result of using inappropriate cut-off points in the VNRI scores which do not reflect voluntary and nonvoluntary consent. The convergent validity of the VNRI rating component was therefore not appropriately assessed.

The DMCI had a sufficiently high level of internal consistency (0.869) and the three subscales were correlated with one another as expected. That is, participants who displayed high levels of self-control, displayed low levels of absence of control and low levels of others control.

The reliability and validity of the Survey of Influences were not appropriately assessed. The intention was to compare the presence of controlling (intentional, illegitimate and casual) influences as detected in the Survey of Influences to the researcher's analysis of the presence of controlling influences from what the participants described in their VNRI narratives. A strong correlation between the two would have supported the construct validity of the Survey of Influences. However, this was not possible for two reasons. First, only one controlling influence was identified by the Survey of Influences. Second, there was a large discrepancy in the influences reported spontaneously in the VNRI narratives and those identified in the Survey of Influences: the VNRI narratives under-reported the presence of all but one influence. As influences were often not described in

the VNRI narratives, it was impossible for the researcher to use the VNRI narratives to assess the presence of controlling influences.

Overall further research is needed to establish the reliability and validity of the Voluntariness Assessment Instrument. Anecdotalisim in the analysis of the VNRI narratives was combated by reporting frequency counts for each theme and a high level of inter-coder reliability was observed. The VNRI narrative is valuable as it shows what factors participants considered in forming their perception of voluntariness. This is an advantage over quantitative methods. The DMCI, for example, merely assesses perceived voluntariness but the researcher has no way of knowing what factors undermined perceived voluntariness for a particular participant, making remedial action impossible. However, collecting and analysing narrative data is time consuming and labour intensive and is unlikely to be feasible to implement in large clinical trials. As such it is recommended that VNRI narratives may be most suited for use with participants who have displayed low levels of perceived voluntariness (based on the DMCI for example). Administering the VNRI narrative to participants with low perceived voluntariness may provide further insight into why participants perceive their consent to be less than fully voluntary on the basis of which remedial action can be taken in order to enhance perceived voluntariness. This study however did provide further support for the reliability of the DMCI which had a high internal consistency and moderately strong positive correlations between the three subscales. Further research is needed to assess the validity and reliability of the VNRI rating component and Survey of Influences.

8. Study Limitations

This pilot study has several limitations. First, a major limitation of this study was the small sample size and single research site. A power analysis was not conducted because the study may have been underpowered to detect associations. However, the sample size of 100 participants was necessary to accommodate the large qualitative component of this study. As producing generalisable data was never an aim of the study, the small sample size and single research site were deemed an appropriate compromise.The small sample size and single research site, however, are likely to have contributed to the low levels of

influences and low levels of actual (perceived freedom from controlling influences) and perceived nonvoluntariness being reported. As such, it was largely impossible to conduct meaningful statistical analysis of factors associated with nonvoluntariness. Consequently, data analysis was primarily descriptive. The well-refined community engagement and recruitment practices based on UNAIDS *Good Participatory Practice Guidelines* (2011) implemented at CAPRISA may also be responsible for the low rate of nonvoluntary responses but do not invalidate the results.

A second limitation of this study was the voluntariness cut-off points used in the VNRI ratings and the DMCI. During instrument development a theoretical 'sufficiently voluntary threshold' was determined for both scales using Feinberg's (1986) three 'rules of thumb' (Chapter 2 – section 3). 'Sufficiently voluntary' was placed from the highest possible score to the median score as illustrated below for the VNRI rating scale (Figure 18).

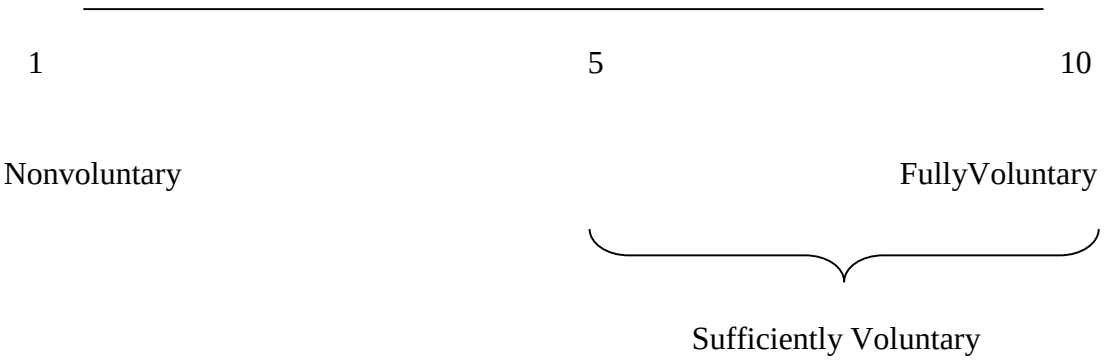


Figure 18. VNRI rating scale: Theoretical sufficiently voluntary threshold

Empirical limitations meant that this theoretical threshold could not be used during data analysis. The low levels of perceived nonvoluntariness reported by participants meant that grouping of data for perceived voluntary and nonvoluntary consent was done in a way that ensured that sufficient data was present in each category to enable statistical comparisons to be made. That is, instead of using the theoretically determined cut-off point for sufficiently voluntary, the categories of fully voluntary or less than fully

voluntary were used, as illustrated in Figure 19. For example, for the VNRI rating the data had to be divided into fully voluntary (a rating of 10) and less than fully voluntary (a rating of less than 10). It would have been more accurate to divide the data into 'fully voluntary,' 'sufficiently voluntary' and 'nonvoluntary' as per Figure 18 but if this had been done the number of cases in the sufficiently voluntary and nonvoluntary categories would have been too few to warrant meaningful statistical analysis. The same applied to the DMCI data.

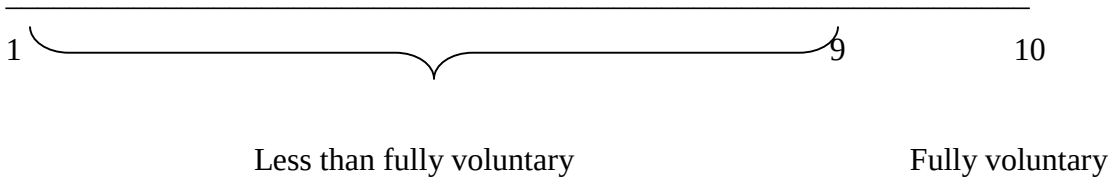


Figure 19. VNRI rating scale: Actual cut-off points used

The third limitation is that perceptions of voluntariness appear to vary over time (Miller et al., 2011). As such, it is difficult to determine the optimal point in time to investigate the voluntariness of informed consent. Assessing voluntariness immediately after or as close to the consent decision as possible is advantageous as it removes the risks of other factors (such as trial experiences) altering participants' perceptions of voluntariness. Administering the assessment instrument too soon, however, may mean that participants have not had adequate time to reflect on the voluntariness of their consent decision. A limitation of this study was that the time between participants' consent decision and completion of the Voluntariness Assessment Instrument varied from one participant to the next, in some cases the gap was over a year.

