ASSESSING PARTICIPANTS' UNDERSTANDING AND VOLUNTARINESS OF INFORMED CONSENT IN A CLINICAL TRIAL IN NIGERIA

by

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STATEMENT OF ORIGINAL AUTHORSHIP

"I, Dr. **ADEWALE Babatunde,**declare that the thesis titled: "**ASSESSING PARTICIPANTS' UNDERSTANDING AND VOLUNTARINESS OF INFORMED CONSENT IN A CLINICAL TRIAL IN NIGERIA**", which I hereby submit for the degree of Master of Social Science at the School of Psychology, Faculty of Humanities, Development and Social Science,University of KwaZulu Natal, is my original work and has not previously been submitted by me for a degree at another university".

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DEDICATION

To GOD, the custodian and fountain of knowledge and to my family for their unwavering support and steadfastness during my sojourn in South Africa.

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TO GOD BE THE GLORY.

ABSTRACT (with keywords)

Introduction: Citizens of developing countries are often in vulnerable situations because of illiteracy, unfamiliarity with medical interventions, effects of war resulting in famine, and extreme poverty. The health-related conditions that arise out of these situations however make research in these populations vital and increasing funding for research on diseases that affect the world's poor is making such research possible. The resulting tension between the need for research and the possibility of exploitation of participants' vulnerability, mandates the development of reliable ways of ensuring that participants' consent is voluntary, adequately informed and well understood. The Nuremberg Code emphasises the requirement of voluntariness in informed consent by insisting that participants should be able to exercise freedom of choice without the intervention of any element of force, fraud, deceit, duress, or other forms of constraint or coercion.

Aim: This study assessed research participants' understanding and voluntariness of informed consent in a clinical trial.

Methods: The study design was a cross-sectional analysis of the informed consent process. It consisted of qualitative and quantitative components. It was a cross-sectional survey of 75 research participants in a malaria clinical trial using questionnaires in the from of forced-choice checklistsand patient self-report to assess voluntariness and understanding of informed consent. Data were analysed using SPSS V 17.

Results: All the respondents involved in the clinical trial gave consent before they were recruited. The reasons for consenting to participate in the clinical trial ranged from the opportunity to get treatment (28%), opportunity for diagnosis of ailments (32%), to prevent illness (36%) and to receive information about medical care (4%). The major benefits participants attributed to taking part in the research were the opportunity to obtain treatment (59%), diagnostic tests (35%) and education (6%).Among the research participants, 10.7% believed that they should be paid for participation and about 8% felt that payment could influence their decision to participate because it could act as a motivation. They could however not proffer an amount that they would consider significant enough to influence their decision. There was no significant association

between factors that influenced participation and age (p=0.533), sex (p=0.342), education (p=0.078), religion (p=0.144) and marital status (p=0.239). Almost all (98.7%) participants claimed that they had understood the information given to them during the consent procedure and they all gave consent without consulting anybody apart from the medical personnel.The majority of respondents - 74 (98.7%) - stated that they were not allowed to go home with the informed consent document, while 1(1.3%) of the respondents said there was no need to go home with the informed consent document. In the assessment of understanding using the forced-choice checklist, however, only 37% understood issues concerning randomization of participants and only 28.8% understood issues about compensation for research related injury.

Discussion and Conclusion: In this study, the voluntariness of participants was influenced by factors related to the benefits accrued through participation. The need for participants to make free and informed choices based on adequate information given by the investigator cannot but be emphasized as a right and not a privilege. In light of the limited understanding about randomization and injury compensation identified in this study, there is a need for additional protection of vulnerable populations. This could be in the form of allowing adequate time to enable the improvement of participants' understanding of the consent form, using innovative ways of explaining complex concepts such as randomization, and providing the necessary support to facilitate participants' right to self-decision, except when they are incapable of consenting.

Key words: Understanding, Voluntariness, Informed Consent, Clinical trial.

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CHAPTER ONE

INTRODUCTION

Respect for the autonomous choice of a person is a basic principle of morality and is based on the fundamental ethical principle of respect for persons and respect for human dignity (Lindegger & Bull, 2002). Personal autonomy encompasses, at minimum, self-rule that is free from both controlling interference by others and from certain limitations such as inadequate understanding that prevents meaningful choice. Therefore, a major trait of an autonomous person is the capacity for self-governance, which involves understanding, reasoning, deliberating, managing and choosing independently. Health professionals should always inquire in general terms about their patients' wishes to receive information and to make decisions, and they should never assume that because a patient belongs to a particular community or culture, he or she affirms that community's worldview and values. The fundamental requirement is to respect a particular person's autonomous choices, whatever they may be, though other principles such as beneficence, non-maleficence and justice should also be taken into consideration. Respect for autonomy is not a mere ideal in health care, it is a professional obligation. Autonomous choice is a right, not a duty, of patients (Beauchamp & Childress, 2009).

Respect for autonomy involves acknowledging the value and decision-making rights of an autonomous person. Therefore, an autonomous person acts intentionally with understanding and without controlling influences that determine their actions.

Since the Nuremberg trials, biomedical ethics has placed informed consent at the forefront of its concerns. The focus of this concern has shifted from the physician's or researcher's obligation to disclose information to the quality of a participant's understanding and consent. The forces behind this shift of emphasis were autonomy driven (Beauchamp & Childress, 2009).

The need for participants to consent to take part in medical research is recognised in international human rights instruments (Office of the United Nations High Commissioner for Human Rights [OHCHR], 1976),and documented in both international guidance on research ethics (National Commission for the Protection of Human Subjects of Biomedical and

Behavioural Research [NCPHSBBR], 1998) and in the national forms of guidance and/or regulations in many countries (World Medical Association [WMA], 1996).

Informed consent is universally recognised as a central component of ethical conduct of research and derives from a legal doctrine that calls for potential research subjects to have meaningful choice. It serves a function to allow subjects to make an informed and voluntary choice to participate or refuse to participate in a project where they will be asked to take risks for the benefits of others (Cahana & Hurst, 2008; Emanuel, Wendler & Grady, 2000). The provision of information, comprehension of information and voluntary participation are foundational in the consent discussion (Marshall, 2006). According to Appelbaum, Lidz and Klitzman (2009), it comprises three elements: relevant information, competence to make a decision, and a person who is situated to do so voluntarily. Existing literature on informed consent has focused extensively on the information disclosed and how well it is communicated and, more recently, on the theoretical and practical aspects of the assessment of decisional competence. The nature of the requirement of voluntariness is however still inadequately explored (Appelbaum et al., 2009; Dunn & Jeste, 2001). This study therefore assessed the understanding and voluntariness of informed consent in a cross-sectional survey of research participants in a malaria clinical trial using questionnaires and a forced-choice checklist.

1.1 Justification for the Study

Voluntary decision-making is a challenge in research settings in developing countries. Medical doctors and researchers occupy positions of authority and patients are often unwilling or unable to challenge or question their opinion. Physicians have credibility and great influence over patients because of their belief that a doctor will always “do good” for his/her patient. Furthermore, participants are often illiterate, uneducated or gullible and often do not question terms of participation. The distinction between care and research might also not be clearly delineated when the physician is also the researcher (Falusi, 2007).

Though voluntary informed consent is universally accepted as a precondition for scientific research involving human beings, citizens of developing countries are often in vulnerable situations because of their lack of political power, lack of education, unfamiliarity with medical interventions, effects of war, pandemics, famine, extreme poverty or dire need for

health care and nutrition (Barsdorf & Wassenaar, 2005; Minnies, Hawkridge, Hanekom, Ehrlich, London & Hussey, 2008). It is the dire need of these populations that makes them both appropriate participants of research and especially vulnerable to exploitation (Glantz, Annas, Grodin & Mariner, 2001).

The Nuremberg Code brought informed consent to the forefront of ethical practice in research. Volunteers competent to consent should be provided with accurate information, understand the information, and then make a voluntary decision about participation (Emanuel, Wendler, Killen & Grady, 2004). In the view of Barsdorf and Wassenaar (2005), information disclosure and understanding have been heavily researched with insufficient empirical attention to voluntariness. There is therefore a need not only to look at perceptions of understanding, but to go beyond that to perceptions of voluntariness among the patients enrolled in clinical trials in developing countries.

International organisations such as the Bill and Melinda Gates Foundation, United States National Institutes of Health, the Wellcome Trust, EDCTP and others are increasing funding for research on diseases that affect the world's poor. The goal is to develop superior diagnostic tools, prevention strategies and interventions to counter the debilitating impact of these diseases. Successful completion of this research and adoption of the resulting technologies will depend on successful engagement with the intended beneficiaries (Tindana, 2007) whose informed consent is a prerequisite for their involvement in such research activities.

For these reasons, this research project investigated the voluntariness and understanding of informed consent among participants in a clinical trial with the aim of achieving the following objectives:

1.2 General objective:

To assess the understanding and voluntariness of informed consent given by research participants in a clinical trial in Nigeria.

1.3 Specific Objectives:

1. To assess research participants' level of understanding of the informed consent document.

2. To assess the process of obtaining informed consent of participants in a clinical trial and suggest ways of improving the process.
3. To assess the voluntariness of participants who participate in a clinical trial.

CHAPTER TWO

LITERATURE REVIEW

According to Murray (1990), it was the belief in ancient Greece that patients' participation in decision-making for medical treatment was undesirable. It was generally accepted that the physician's primary task was to inspire the confidence of the patient in the treatment and that any disclosure of possible difficulties might erode the patient's trust. Later, during medieval times, medical writing encouraged doctors to use their conversations with patients as an opportunity to offer comfort and hope while emphasising the need for the doctor to be manipulative and deceitful. To effect a treatment cure, it was widely felt that authority must be coupled with obedience (Southwich, 1988).

The doctrine of assault and battery has its roots in English common law in the early nineteenth century. This doctrine forms the basis for the possibility of demonstrating "injury" or assigning "liability" incurred from surgery without proper consent (Murray, 1990). Common law is the combination of customs, traditions, and case law; it is distinct from legislative law which is law enacted by a governing body. Many of these English common law doctrines have influenced our tort system of justice. Assault is a threat by one person to do bodily harm to another while battery is the actual touching of a person by another. Therefore, the theory of tort battery became the unauthorised touching of a person by another (Murray, 1990).

As the concept of informed consent gained popularity during the twentieth century, the courts extended the English common law tort doctrine of negligence to the field of surgery by equating negligence with breach of duty and breach of duty with incomplete patient consent. Currently, the failure of a physician to provide adequate information to the patient about his/her own treatment is interpreted by the courts as a breach of duty by the physician (Southwich, 1988; Murray, 1990).