Fourth, the conceptualisation of voluntariness adopted in this study did not take into account the role that permission from others and freedom to withdraw plays in perceived voluntariness. The exclusion of these two influences was supported by the VNRI narratives (no participants mentioned obtaining permission from others or not having the freedom to withdraw). However, in retrospect collecting this data in the Survey of Influences would have facilitated comparison with data collected in previous empirical

studies where much of the focus was on these two domains (cf. Abdool Karim et al., 1998; Joubert et al., 2003; Kass et al., 2005; Kiguba et al., 2012; Lansimies-Antikainen et al., 2010; Marshall et al., 2006). Collecting this data would have also enabled its comparison with perceived voluntariness scores in order to determine if permission from others or freedom to withdraw undermined participants' perception of voluntariness. Future modifications of the Survey of Influences should include these elements.

Fifth, as with all measures of voluntariness, this instrument relies on participants' self-report. While appropriate for measures of perceived voluntariness, reliance on participants' self-report of actual voluntariness is inherently problematic. The first problem was also reported by Appelbaum et al. (2009b): Voluntariness assessment instruments cannot detect problematic influences not recognised or reported by the participants themselves (Appelbaum et al., 2009b). Second, asking research participants to identify intentional, illegitimate and causal influences from others is inherently subjective and, as with all self-report measures, what is produced is participants' *perception* of intentional, illegitimate and causal influences from others. Any reasonable attempt to measure actual voluntariness is then just a measure of *perceived* freedom from controlling influences. Despite this inherent limitation, distinguishing between perceived and actual voluntariness is essential. Measures of general perceived voluntariness (such as the DMCI) take all influences into consideration. Measures of perceived freedom from controlling influences of others, however, focus only on the influences that actually have the potential to undermine the voluntariness and subsequent validity of consent and therefore are a more accurate reflection of nonvoluntary consent (even with its limitation of subjectivity) than measures of general perceived voluntariness.

Sixth, although both the researcher and research assistant were external to CAPRISA and participants were informed that their responses would remain confidential and not impact their participation in the host trials in any way, some of the study findings indicate social desirability bias. For example, when a significant relationship was demonstrated between voluntariness and demographic characteristics, the direction of the relationship was observed to be counter-intuitive. For example, participants with no income were more

likely to perceive their participation as voluntary (DMCI score >45) than participants with an income of less than R1,000 per month (X^2 = 6.883, *df*=2, *p*=.032, p<.05). These findings may reflect a social desirability bias, whereby participants responded in a manner they viewed as favourable to the researcher (Bryman, 2004).

Seventh, the VNRI narratives identified influences (e.g., altruism and HIV prevention) not systematically explored in the Survey of Influences. These findings may reflect the limitation of using literature as a proxy for formative research as was done during instrument development. Conducting focus groups with a small sample of the research population may ensure that the non-controlling influences explored in future versions of the Survey of Influences are exhaustive and that they accurately represent the influences that a particular research research population is exposed to.

Another potential limitation is that the pilot study was only conducted with individuals who had consented to research participation. It is conceivable that these individuals may differ systematically from those who go through the consent process but ultimately refuse participation. Furthermore, the participants sampled in this pilot study had all participated in previous research. Participants therefore had experience making similar consent decisions in the past which may account for the high levels of perceived voluntariness and low levels of controlling influences detected. It is possible that research niave populations display lower levels of voluntariness. Lastly, pilot study participants were all female therefore this study provides no insight into the influences male research participants are exposed to or their levels of perceived voluntariness.

The final limitation of this study is the use of a 0.10 significance level in some instances instead of the traditional .05 level of significance. This decision is however justified as this was an exploratory pilot study. Future confirmatory studies using a 0.05 level of significance are however justified by the present findings and are recommended.

9. Recommendations for Future Research

On the basis of the pilot study, the following recommendations for future research are proposed:

> *Recommendation 1*: The VNRI be used when concerns about voluntary consent are present.

The generation of the two reference narratives and consent narrative in the VNRI is an intensive and time-consuming process making it impractical to conduct with a large number of research participants. The strength of the VNRI is that it allows participants to engage with and become sensitised to the concept of voluntariness and what it means for them. The VNRI narrative component allows researchers to identify what factors shape individual participants' perceptions of voluntariness. Establishing what voluntariness means for participants and exploring what factors undermine voluntariness from the participants' point of view has not been done in any previously published studies of voluntariness available to the researcher. The VNRI is therefore recommended for use in qualitative studies of voluntariness where researchers hope to obtain a detailed understanding of the voluntariness of research participants' consent decision. The VNRI may be appropriate for use in the research context when low levels of perceived voluntariness have already been detected by other shorter instruments that are easier to administer, such as the DMCI. The VNRI narrative component could be administered to participants who obtain low DMCI scores in order to gain a better understanding of why consent is perceived as nonvoluntary and to establish what remedial action should be taken.

> *Recommendation 2*: Future research using the VNRI should question participants about specific influences on their consent decision in addition to enabling participants to spontaneously identify influences on their own.

The VNRI narratives allowed participants to spontaneously identify factors affecting voluntariness while the Survey of Influences questioned participants about specific influences. The results of the two instruments were compared (Table 60 and Figure 19). The Survey of Influences resulted in more influences being reported in all but one of the categories than in the VNRI narratives. This suggests that questioning participants about specific influences may be a more valid means of data collection than allowing participants to spontaneously identify influences on their own. While questioning participants about an 'exhaustive' list of influences as done in the Survey of Influences is time consuming and involves complex skip patterns, this is outweighed by the benefit of participants being forced to systematically consider a variety of possible types of influences from various sources.

> *Recommendation 3*: Focus groups should be used to identify potential influences relevant to the research population and study context prior to future empirical assessments of voluntariness.

The VNRI narratives identified influences not explored in the Survey of Influences, namely, HIV prevention, altruism, distrust in the researcher and misunderstandings. This suggests that a formal assessment of voluntary consent should incorporate these issues in the future. This further suggests that using the literature as a proxy for focus group discussion during instrument development, as was done in this study, is limiting. While the literature may ensure that expert opinions are captured, it may result in potentially important influences relevant to the research population and study context being neglected.

> *Recommendation 4*: Future research is needed to identify the extent to which nonvoluntary research participation is a relevant concern.

Ethicists and researchers are increasingly advocating for the assessment of voluntariness to be formally included in the informed consent process, especially when research is conducted with vulnerable participants from African countries (Kass et al., 2005). The

findings from this pilot study, however, do not provide support for this recommendation. The high levels of voluntary and valid consent documented in this study may suggest one of two things, assuming that the conceptualisation of voluntariness adopted is valid and the assessment method is appropriate. First, it may suggest that when conceptualised correctly (cf. Appelbaum et al., 2009a; Wertheimer, 2012) nonvoluntary research participation is far less of a concern than many commentators suggest. Second, it may suggest that nonvoluntary consent is prevented by exemporary community engagement and research practices implemented by CAPRISA. Future research needs to determine whether nonvoluntary participation is as much of a problem as commentators suggest or if the findings of high levels of voluntary and valid consent are similar in other research populations in other countries. If high levels of voluntariness are not documented in future studies in which this study's conceptualisation and assessment methods are adopted, then CAPRISA's research practices should be carefully investigated to establish what elements enhance participants' voluntary consent.