According to Faden, Beauchamp, and King (1986), the US President's Commission for the study of ethical problems in medicine and biomedical and behavioural research argued that although informed consent has emerged primarily from a history in law, its requirements are essentially moral and policy oriented. This is ultimately based on the principle that competent persons are entitled to make their own decisions from their own values and goals, but that the

context of informed consent and any claim of "valid consent" must derive from active, shared decision-making. The principle of self-determination was described as the "bedrock" of the commission's viewpoint. According to Frimpong-Mansoh (2008), this shows us that the process of informed consent has undergone widespread changes under the influence of culture and moral requirements of informed consent, and that informed consent is an evolving process.

The ethical requirement of obtaining informed consent of research participants is based on the moral requirement of respect for persons, which is rooted in the principle of autonomy. To respect an autonomous agent is to recognise with due appreciation that person's capacities and perspective, including his or her right to hold certain views, to make certain choices, and to take certain actions based on personal values and beliefs (Faden, Beauchamp & King, 1986). This obligates professionals in health care and research involving human research participants to disclose information, probe for and ensure understanding and voluntariness and to foster adequate decision-making (Beauchamp & Childress, 2001). Autonomy can be influenced by factors such as threats of physical harm, promises of love and affection, economic incentives, reasoned argument, lies, and appeals to emotional weaknesses.

These problems could be overcome by informed consent through the concept of voluntariness which is sometimes treated as synonymous with autonomy. Informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation (Council for International Organizations of Medical Sciences[CIOMS], 2002).

The role and importance of voluntariness for informed consent is emphatic and unconditional in the Nuremberg Code (Faden et al., 1986). The horrifying accounts of medical experimentation in concentration camps that were exposed during the Nuremberg trials brought to the forefront the issue of consent in biomedical ethics. The term informed consent, however, did not receive detailed examination till the early 1970s and did not appear in ethical documents until a decade after these trials.

The gross violations investigated at Nuremberg were gradually perceived by the medical community as a general threat to the reputation and integrity of biomedical research. Partially in response to this perceived threat, the World Medical Association (WMA) began in the early 1960s to draft a more suitable code to distinguish ethical from unethical clinical research. A draft of the WMA's code was produced in 1961, but the code was not adopted until a meeting at Helsinki in 1964, and hence became known as the Declaration of Helsinki (World Medical Association [WMA], 1996). Like the Nuremberg Code, the Declaration of Helsinki made consent a central requirement of ethical research (Faden et al., 1986). After the Tuskegee syphillis study was made public in the 1970s, a national commission was established in the USA to develop principles and guidelines for the protection of research subjects. The new system of protection was described in the Belmont Report (NCPHSBBR, 1998). Although largely compatible with the World Medical Association's Declaration of Helsinki, the Belmont Report articulated three principles: respect for persons (the recognition of the right of persons to exercise autonomy), beneficence (the minimisation of risk incurred by research and the maximisation of benefits to them and to others), and justice (the principle that therapeutic investigations should not unduly involve persons from groups unlikely to benefit from subsequent application of research) (Varmus & Satcher, 1997).

Ideally, informed consent describes an interactive process in which an individual or his or her parent or surrogate voluntarily agrees to join a study after the purpose, risks, benefits and alternatives have been thoroughly described and understood (Faden et al., 1986; Levine, 1988; Veatch, 1987). This postulates that a person gives informed consent to an intervention if and only if the person receives thorough disclosure about the procedure, comprehends the disclosed information, acts voluntarily, is competent to act, and consents (Faden et al., 1986). Similarly, a person who intentionally refuses to authorise an intervention but otherwise satisfies these conditions, gives an informed refusal. This principle derives from the philosophical premise that informed consent is fundamentally a matter of protecting and enabling the autonomous or self-determining choice of patients and participants and that the final authority for making decisions about medical treatment or research participation properly rests with patients and participants, not with physicians or research scientists (Faden et al., 1986). According to Fadenetal. (1986) the definition of informed consent as stated above is attractive because of its consistency and standard usage in medicine and law. The informed consent process forms the medium through which the research participant isinformed about the procedures, inherent benefits, procedural risks and therapeutic options

involved in research. Therefore, according to Oduro et al. (2008) any conduct of research that promotes a climate consistent with high ethical standards should contain an informed consent process. The following are the key elements of informed consent (Meisel & Roth, 1981; National Cancer Institute [NCI], 2001): (1) competence, (2) disclosure, (3) understanding, (4) voluntariness, and (5) consent.

2.1. **Elements of Informed Consent**

2.1.1. **Competence**: This is a criterion of an autonomous person and primarily serves a gatekeeper function by identifying persons from whom it is appropriate to obtain informed consent. If a person is autonomous and situated in a context in which consent is appropriate, it is a *prima facie* moral principle (derived from the basic principle of respect for autonomy) that informed consent should be sought from the person. By contrast, if a person is non-autonomous and situated in a context in which consent is required, it is a *prima facie* moral principle (not derived from the principle of respect for autonomy, but rather from beneficence) that some mechanism for the authorisation of procedures or decisions other than obtaining the person's consent should be instituted. Thus, gate keeping is accomplished through allowing autonomous persons – competent persons – to give informed consent and not allowing non-autonomous persons –incompetent persons – to give informed consent and is based on an appeal to the moral principle that autonomous persons are rightfully their own decision-makers (Faden et al., 1986).

2.1.2. **Disclosure**: This is the delivery of information to either a patient or a participant and forms the basis for the patient's or participant's decision. The professionals are generally obligated to disclose a core set of information, including (1) those facts or descriptions that patients or participants usually consider material in deciding whether to refuse or consent to the proposed intervention or research, (2) information the professional believes to be material, (3) the professional's recommendation, (4) the purpose of seeking consent, and (5) the nature and limits of consent as an act of authorisation (Wendler & Grady, 2008). If research is involved, disclosure should generally cover the aims and methods of the research, anticipated benefits and risks, any anticipated inconvenience or discomfort, and the subjects' right to withdraw, without penalty, from the research (Beauchamp & Childress, 2001).

In recent years, the focus has shifted from the physician's or researcher's obligation to disclose information, to the quality of a patient's or research participant's understanding and consent (Beauchamp & Childress, 2001).

2.1.3. **Understanding**: Clinical experience and empirical data have indicated that patients and participants exhibit wide variation in their understanding of information about diagnosis, procedures, risks, and prognoses (Agrawal, 2003) and understanding could be limited by illness, irrationality and immaturity (Beauchamp & Childress, 2001). There is no consensus about the nature of understanding but it is generally accepted that persons are perceived to understand if they have acquired pertinent information and have justified, relevant beliefs about the nature and consequences of their actions. Some facts are irrelevant or trivial while others are vital and perhaps decisive and, in some cases, a person's lack of awareness of even a single risk or missing fact can deprive him or her of adequate understanding. A grasp of the central facts is however generally sufficient and for that purpose, the following information is typically essential: diagnoses, prognoses, the nature and purpose of the intervention, alternatives, risks and benefits, and recommendations.

According to Katz (1984), the primary goal of informed consent in medical care and in research is to enable potential participants and patients to make autonomous decisions about whether to grant or refuse authorisation for medical and research interventions. Faden et al. (1986) argue that informed consent represents permission to enter a person's private sphere, especially when a physical intervention is involved in both research and clinical care. Cahana and Hurst (2008) similarly argue that informed consent is crucial both in research participation and clinical care, since, even though the two types of situations are not identical, all medical interventions can be invasive in the sense that they require a breach of the patient's or participant's private sphere (physically or mentally). This intrusion into patients' and participants' private sphere cannot be justified without their actual or presumed consent despite the potential benefits that may accrue to patients (Cahana & Hurst, 2008).

The role of healthcare providers in clinical care is often known and expected by patients, and usually aligned with their interest. Research is however often an

unknown concept. The expectation that healthcare providers will put the interests of individual patients first, however, is so strong that it can lead to misunderstandings at the time of enrollment and during the conduct of research. Participants may not understand that the defining purpose of clinical research is to produce generalisable knowledge (Henderson et al., 2007) and may mistakenly believe that their interests are the sole basis for clinical decisions within the research protocol. This is called the "therapeutic misconception" which exists when individuals do not understand that the defining purpose of clinical research is to produce generalisable knowledge, regardless of whether the participants enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial (Cahana & Hurst, 2008; Marshall, 2006; Wendler & Grady, 2008).

2.1.4. **Voluntariness**: Some studies, particularly in the developing world, have demonstrated short-comings in the quality of consent in research (Joffe et al., 2001; Lynoe et al., 1991; Yuval et al., 2000), particularly where voluntary participation, one of the fundamentals of a morally valid informed consent process, has at times been relegated to the background(Lynoe, Chowdhury & Ekstrom, 2002; Upvall & Hashwani, 2001). The Nuremberg Code is emphatic on the requirement of voluntariness in informed consent and insists that the participant should be so situated as to be able to exercise free choice, without the intervention of any element of force, fraud, deceit, duress, or other ulterior forms of constraint or coercion (Appelbaum, Lidz & Klitzman, 2009).

Voluntariness has been variously defined by different authors. According to Stanley and Guido (1996), it implies that the research participant should be free from coercive influences and undue pressure in reaching a decision about whether or not to participate in research. Beauchamp and Childress (2001) assert that "a person acts voluntarily to the degree that he or she wills the action without being under the control of another's influence". Others agree that it is "a choice or action that is free from coercion and undue influence from other people" (Agrawal, 2003; Nelson & Merz, 2002). In a study of the perception of voluntariness in research by Barsdorf and Wassenaar (2005), voluntariness was defined as the situation specific experience of willed action with freedom from coercion or control by others in decision-making.

According to a recent landmark review by Appelbaum et al.(2009), voluntariness to informed consent can be potentially impaired or compromised in the following situations: when substantial monetary or other compensation is offered in exchange for entering a research study (Kuczewski & Marshall, 2002); participants are recruited by their own physicians or in facilities where they receive care especially if they are poor, elderly or suffering from chronic conditions (Ibid, 2000); participants are recruited in their communities through the community leaders (Marshall, 2006); drug abusers are recruited for studies that involve the administration of their drug of choice or paid for participation and thought likely to use the money to purchase drugs (Charland, 2002); involuntarily committed psychiatric or substance-abuse patients are recruited for research (Appelbaum, 1995); and patients who otherwise lack access to medical care are invited to participate in studies that promise treatment for their conditions (de Zoysa, Elias & Bentley, 1998).