> *Recommendation 5*: Future research should pair assessments of adequate disclosure and understanding with assessments of voluntariness.

This study assumed that disclosure and understanding were prerequisites for voluntary consent. Adequate levels of both were taken as a given in this study. However, a fifth of the VNRI narratives revealed a misunderstanding of the effectiveness of the study product. Misunderstanding the effectiveness of the study product may result from either inadequate disclosure by the researchers, misunderstanding on the participants' part or 'false beliefs' / therapeutic optimism. The sources of misunderstanding therefore need to be explored. Participants cannot be expected to make a voluntary consent decision if they do not have all the necessary information disclosed to them or if they do not understand that information (Barsdorf & Wassenaar, 2005). It is recommended that future research assesses disclosure and understanding in order to ensure that a voluntary decision can be made in the first place.

10. Summary

The results of the Voluntariness Assessment Instrument piloted were discussed in this chapter. The high levels of perceived voluntariness documented were discussed in relation to participants' pre-existing vulnerabilities. Factors associated with lower perceived voluntariness were also explored. Potentially controlling influences, including the means through which others exerted these influences and the effect of these influences, were explored. Only one participant was deemed to have been exposed to controlling (intentional, illegitimate, causal) influences from another person. The non-controlling influences participants were exposed to were also discussed. This chapter concluded with a discussion of the limitation of the pilot study and recommendations for future research.

Chapter 9: Conclusion

This concluding chapter provides a summary of this study as a whole and attempts to integrate the conceptualisation of voluntary consent as a legal and moral imperative and the assessment of voluntary consent through the Voluntariness Assessment Instrument developed. The strengths, limitations and recommendations of the study are also reflected upon.

Following a brief introduction of the study topic, the literature of voluntariness of consent to research was reviewed. The literature review established the importance of obtaining voluntary informed consent from potential research participants as a means of respecting their autonomy (Beauchamp & Childress, 2009). Voluntary informed consent allows research participants to make a meaningful choice whether or not to participate in research and should therefore reflect the will of the consenter, not of other persons (Appelbaum, Lidz & Klitzman, 2009b). Every major research ethics guidance document drafted since World War II emphasises the importance of obtaining voluntary informed consent (Nelson & Merz, 2002). Yet, as elaborated on in Chapter 2, review of these guidelines reveals a failure to consistently describe what factors are necessary and sufficient to undermine voluntary consent.

As a result, considerable controversy exists in the research ethics literature, with researchers and ethicists advancing numerous concerns about the voluntariness of consent to research. The literature review identified the following factors as being frequently attributed to undermining voluntary consent: coercion; persuasion; inducements; difficult or desperate background conditions; addictions and disorders; social roles, norms and inequalities; social desirability and trust in the researchers; emotions, perceptions, internal representations and personal beliefs; actions of a third party; and African communitarian culture and relational decision-making. Findings from existing empirical studies report varying degrees of voluntariness among research participants based on markedly different assessment methods. Mutenherwa (2012), for example, assessed the perceived voluntariness of the enrolment of Zimbabwean clinic patients in a randomised

controlled trial of the impact of a new diagnostic test for tuberculosis using an instrument developed by Appelbaum et al. (2009b) to detect the presence of external, intentional, illegitimate and causal influences. Mutenherwa (2012) found that 98% of 100 respondents perceived their participation to be voluntary and uncoerced. While Horwitz et al. (2013) identified 11% of 429 participants enrolled in an HIV vaccine trial in Haïti as making a less than voluntary decision to enroll based on the following five open-ended questions about "(1) the purpose of the study, (2) reasons for volunteering, (3) hopes for study participation, (4) "bad things" that could happen, and (5) reaction if something in the study made them unhappy" (Horwitz et al., 2013, p. 222).

Despite the definitional discrepancies in normative guidelines, researchers' concerns and empirical studies, the conceptual review (Chapter 4) revealed four prominent theories of voluntariness. These theories were classified as value-neutral or moralised accounts (cf. Wertheimer, 2012). Essentially the voluntariness of a consent decision can be thought of in two ways. First, the voluntariness of a consent decision can be determined based on *a priori* conceptualiations of voluntariness (value-neutral accounts), or the validity of the consent provided can be assessed independently of whether the consent decision can reasonably be described as voluntary or not according to *a priori* definitions (moralised accounts) (Wertheimer, 2012).

The most prominent value-neutral account of voluntariness identified is that of Beauchamp and Childress (2009) who claim that a person acts voluntarily "if he or she wills the action without being under the control of another's influence" (p. 132). Faden and Beachamp (1986), Beauchamp and Childress (2009) and Nelson et al. (2011) argue that in terms of influences from another person only coercion (when one person intentionally and successfully influences another person by presenting a credible threat of harm so severe that the coercee has no choice but to act in order to avoid the threat of harm) (Chapter 2 – section 2.1) and certain types of manipulation (such as deception) can be controlling and therefore be considered to undermine the voluntariness of consent (Chapter 2 – section 2.3). A second, popular but flawed, value-neutral account of voluntariness is provided by Olsaretti (1998). According to Olsaretti (1998) a decision

may be deemed ‘free’ if it is not subject to the influences of other people. A decision however may only be deemed ‘voluntary’ if an acceptable alternative is available or, in the absence of an acceptable alternative, if a person would have made a given decision had an acceptable alternative been available (Olsaretti, 1998). A decision should therefore be considered nonvoluntary if it is made because no other acceptable alternative is available. The primary criticisim of this account is that voluntariness of consent is held to an unrealistically high standard (Wertheimer, 2012). ‘Acceptable alternatives’ are rarely available in daily life decision-making, it is unrealistic to expect research participants to provide consent based on ‘acceptable alternatives’ when they would not be expected to do so in other equally important decision-making contexts such as consent for medical treatment or employment (Wertheimer, 2012).

The first moralised account of voluntariness reviewed was that of Appelbaum et al. (2009a). Appelbaum et al. (2009a) state that for legal purposes a decision “is presumed to be voluntary if no evidence exists that someone else has unduly influenced it or coerced the person deciding” (p. 32). According to the legal definition, consent is presumed voluntary even if it is influenced by the consenter’s internal determinations (e.g., values or emotions) or external circumstances (e.g., poverty or illness). Consent is even presumed voluntary, in terms of the law, if one person has exerted a controlling influence over another or has made other alternatives unacceptable if the first person’s actions are legitimate. Appelbaum et al. (2009a) hypothesise that a decision is nonvoluntary only if it is subject to an influence that is external (comes from another person), intentional (the influencer intended to influence the decision-maker’s consent decision), illegitimate (the influencer did not have the right to exert the influence or by exerting the influence they undermined the rights of the decision-maker) and causally linked to the choice of the research participant. A distinct advantage of Appelbaum et al.’s (2009a) conceptualisation is that each element can easily be operationalised and assessed.

Wertheimer (2012) provides the last account of voluntariness reviewed. As a starting point, Wertheimer (2012) assumes that for research to be ethical it requires that participants provide valid consent and that for consent to be valid it must be voluntary.

Wertheimer (2012) refers to this as the *validity requires voluntariness principle*. Wertheimer (2012) advocates for "a moralised account of voluntariness in which the voluntariness of a person's consent turns on the legitimacy of the *means* by which their consent is solicited" to be adopted (p. 27). Whether consent is deemed to be nonvoluntary by value-neutral accounts or voluntary by other accounts, researchers will still be tasked with determining whether such consent should be regarded as valid and this, according to Wertheimer (2012), can only be done by means of a moral analysis. In turn, this moral analysis centres on the legitimacy of the influence i.e., does the law view an influencer as acting within their rights and not violating any of the decision-maker's rights when exerting the influence?

The conceptual complexity of the term voluntariness has resulted in relatively few empirical studies of the voluntariness component of consent to research being conducted, especially when compared with research on the informational and understanding elements of informed consent. However, as the call for a formal assessment of voluntariness to be incorporated into the consent process intensifies (Stiles et al., 2011), more researchers have responded to the challenge of developing a suitable measure of voluntariness (cf. Appelbaum et al., 2009b; Dugosh et al., 2010; Miller et al, 2009). In order to identify empirical studies of voluntariness of consent to research, a comprehensive search of electronic sources was conducted (Chapter 5). The search and selection process yielded 15 studies using different voluntariness assessment instruments. For each of the 15 studies, information was extracted on the nature of the study (aims, method, findings); administration characteristics (location, sample, format, administration time, timing of administration); psychometric properties of the instrument (reliability, validity, standardisation and norming procedures) and domains assessed. The review provided useful insight into how voluntariness of consent has been assessed to date and how it may be assessed, particularly the way different influences may be identified and measured. The empirical review found studies of voluntariness of consent to research to be equally distributed between the developed and developing world. This review also revealed that most studies had small sample sizes and single study populations. The majority of studies used brief quantitative instruments. Instrument administration time

ranged from 5–60 minutes. Most studies assessed voluntariness directly after consent was obtained, suggesting that this may be perceived as the optimal administration time. Futhermore, all existing instruments that assess the voluntariness of consent to research are novel measures that lack well-established validity and reliability. Only five of the 15 studies made preliminary attempts to assess the validity and reliability of the instruments. Furthermore, only six of the 15 studies reviewed attempted to explicitly define how voluntariness was conceptualised for the purposes of the study. This finding reflects the general lack of theory and construct clarity found in the literature on voluntariness of consent. Failure to adequately define voluntariness prior to instrument development may also result in voluntariness of consent being conflated with related constructs such as exploitation, vulnerability, unfortunate circumstances or misunderstandings. Different conceptualisations of factors that impact voluntariness, such as offers and threats, also limit the usefulness of existing measures. In addition, many existing voluntariness assessment tools identify the presence of an influence but make no attempt to identify the exact source of the influence or establish the legitimacy of the influence. Other studies assess participants' knowledge that consent is supposed to be voluntary but fail to determine whether or not it was in fact experienced as voluntary. Essentially, this review revealed the relatively underdeveloped state of empirical research on the voluntariness of consent to research.

The literature review (Chapter 2), conceptual review (Chapter 4) and the empirical review (Chapter 5) summarised above led to the development of a new conceptualisation of voluntariness in which voluntariness of consent to research was seen to comprise a legal and moral imperative (Study aim 1) and the development (Study aim 2) and piloting (Study aim 3) of the Voluntariness Assessment Instrument. The remainder of this concluding chapter aims to bring the three study aims together and reflect on the strengths, limitations and recommendations of this study as a whole.

1. Voluntary Consent as a Legal and Moral Imperative

The purpose of constructing a new conceptualisation of voluntariness was, first, to provide a way of understanding the voluntariness of consent that addresses the gaps in previous conceptualisations and second, develop an appropriate means with which to assess voluntariness of consent.

The conceptualisation of voluntary consent as a legal and moral imperative is a moralised account of voluntariness as it relies on determining the legitimacy of the controlling influences of others in order to establish the validity of the consent provided. Linking voluntariness with the validity of consent is practically useful as it allows researchers to determine when concerns about voluntariness are relevant or not. However, conceptualising voluntary consent as a legal and moral imperative also acknowledges the importance of the research participants' subjective experience of voluntariness. That is, internal and contextual conditions may impact participants' subjective perceptions of voluntariness even if these are insufficient to render consent nonvoluntary and invalid. The conceptualisation of voluntariness adopted in this study attempted to take into account both researchers' legal imperative to obtain voluntary and valid informed consent (cf. Appelbaum et al., 2009a; Wertheimer, 2012) and researchers' moral imperative to ensure that consent is perceived as voluntary by the person providing consent (cf. Bull & Lindegger, 2011).

2. The Legal Imperative

2.1 Conceptualising the legal imperative

Voluntariness of consent as a legal imperative means that consent will be considered voluntary (and subsequently valid) if it is free from controlling influences of others. Controlling influences are further defined as intentional, illegitimate and causal (cf. Appelbaum et al., 2009a). This conceptualisation of voluntariness assumes that all

influences fall into the categories of non-controlling influences and potentially controlling influences (Chapter 4 – Figure 2).

2.1.1 Non-controlling influences

Non-controlling influences consist of influences such as a person's socio-economic situation, illness, social roles/power differentials, culture/beliefs and internal determinations. As such, the circumstances of the potential research participant (including their pre-existing values, beliefs, psychological state, social role, financial situation and physical wellbeing) were accepted exactly as they are (cf. Feinberg, 1986). Against those background circumstances it was determined whether the potential research participant's consent decision was voluntary or whether another person intervened to undermine it (Feinberg, 1986).

2.1.2 Potentially controlling influences

Potentially controlling influences, on the other hand, are influences exerted by other people. Only potentially controlling influences have the ability to undermine the voluntariness of consent. This conceptualisation is in line with the legal doctrine of informed consent in which consent is "presumed voluntary if no evidence exists that someone else has unduly influenced it or coerced the person deciding" (Appelbaum et al., 2009a). Potentially controlling influences from other people are exerted through coercion, persuasion, inducement and pressure.

2.1.3 When potentially controlling influences become controlling

Whether any of these potentially controlling influences are actually experienced as controlling or not for a particular person can be determined by examining the intentionality, legitimacy and causality of the influence (cf. Appelbaum et al., 2009a). An influence from another person was only considered controlling if it is intentional, illegitimate and causally linked to the choice of the research participation (Appelbaum et

al., 2009a). For an influence to be intentional the decision-maker must perceive it to result from the deliberate action of another person who means to influence their decision in a certain way (Appelbaum et al., 2009a). An influence is illegitimate if the person exerting the influence does not have the right to exert that influence or if by exerting that influence they are violating the decision-maker's rights (Appelbaum et al., 2009a; Wertheimer, 2012). Finally, to be controlling, the intentional and illegitimate influence has to actually cause a particular decision to be made (Appelbaum et al., 2009a).