Financial incentives and their impact on voluntariness (Kuczewski & Marshall, 2002) have been examined by several research groups (Appelbaum et al., 2009). A study of pharmacy students found that levels of both monetary incentives and risk influenced decisions about hypothetical enrollment in a study. When higher incentives were at stake, respondents indicated less willingness to tell investigators about restricted activities that might result in their exclusion from the protocol (Bentley & Thacker, 2004).

Barsdorf and Wassenaar (2005), in a study on racial differences in public perceptions of voluntariness of medical research participants in South Africa, noted racial differences in perceptions of voluntariness, which were found to be independent of level of education, knowledge of medical research procedures, and close or personal experience of medical research. The study showed that Black participants, known to have suffered most from the injustices of the apartheid regime, had poorer perception of voluntariness in research participation than their White and Indian counterparts.

2.1.5. **Consent**: This refers to an individual's actual choices and not a presumption about the choices the individual would or should make. It is expressed in verbal, non-verbal or written form and it is clearly and unmistakably stated (Beauchamp &Childress, 2001).

According to Beauchamp and Childress (2001) the following seven elements express the analytical components of informed consent more adequately than the above five elements:

I. Threshold elements (preconditions)
   1. Competence (to understand and decide)
   2. Voluntariness (in deciding)

II. Information elements
   3. Disclosure (of material information)
   4. Recommendation (of a plan)
   5. Understanding (of terms 3 and 4)

III. Consent elements
   6. Decision (in favour of a plan)
   7. Authorisation (of the chosen plan)

It is debatable whether the two elements of recommendation and authorisation add any value to the informed consent process.

The two most vexing elements of informed consent seem to be voluntariness and understanding. According to Cahana and Hurst (2008), voluntariness is perhaps the most difficult aspect of informed consent to study, as it requires greater conceptual clarity. Voluntary participation depends, in part, upon an accurate understanding not only of the purpose of the study, but also of the possibility to withdraw from a study (Marshall, 2006). In a study conducted by Karim et al. (1998) on peri-natal HIV transmission among a largely black population in South Africa, participants reported high levels of knowledge about HIV transmission. Most of the women interviewed however said they felt compelled to participate in the project and most believed that researchers would not allow them to quit the study. Research participants should be aware that they can withdraw from the study and continue to receive the best possible treatment (Bergler et al., 1980).

Ideally, the signing of a consent document begins a process of deliberation between the research team and the participants, which enables them to decide whether to continue in the research study or not. The process is expected to ensure that participants have the opportunity to ask questions and raise concerns before, during, and even after the study and to be updated

if any new information emerges. The process is therefore continuous and interactive rather than a once-off information session (CIOMS, 2002; NCI, 2001). The challenge here is whether the participants truly comprehend the basic information provided regarding the research they are asked to take part in.

Studies have shown that the comprehension of risks and benefits in both research and clinical settings is generally poor (Yuval et al., 2000; Bergler et al., 1980). The choice faced by patients or participants is dependent on the information received and the risks and benefits of the clinical intervention or research protocol are part of the important elements that the patients or participants should understand. A potential participant must understand that he or she is being asked to participate in research (Wendler & Grady, 2008) and that this does not form part of routine clinical care. Participants furthermore tend to misunderstand certain aspects specific to research such as randomisation (Harrison, Eshleman & Ngugi, 1995; Hietanen, Aro, Holi & Absetz, 2000; Howard & DeMets, 1981) or the double-blind study design (Howard & DeMets, 1981).

A number of researchers (Dickert & Sugarman, 2005; Wang, Erickson, Li & Berry, 2004) have noted that the comprehension of informed consent is enhanced when researchers provide the study community or individuals with information prior to obtaining consent and when communities are engaged in discussions about the research through meetings with local leaders or in public forums.

In 1966, Henri Beecher published a landmark article in *The New England Journal of Medicine* on ethics and clinical research. He reviewed numerous examples of insufficient disclosure of information, such as one case concerning the suboptimal treatment of streptococcus pharyngitis during which over 500 men were denied effective penicillin treatment, and another of the injection of cancer cells into chronically ill patients who were simply told of the injection of cells without any mention of cancerous cells (Beecher, 1966). It was found that the participants were not informed, did not consent and were not aware that they had been involved in an experiment. According to Cahana and Hurst (2008), there has been some progress since then and according to assessment of consent forms used in the recruitment of phase I oncology trials by cancer centresin 1999, 99% of researchers mentioned that the trial was research, 92% stated the study purpose as safety testing, 99% mentioned the right to withdraw, 67% mentioned death as a risk, 84% stated that there were

unknown risks involved and only 5% mentioned cure as a possible benefit (Horng, Emanuel, Wilfond, Rackoff, Martz & Grady, 2002).

Conversely however, according to Cahana and Hurst (2008), to give more information to patients and research subjects is sometimes perceived as a potential hazard to them, and this raises concerns about increased anxiety or decreased consent to clinical interventions by patients or accrual in research. In a study conducted by Adams et al. (2005) with Tibetans as part of a feasibility study for a future trial involving pregnant women, it was noted that disclosure of risks was viewed as problematic because of individuals' concerns about openly discussing potential hazards.