2.2 Assessing the legal imperative

The primary concern of this study was therefore to determine whether consent was voluntary and valid according to this legal imperative, i.e., free from the controlling (intentional, illegitimate and causal) influences of others. In order to do this the Survey of Influences was developed. As described in Chapter 5 – Table 5, the Survey of Influences identified the presence of non-controlling and potentially controlling influences. In terms of potentially controlling influences, the Survey of Influences also assessed who exerted the potentially controlling influences (e.g., partner) and how this was done (e.g., coercion). Whether each potentially controlling influence identified was in fact experienced as controlling or not was then established by assessing the perceived intentionality, legitimacy and causality of that influence. The narrative component of the Voluntariness Narrative Rating Instrument (VNRI) (Chapter 5 – section 4.1.1) asked participants to describe how they came to consent to enroll in the host study. This narrative provided further insight into the non-controlling and potentially controlling influences that participants were exposed to.

2.3 Main pilot study findings relating to the legal imperative

2.3.1 Non-controlling influences

A need for health care (89%), trust in the researchers (84%), illness (53%), a need for money (13%) and a desire to please another person (partner, researchers, someone else) (12%) were identified as non-controlling influences by the Survey of Influences. The VNRI narratives further identified HIV prevention and altruism as non-controlling influences. CAPRISA 009 participants were significantly more likely to be influenced to enroll in the host trials by illness than CAPRISA 008 participants. Participants who were older, single and had a higher income were significantly more likely to be influenced to enroll in the host trials by illness. Participants who enrolled more than a year ago were significantly more likely to be influenced to enroll in the host trials by the need for health care than those who enrolled less than a year ago. Participants who were not employed and participants with no income were significantly less likely to be influenced to enroll in the host trials by a need for money. Participants who were not employed and participants with no income were significantly less likely to participate because they had no other choice.

2.3.2 Potentially controlling influences

Research staff (18%), friends (13%), partners (11%), family members (10%), and health care providers (1%) were identified as potentially controlling influences on participants' consent decision. Of the 100 participants, three reported being threatened to prevent their participation (one by a family member and two by a friend), one reported being pressured not to participate by their partner and only one participant reported being pressured to participate bu their partner. Two participants were advised by their partner, three were advised by their family, three were advised by a friend and 11 participants were advised by the CAPRISA research staff. The pilot study also found that friends had significantly less influence in causing a consent decision to be made than the other groups. CAPRISA staff members had the most influence in causing a consent decision to be made.

2.3.3 Controlling influences

All except one participant (99%) perceived influences from other people as intentional and legitimate and not causing them to make the consent decision they did. Subsequently, according to the conceptualisation of voluntariness adopted in this study only one participant was subject to a controlling influence and therefore participated nonvoluntarily and provided invalid consent. Ideally, this participant should be educated about the voluntary nature of participation and re-consented, however, the anonymous nature of the pilot study prevented this from being done.

3. The Moral Imperative

3.1 Conceptualising the moral imperative

Adopting the legal imperative neglects a wide range of subjective experiences of voluntariness frequently cited in the literature. Bull and Lindegger (2011) argue that in addition to ensuring that there is no objective evidence of controlling influences from others, researchers also have a moral obligation to determine whether participants feel that they have made a voluntary consent decision.

In addition to obtaining voluntary consent according to the legal imperative, the moral imperative states that researchers should also ensure that the participants themselves feel that their consent is voluntary. A secondary concern of this study was then to determine if participants also had a subjective experience of voluntariness. The participants' personal interpretation of the voluntariness of their consent decision is referred to as *perceived voluntariness*. If consent is nonvoluntary according to the legal doctrine, it is invalid. However, if consent is not perceived as voluntary it may still be voluntary and valid according to the legal doctrine of informed consent. While only controlling influences are considered important in terms of the validity of consent, in addition to potentially controlling influences of others, non-controlling influences (from conditions) (Chapter 4 – Figure 2) also affect participants' perceived voluntariness. Ideally, research participants

should provide voluntary and valid consent (free from intentional, illegitimate and causal influences of others i.e., controlling influences) and perceive themselves to have provided voluntary consent.

3.2 Assessing the moral imperative

In order to assess participants' perceived voluntariness of consent, the Voluntariness Narrative Rating Instrument (VNRI) was designed to allow participants to describe how they came to enroll in the host research (VNRI narrative) and rate the degree to which they perceived their enrolment as voluntary (VNRI rating). To assist research participants to do this, the VNRI allowed the participants to think through what voluntariness means to them by getting the research participants to complete a Nonvoluntary Reference Exercise followed by a Voluntary Reference Exercise. Miller et al.'s (2011) Decision Making Control Instrument (DMCI) was also administered to provide an additional quantitative assessment of perceived voluntariness.

3.3 Main pilot study findings relating to the moral imperative

High levels of perceived voluntariness were documented. The overwhelming majority of participants (*n*=93) reported that they perceived their consent decision as voluntary during their VNRI narratives. Similarly, in the VNRI ratings 89% of participants rated their participation as fully voluntary with a score of 10 and only one participant produced a rating (4) in the bottom half of the scale. Lastly, the DMCI scores also revealed high levels of perceived voluntariness with 80% of participants scoring above 50 and only one participant obtaining a score (of 21) in the lower half of the range of possible scores.

In terms of the VNRI, lower perceived voluntariness was significantly associated with having more than a primary school education and taking more than 24 hours to reach a consent decision. Lower perceived voluntariness was also associated with feelings of having no choice but to participate. In terms of the DMCI, lower perceived voluntariness was significantly associated with earning between R1–R1,000 per month, not being

influenced by a CAPRISA staff member and with not needing health care. Lower perceived voluntariness, in relation to DMCI scores, was further significantly associated with the need for money, a desire to please the researchers and feelings of having no choice but to participate.

4. Strengths, Limitations and Recommendations for Future Research

Overall, the data suggests that it is possible to obtain voluntary and valid consent for research participants in ethically complex HIV clinical trials in an impoverished developing country context. The primary strength of this study is that it attempted to combine a careful conceptualisation of voluntariness with the development and piloting of a Voluntariness Assessment Instrument.

A strength of the conceptualisation adopted and the subsequent assessment method developed is that both actual voluntariness (perceived freedom from controlling influences of others) and perceived voluntariness were taken into account. By doing so, this conceptualisation addresses a gap in previous conceptualisations that either focus on actual or perceived voluntariness: An exclusive focus on actual voluntariness (perceived freedom from controlling influences) renders most concerns about the voluntariness of consent to research expressed by ethicists, researchers and participants themselves (i.e., perceptions of voluntariness) inconsequential (cf. Appelbaum et al., 2009b). While an exclusive focus perceived voluntariness fails to explain when concerns about voluntariness affect the validity of a consent decision (cf. Miller et al., 2011).