Despite this, obtaining informed consent of participants and patients in research or clinical intervention is paramount before enrollment of subjects. Consent is thus not a luxury; it is an ethical prerequisite to entering research. Without a valid and reliable methodology for ensuring that participant's consent is voluntary, informed and that they have understood the information provided, it is impossible to obtain truly informed consent. Therefore, all research participants and patients should be allowed to either give informed consent or refuse their consent (informed refusal) should they wish to do so. This is the prerogative of all participants and patients.

CHAPTER THREE

METHODOLOGY

3.1. Study Design

The study design was a cross-sectional descriptive analysis of the informed consent process. It consisted of quantitative components. The assessment of understanding was done using the method of Lindegger, Milford, Slack, Quayle, Xabaand Vardas (2006) which involves a combination of a questionnaire in the form of a forced-choice checklist and self-report methods. Voluntariness was assessed using a questionnaire adapted from Barsdorf and Wassenaar (2005), which was demonstrated to have excellent internal reliability. It is believed that this questionnaire, which obtained an acceptable reliability score, (Barsdorf & Wassenaar, 2005) would adequately measure the level of voluntariness of the participants.

As recommended by Barsdorf and Wassenaar (2005), minor alterations were made to the questionnaire in the framing of questions on how the informed consent procedure was carried out and also to suit the socio-cultural values of the people in order to improve the understanding of the questions by the respondents as well as the validity of the questionnaire, taking into account the various threats to voluntariness such as misunderstanding, coercion and unfair selection as stated by Faden et al. (1986) as well as by Pace and Emanuel (2005).

3.2. Inclusion Criteria

Adults older than 18were approached to participate in this study. They all had to be residing in the Ijede community, consented to participation in an anti-malaria trial (either on behalf of themselves or on behalf of a child not older than 5 years) within the last 6–12 months and had to be willing and able to give informed consent for participation in the study.

3.3. Methodology

The study was carried out in a rural community called Ijede, in Ikorodu Local Government Area of Nigeria where there was an ongoing hospital-based anti-malaria clinical trial. The Principal Investigator of the trial and the hospital administrator were approached for permission to interview a sample of the participants involved in the trial.

Voluntariness was assessed by means of a semi-structured questionnaire which was adapted from Barsdorf and Wassenaar (2005). The questionnaire comprised four sections and a total of 43 questions. The questionnaire was translated into the local language using the double-back translation method.

Understanding was assessed in two ways. Participants first completed a questionnaire which consisted of a forced-choice checklist consisting of true and false options to statements. There were three statements for each component. Participants were then requested to complete a self-report that was based on seven components identified by Lindegger et al. (2006). The components were: trial aims, eligibility to participate, risk of participating in the trial, risk of falsely believing the test product would protect one from infection and thus increase one's risk behaviour ("false sense of security"), methodologic considerations – such as randomisation, placebo and blinding, compensation for research-related injury, and the right to withdraw. Participants were required to estimate their level of personal understanding of each of these components.

The process of obtaining informed consent was assessed through questions in section 4 of the questionnaire (Appendix 1).

3.4. Sample Size

This was a cross-sectional study with a power of 80% and level of significance of 95%. There were 360 participants in the anti-malaria trial. Assuming a prevalence of involuntariness and misunderstanding of 50% (Barsdorf & Wassenaar, 2005; Bhansali et al., 2009), a sample size of 75 was calculated. This sample size lies between the two sample sizes used in the studies of Barsdorf and Wassenaar (2005) and Bhansali et al. (2009) mentioned above.

3.5. Data Analysis

Completed questionnaires were pre-cleaned, coded and analysed using SPSS for windows (SPSS inc., 1999). Basic descriptive analysis (such as means, proportions, frequencies, range, correlation and chi-squares) and limited analysis of the possible association between the predictor variables and the outcome variables (involuntariness and inadequate understanding) were done using a chi-square test. A p-value of 0.05 was taken as significant. Age was the only variable that was categorized (refer questionnaire in Appendix 1).

3.6. Ethical Considerations and Approval

The participants were informed about the possible benefits and risks involved in participating in the study. They were further assured of the confidentiality of the information given, and also of their right to decline to participate or withdraw at any time without penalty. After it was confirmed that they understood all the information, and that they were willing to participate in this study, participants signed the informed consent document to signify their willingness to participate in the study. Confidentiality was assured by not using any personal identifiers in the collection, analysis or reporting of the data. The proposal was approved by ethics committees of the University of KwaZulu-Natal (Approval Number: HSS/0247/2010 M; Appendix 4) and the Nigerian Institute of Medical Research (Appendix 5). Approval was obtained before the commencement of the project.

Permission to contact and interview the anti-malaria trial participants was obtained from the principal investigator of the clinical trial and the relevant hospital authority. The researchers and administrators were fully informed of the purpose of the study and all attempts were made to foster a mutually beneficial and professional working relationship between the two sets of researchers. In the course of the study, observed involuntariness and misunderstanding of the informed consent document of the clinical trial were reported to the principal investigator of the clinical trial for further management.

CHAPTER FOUR

RESULTS

4.1. Demographic Data of Respondents

A total of 75 persons participated in this study with a mean age of 36.5 ± 10.3 years (range 15–57 years). The majority of the respondents –17 (22.7%) – were aged 35–39 years, followed by those in the 40–44 years age group – 15 (20%). The majority –53 (70.7%)– of the respondents were females and 64 (85.3%) of all participants were married. The educational background of the respondents ranged from primary education (14.7%) to tertiary educational level (14.7%). While 6.6% of participants were illiterate, the majority (64%) had secondary education and they were mostly (53.3%) involved in trading.

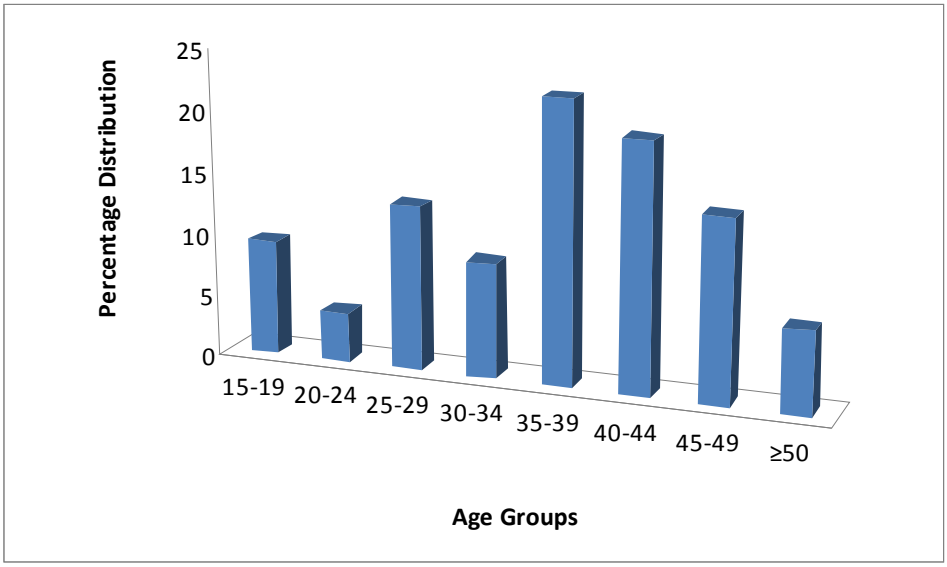

FIG 1: AGE DISTRIBUTION OF RESPONDENTS

4.2. Informed Consent Process

All the respondents –75 (100%)– knew they were taking part in a malarial clinical trial research project and they had all given consent before they were recruited into the study. The majority – 67 (89.3%) – gave written consent while 8 participants (10.7%) gave verbal consent.

Most of the respondents – 66 (88.0%) – were given information leaflets, a few were not – 7 (9.3%) – while2 (2.7%) could not remember if they had been given any information leaflet or not. The majority of respondents – 74 (98.7%) – stated that they were not allowed to go home

with the informed consent document, while 1 (1.3%) respondent said there was no need to go home with the informed consent document.

4.3. Voluntariness of Informed Consent

Most of the respondents – 59 (79.7%) – thought people get involved or are chosen for medical research because they are ill, while the remainder – 15 (20.3%) – thought the research participants are volunteers.

Their reasons for consenting to be part of the clinical study were because they believed their illness would be diagnosed – 24 (32%), they were ill–27 (36%), they could get treatment for their illness –21 (28%), and they got the news about the study that people that were ill were getting treated for free–3 (4%). (Fig. 2.)

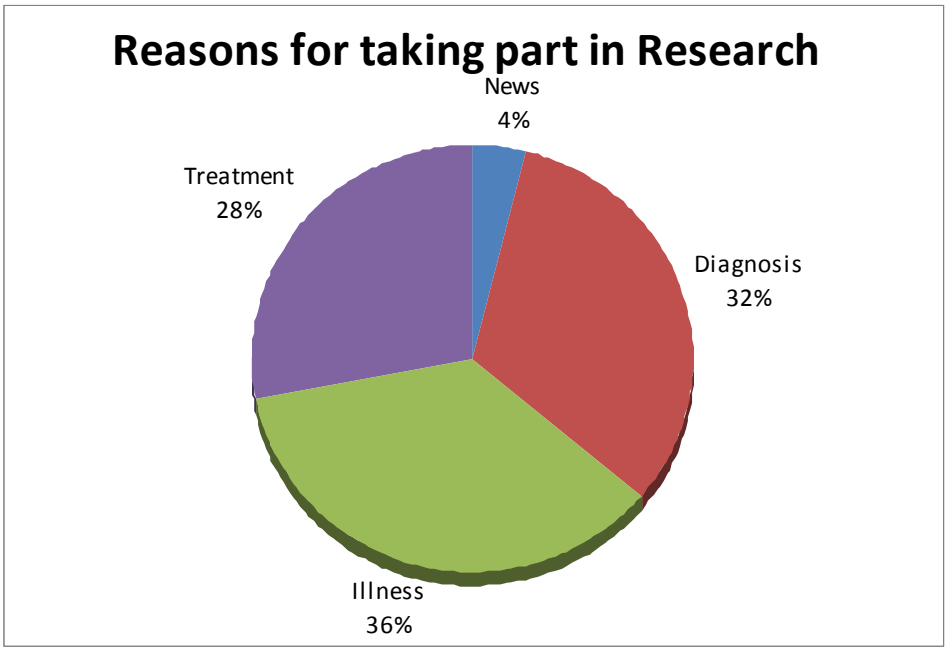

FIG 2: REASONS FOR TAKING PART IN RESEARCH

Almost all the respondents – 74 (98.7%) – gave consent immediately after the clinical trial information had been given. The majority of the people thought that they were given enough time to think about the issues – 67 (89.3%) – while about 8% said they were not given enough time.