The strength of the Voluntariness Assessment Instrument developed is that it addresses gaps in existing instruments. The VNRI allowed participants to engage with the concept of voluntariness and what it means for them and it allows researchers to identify what factors shape individual participants' perceptions of voluntariness. Establishing what voluntariness means for the participant and exploring what factors undermine voluntariness from the participants' point of view is not something that any previous studies of voluntariness of consent to research have done. The Survey of Influences, on

the other hand, allowed researchers to systematically explore all possible potentially controlling influences participants may have been exposed to and the effect these influences have on the voluntariness of the consent decision.

The primary limitation of this study is that the data generated from the pilot study needs to be interpreted with caution as it is derived from a relatively novel conceptualisation of voluntariness (despite building on the work of Appelbaum et al. (2009a)) and a previously untested assessment method. In addition, pilot data was collected from a small sample of participants and the reliability and validity of the Voluntariness Assessment Instrument developed for this study was not appropriately assessed.

Despite these limitations, several important recommendations can be drawn from this study. The conceptualisation of voluntariness (Chapter 4) adopted builds on several reputable theories of voluntariness and is thought to be comprehensive and robust. However, future peer review of this conceptualisation is still needed to expose this conceptualisation to rigorous thought experiments by other experts in the field in order to establish whether it can hold up against various hypothetical scenarios. Second, a broader review of empirical studies of voluntariness is needed. The review of empirical studies of voluntary consent (Chapter 5) was limited to published literature focusing specifically on the assessment of voluntary consent to research. It is recommened that a broader review be conducted that includes grey literature and empirical studies assessing voluntariness of consent in other contexts, such as, consent to medical treatment. Broadening the review in this way will greatly improve the generalisability of the findings. Third, it is recommended that further research be conducted with the Voluntariness Assessment Instrument in order to establish whether it is a reliable and valid measure of voluntary consent to research. It is also recommended that researchers begin to focus on enhancing voluntary consent now that progress is being made in the areas of conceptualising and assessing voluntariness.

While the reliability and validity of assessment methods such as the Voluntariness Assessment Instrument are being established, researchers should focus their attention on

how to deal with participants whose consent is either perceived as less than fully voluntary or whose consent is found to be nonvoluntary and subsequently invalid. Researchers are faced with a choice of either removing participants whose consent is deemed nonvoluntary from studies or educating and empowering them to make a voluntary decision and re-consenting them. The risks and benefits of a particular study will need to be carefully considered in order for such a decision to be reached. High risk studies necessitate that participants not be enrolled unless their consent is fully voluntary. However, for some lower risk studies it may be appropriate for participants to be enrolled or continue participation when it can be demonstrated that researchers have made adequate attempts to educate and empower participants to make a voluntary decision. All potential research participants should be assisted in identifying potentially controlling influences affecting their consent decision and shown how to mitigate these influences. To this end the research agenda moving forward should focus on the development and assessment of interventions to educate and empower potential research participants to make voluntary consent decisions.

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Appendices

Appendix 1: Permission to use the DMCI

From: Miller, Victoria A [MILLERV@email.chop.edu]
Sent: 09 April 2013 07:50 PM
To: Nicole Mamotte
Subject: RE: Permission to use the DMCI
Dear Nicole,

Thank you for your interest in the DMCI, and you have my permission to use it in your study. I would appreciate being kept apprised of your research findings as they become available.

Best of luck with your project.

Victoria

Victoria A. Miller, Ph.D.
Assistant Professor of Anesthesiology and Critical Care Medicine
Perelman School of Medicine at the University of Pennsylvania
Pediatric Psychologist, The Children's Hospital of Philadelphia

The Children's Hospital of Philadelphia
CHOP North, Room 1425
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Appendix 2: Protocol Deviation

UNIVERSITY OF
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INYUVESI
YAKWAZULU-NATALI

RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

07 November 2013

Ms. N Mamotte
Department of Psychology
University of KwaZulu-Natal
Pietermaritzburg Campus

Dear Dr Mamotte

PROTOCOL: Assessing voluntariness of consent to research in a South African HIV prevention and treatment trial. REF: BE229/11

We wish to advise you that your correspondence dated 10 October 2013 informing BREC of a Protocol Deviation for the above study has been noted by a sub-committee of the Biomedical Research Ethics Committee.

At a meeting held with the PI on 31 October 2013 at the BREC Office, the following was noted:

Background

The PI, Ms N Mamotte reported a protocol deviation in the development of her instrument to assess voluntary consent. Briefly, the PI used participants from CAPRISA TRUTH study which was not authorised as per her protocol. All study participants and the PIs of this study gave permission. She informed her supervisor, Prof D Wassenaar and BREC.

Findings:

1. The PI has acknowledged the deviation and took remedial measures immediately.
2. The PI accidentally overlooked the role of BREC and her collaborators in authorizing any deviation.
3. No individual has been adversely affected.

The PI has been appropriately reprimanded on the seriousness of the deviation. BREC recommends no further disciplinary action is taken.

Yours sincerely

Prof V Rambiritch
Deputy Chair: Biomedical Research Ethics Committee

cc: Prof Jack Moodley (SAE Officer)
Prof D Wassenaar (Supervisor)

Appendix 3: Informed Consent Form

INFORMATION SHEET AND CONSENT FORM

Voluntariness Study

Hello, I am Nicole Mamotte. I am a PhD student in Psychology at the University of KwaZulu-Natal.

I am conducting research on the voluntariness of consent to research. You are being asked to volunteer to participate in this study. The purpose of this study is to find out about how you came to participate in CAPRISA 008 or 009, what influenced your participation and whether you felt the decision to participate was yours alone.

Your participation

In order to assess the voluntariness of your decision to participate in CAPRISA 008 or 009, I would like to ask you to participate in an interview. The interview will take approximately 60 minutes to complete. I would also like to ask your permission to audio record the interview.

Please understand that your participation is voluntary and you are not being forced to take part in this study. The choice of whether to participate or not, is yours alone. If you choose not to take part, you will not be affected in any way whatsoever. If you agree to participate, you may stop participating in the research at any time. If you do this there will be no penalties and you will not be prejudiced in any way. If you chose not to take part or chose to withdraw from this study, your participation in CAPRISA 008 or 009 will not be affected in any way nor will the care and treatment your receive as part of that trial.

Confidentiality

I will not be recording your name anywhere on the questionnaire. You will be assigned a participant code. If your name is mentioned during the interview and audio recorded, it will be replaced with your participant code during transcription [writing out the audio recordings]. All study data will be stored in lockable file cabinets accessible only to the study researcher

and electronic data will be stored in password protected files on the researcher's computer and destroyed after five years.

Risks/discomforts

At the present time, we do not see any risks in your participation.

Benefits

You will not benefit from participation in this study. However, this study will potentially contribute to the development of a tool that can be used by trial site staff or other stakeholders to assess the voluntariness of participants consent to research.

Compensation

You will be compensated R50 for your time for participating in this study.

Who to contact if you have been harmed or have any concerns

If you ever have any questions about your participation in this study you can contact Nicole Mamotte at mamotten@ukzn.ac.za.

This research has received ethical approval from the University of KwaZulu-Natal Biomedical Research Ethics Committee. If you have any questions or complaints about ethical aspects of the research or feel that you have been harmed in any way by participating in this study, please contact the University of KwaZulu-Natal Biomedical Research Ethics Committee:

Biomedical research ethics administration
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X54001
Durban
4000
Tel: 031 260 4769
Fax: 031 260 4609
Email: brec@ukzn.ac.za

CONSENT

I hereby agree to participate in research on the voluntariness of consent to research. I understand that I am participating freely and without being forced in any way to do so. I also understand that I can stop participating at any point should I not want to continue and that this decision will not in any way affect me negatively.

I understand that this is a research project whose purpose is not necessarily to benefit me personally.

I understand that my participation will remain confidential.

……..

Signature of participant Date:……..

I hereby agree to the audio-recording of my interview.

……..

Signature of participant Date:……..

Appendix 4: Demographic Questionnaire

Interviewer code: Participant code: Host trial: Site:

DEMOGRAPHICS

1 Gender		**7 Which best describes your total monthly income**	
Male	1	No income	1
Female	2	Less than R1000 per month	2
2 Race		R1001-R5000 per month	3
African	1	Above R5000 per month	4
White	2		
Coloured	3		
Indian	4		
Other, specify	5		
3 Age		**8 Which health services do you use**	
Under 20	1	Private health care	1
21-30	2	Government health care	2
31-40	3	I have no access to health care services	3
41-50	4	**9 When did you enroll [refuse enrolment] in this study**	
51-60	5	1 week ago	1
Over 60	6	Between 1 week - 1 month ago	2
4 Marital Status		Between 1- 3 months ago	3
Married	1	Between 3- 6 months ago	4
In a relationship	2	Between 6 – 12 months ago	5
Divorced	3	Over a year ago	6
Widowed	4	Over 2 years ago	7
Single	5	**10 How long after the consent form was discussed with you, did you make your decision to [not to] participate**	
5 Are you employed		Immediately	1
Yes	1	24 hours	2
No	2	Between 2 and 7 days	3
Other, specify	3	More than a week	4
6 Education			
Completed primary school	1		
Completed high School	2		
Completed tertiary education	3		

Appendix 5: Voluntariness Narrative Rating Instrument

Voluntary reference narrative

1. I would like you to think about a time in your life when you made a decision that you felt was totally free; in other words, a decision that you made without any pressure from anyone else, with no threats from anyone. A decision which you made freely yourself. Would you be comfortable sharing this situation with me? If yes, please briefly describe the situation in a few words.

2. Now if you think of a score to give this story, with 10 points being totally free/voluntary, and 1 point being totally unfree/forced/nonvoluntary, how free do you think you were in the situation you described in this story?

1 2 3 4 5 6 7 8 9 10

Non-voluntary Fully Voluntary

Non-voluntary reference narrative

1. Now I would like you to think about a time in your life when you made a decision but you did not feel that the choice was yours – a time when another person coerced / forced you to make a decision or to do something that you did not want to do using a threat of harm. For example, when a teacher threatened to give you detention if you did not do your homework or a parent threatened to punish you if you did not do what they asked you to do. Would you be comfortable sharing this situation with me? If yes, please briefly describe the situation in a few words.

2. Now if you think of a score to give this story, with 10 points being totally free/voluntary, and 1 point being totally unfree/forced/nonvoluntary, how free do you think you were in the situation you described in this story?

1 2 3 4 5 6 7 8 9 10

Non-voluntary Fully Voluntary

Voluntary Consent

Now I would like you to think about your decision to/not to enter the study. You are free to say whatever you like – you do not have to say that you liked the experience or not – we really do not mind if you have negative or positive views – we just want to hear your true feelings. We are not part of the staff here and your personal answer will not be told to any of the staff here. We are just interested in how free you felt about participating in this study.

1. I would now like you to think about how you came to enroll in the CAPRISA study. Please will you tell me the story of how you came to enroll. Please describe in as much detail as possible: a) how you came to be enrolled in this study, b) why you decided to participate, c) how free you felt about participating in this study, d) if any other person influenced your decision, e) or if any other factor, situation, circumstance influenced your decision. [AUDIO RECORD]
2. "Now, if you compare the three stories, you scored the first one with an X, and the second with a Y, how would you score how free/voluntary your decision to enroll in the CAPRISA study was?

1 2 3 4 5 6 7 8 9 10

Non-voluntary Fully Voluntary

Appendix 6: Decision Making Control Instrument (Miller et al., 2011)

To what extent do you agree/disagree with the following statements	**Strongly Disagree**	**Disagree**	**Somewhat Disagree**	**Somewhat Agree**	**Agree**	**Strongly Agree**
I was powerless in the face of this decision	1	2	3	4	5	6
Someone took this decision away from me	1	2	3	4	5	6
I made the decision	1	2	3	4	5	6
I was passive in the face of this decision	1	2	3	4	5	6
The decision about the protocol was inappropriately influence by others	1	2	3	4	5	6
I was not in control of this decision	1	2	3	4	5	6
Others made this decision against my wishes	1	2	3	4	5	6
I was not the one to choose	1	2	3	4	5	6
The decision was up to me	1	2	3	4	5	6

Appendix 7: Survey of Influences

I am now going to ask you a few questions about whether another PERSON influenced your decision to enroll [not enroll] in the CAPRISA study. I am interested in people who influenced your decision or who tried to influence your decision. I am also interested in people who tried to influence you to enroll and people who tried to influence you not to enroll. When I talk about influence I am talking about whether someone offered you something, threatened, pressured, manipulated or advised you. When I talk about 'your consent decision' I am talking about your decision to either enroll in the CAPRISA study or not.

24a. Did you talk to your spouse /partner about participation? 1 Yes 2 No	**24b. Did they…?** 1 Try to influence you TO participate 2 Try to influence you NOT to participate 3 Not try to influence you at all	**24c. How did they try to influence you?** 1 They offered to give you something 2 They threatened to harm you 3They pressured you 4 They advised you 5 Other

To what extent do you agree or disagree with the following statements regarding the aforementioned influence					
	Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly Disagree**
24d This person was purposefully trying to get me to/not to participate in this research when they influenced me	1	2	3	4	5
24e This person had the right to influence my consent decision in the way they did	1	2	3	4	5
24f My rights (to make a free independent decision about participation) were violated when this person influenced me like they did	1	2	3	4	5
24g This influence caused me to make the consent decision I did	1	2	3	4	5

25 a. Did you talk to a family member about participation ? 1 Yes 2 No	25b. Did they… ? 1 Try to influence you TO participate 2 Try to influence you NOT to participate 3 Not try to influence you at all	25c. How did they try to influence you? 1 They offered to give you something 2 They threatened to harm you 3They pressured you 4 They advised you 5 Other	To what extent do you agree or disagree with the following statements regarding the aforementioned influence				
				Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly Disagree**
			25d This person was purposefully trying to get me to/not to participate in this research when they influenced me	1	2	3	4	5
			25e This person had the right to influence my consent decision in the way they did	1	2	3	4	5
			25f My rights (to make a free independent decision about participation) were violated when this person influenced me like they did	1	2	3	4	5
			25g This influence caused me to make the consent decision I did	1	2	3	4	5
26a Did you talk to a friend participation ? 1 Yes 2 No	**26b. Did they… ?** 1 Try to influence you TO participate 2 Try to influence you NOT to participate 3 Not try to influence you at all	**26c. How did they try to influence you?** 1 They offered to give you something 2 They threatened to harm you 3They pressured you 4 They advised you 5 Other	To what extent do you agree or disagree with the following statements regarding the aforementioned influence				
				Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly Disagree**
			26d This person was purposefully trying to get me to/not to participate in this research when they influenced me	1	2	3	4	5
			26e This person had the right to influence my consent decision in the way they did	1	2	3	4	5
			26f My rights (to make a free independent decision about participation) were violated	1	2	3	4	5

			when this person influenced me like they did					
			26g This influence caused me to make the consent decision I did	1	2	3	4	5
27a Did you talk to a health care provider (not part of CAPRISA) For example, nurse or doctor at a government clinic about participation ? 1 Yes 2 No	**27b. Did they… ?** 1 Try to influence you TO participate 2 Try to influence you NOT to participate 3 Not try to influence you at all	**27c. How did they try to influence you?** 1 They offered to give you something 2 They threatened to harm you 3They pressured you 4 They advised you 5 Other	**To what extent do you agree or disagree with the following statements regarding the aforementioned influence**					
				Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly Disagree**
			27d This person was purposefully trying to get me to/not to participate in this research when they influenced me	1	2	3	4	5
			27e This person had the right to influence my consent decision in the way they did	1	2	3	4	5
			27f My rights (to make a free independent decision about participation) were violated when this person influenced me like they did	1	2	3	4	5
			27g This influence caused me to make the consent decision I did	1	2	3	4	5
28a Did you talk to the CAPRISA research staff about participation ? 1 Yes	**28b. Did they… ?** 1 Try to influence you TO participate 2 Try to influence you NOT to participate	**28c. How did they try to influence you?** 1 They offered to give you something 2 They threatened to harm you	**To what extent do you agree or disagree with the following statements regarding the aforementioned influence**					
				Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly Disagree**
			28d This person was purposefully trying to get me to/not to participate in this research when they influenced me	1	2	3	4	5

2 No	3 Not try to influence you at all	3They pressured you 4 They advised you 5 Other	28e This person had the right to influence my consent decision in the way they did	1	2	3	4	5
			28f My rights (to make a free independent decision about participation) were violated when this person influenced me like they did	1	2	3	4	5
			28g This influence caused me to make the consent decision I did	1	2	3	4	5
29a Did you talk to your employer about participation ? 1 Yes 2 No	**29b. Did they… ?** 1 Try to influence you TO participate 2 Try to influence you NOT to participate 3 Not try to influence you at all	**29c. How did they try to influence you?** 1 They offered to give you something 2 They threatened to harm you 3They pressured you 4 They advised you 5 Other	**To what extent do you agree or disagree with the following statements regarding the aforementioned influence**					
				Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly Disagree**
			29d This person was purposefully trying to get me to/not to participate in this research when they influenced me	1	2	3	4	5
			29e This person had the right to influence my consent decision in the way they did	1	2	3	4	5
			29f My rights (to make a free independent decision about participation) were violated when this person influenced me like they did	1	2	3	4	5
			29g This influence caused me to make the consent decision I did	1	2	3	4	5
30a Did you talk to your community leader about	**30b. Did they… ?**	**30c. How did they try to influence you?**	**To what extent do you agree or disagree with the following statements regarding the aforementioned influence**					
				Strongly Agree	**Agree**	**Neither agree nor disagree**	**Disagree**	**Strongly Disagree**

participation ? 1 Yes 2 No	1 Try to influence you TO participate 2 Try to influence you NOT to participate 3 Not try to influence you at all	1 They offered to give you something 2 They threatened to harm you 3They pressured you 4 They advised you 5 Other	30d This person was purposefully trying to get me to/not to participate in this research when they influenced me	1	2	3	4	5
			30e This person had the right to influence my consent decision in the way they did	1	2	3	4	5
			30f My rights (to make a free independent decision about participation) were violated when this person influenced me like they did	1	2	3	4	5
			30g This influence caused me to make the consent decision I did	1	2	3	4	5

I am now going to ask you a few questions about whether anything other than another person influenced you to participate in the CAPRISA study

What influenced you to enroll				**How much did this influence cause you to participate**			**Would you have participated if this influence had not been present**	
	Agree	Disagree	If agree, please explain	A little	A lot	It is the only reason I participated	Yes	No
30 I participated because of health reasons/illness	1	2		1	2	3	1	2
31 I participated because I need health care/ treatment	1	2		1	2	3	1	2
32 I participated because I need the money	1	2		1	2	3	1	2
33 I participated because I have to please the researchers	1	2		1	2	3	1	2
34 I participated because I have to please my partner	1	2		1	2	3	1	2
35 I participated because I have to please someone else, specify	1	2		1	2	3	1	2
36 I participated because I trust the researchers	1	2		1	2	3	1	2
37 I participated because I had no other choice	1	2		1	2	3	1	2
38 I participated because I wanted to	1	2		1	2	3	1	2

Appendix 8: Ethics Approval

UNIVERSITY OF
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Biomedical Research Ethics Administration
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28 March 2012

Ms. N Mamotte
Department of Psychology
University of KwaZulu- Natal
Pietermaritzburg Campus

PROTOCOL: Assessing voluntariness of consent to research in a South African HIV prevention and treatment trial. REF:BE229/11

Dear Dr Mamotte

Further to our letter to you dated 13 January 2012, this letter serves to notify you that a sub-committee of the Biomedical Research Ethics Committee provisionally approved the study pending appropriate responses to queries raised. Your responses dated 13 March 2012 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval and may begin as from 29 March 2012.

The following related study document has been reviewed and approved:

- HPCSA registration number PS0108375 for Research Psychologist
- Letter of permission from CAPRISA
- Postgraduate Committee decision
- CV of Supervisors

This approval is valid for one year from **29 March 2012.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC

Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/ResearchEthics11415.aspx.
BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

PROFESSOR V RAMBIRITCH
Vice-Chair: Biomedical Research Ethics Committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

05 February 2013

Ms. N Mamotte
Department of Psychology
University of KwaZulu-Natal
Pietermaritzburg Campus

PROTOCOL: Assessing voluntariness of consent to research in a South African HIV prevention and treatment trial. REF: BE229/11

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 11 January 2013 for the second phase of the above study which was approved by BREC on 28 March 2012.

The conditions have been met and the **second phase of the study** is given full ethics approval and may begin as from 05 February 2013.

This approval is valid for one year from **05 February 2013.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **12 March 2013.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

PROFESSOR V RAMBIRITCH
Vice-Chair: Biomedical Research Ethics Committee

Professor D Wassenaar (Chair)
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