It was very easy for almost all of the respondents– 74 (98.7%) – to make a decision about participating in the clinical trial, but for 1 (1.3%) of the respondents, it was neither easy nor

difficult. For those who thought the decision was easy, this was based on the fact that they would access treatment – 60 (80.0%), laboratory test – 10 (13.3%), and because they were ill – 7 (9.3%).

4.4. Factors Influencing Voluntariness

According to the respondents, the decision to participate in research could be influenced by illness – 30 (40.0%), news about the study – 29 (38.7%), and the opportunity to obtain treatment – 16 (21.3%).

Only 5 (6.7%) of the respondents had previously participated in clinical trials and all the respondents felt there were benefits in participating in a research study. The major benefits mentioned were the opportunity to obtain treatment – 71 (94.7%), undergo a diagnostic test – 42 (56.0%), and education {on research process and treatment options} – 7(9.3%) though some of the patients chose more than one benefit (Fig.3.)

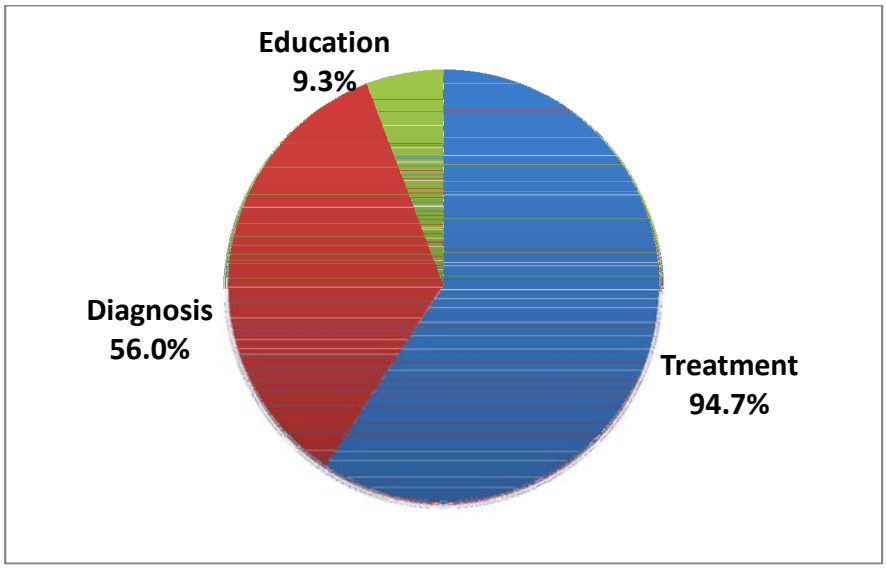

FIG. 3: BENEFITS OF PARTICIPATION IN RESEARCH

The majority of the respondents – 73 (97.3%) –stated that they were not paid to participate in this study. Eight (10.7%) of the participants believed that research participants should be paid, though none of them could proffer an amount that they deemed acceptable payment for participation.

Less than one-tenth of the respondents – 6 (8.0%) – thought that payment could potentially influence their decision to participate in the trial because it would serve as motivation. The majority of the respondents –57 (76.0%)– said payment would not, while the rest –12 (16.0%)– could not say if payment would or would not influence their decision to participate.

None of the respondents aged ≥ 45 years said payment would affect their participation. The few respondents –6 (8.0%)– who said payment could affect their participation were in the age group 15–19 years –1 (14.3%), 20–24 years –1 (33.3%), 25–29 years –2 (20.0%), 35–39 years – 1 (5.9%), and 40–44 years – 1 (6.7%). This represents the percentage of respondents in each age group who said payment could affect their participation.

There was no significant association between what influenced their decision to participate and the age (p=0.533), sex (p=0.342), education (p=0.078), religion (p=0.144), marital status (p=0.239), occupation (p=0.076) and ethnicity (p=0.468) of the respondents.

4.5. Understanding of the Informed Consent

Almost all the respondents – 74(98.7%)– claimed they had understood the information given to them during the consent procedure and they had all given consent without consulting anybody outside the medical field. One of the respondents, identified to be a Yoruba Muslim male aged between 45–49 years, with secondary education and working as a civil servant, was the only one who stated that he did not understand the information given during the informed consent procedures. Though, in the assessment of understanding using the forced-choice checklist of six major aspects of the informed consent document, 63% claimed not to have understood issues concerning randomisation of participants in the clinical trial and 71.2% did not understand compensation issues on research related injury. The comprehension score for all the six major aspects of the informed consent document questions in the forced-choice checklist and self-report form ranged from 28.8% in the comprehension of issues about compensation for research related injury to 100% concerning eligibility to participate and trial aim. The comprehension score for issues about randomisation of participants was 37%. The percentages of the correct responses were greatest for questions dealing with the background information about the project and the rights of the participants.

Three (4.0%) of the respondents were not given the opportunity to ask questions before consenting, but all the others –72 (96.0%)– said they were given the opportunity to ask questions.

Only 10 (13.3%) of the respondents said the risks involved in participation in the research were disclosed. The risks they remembered were dizziness, drowsiness and weakness. The majority of the respondents – 35(46.7%)– claimed that the risks involved in participation were not disclosed to them while a large proportion of the respondents – 30(40.0%) –could not remember if the risks of participation were disclosed or not.(Fig. 4.)

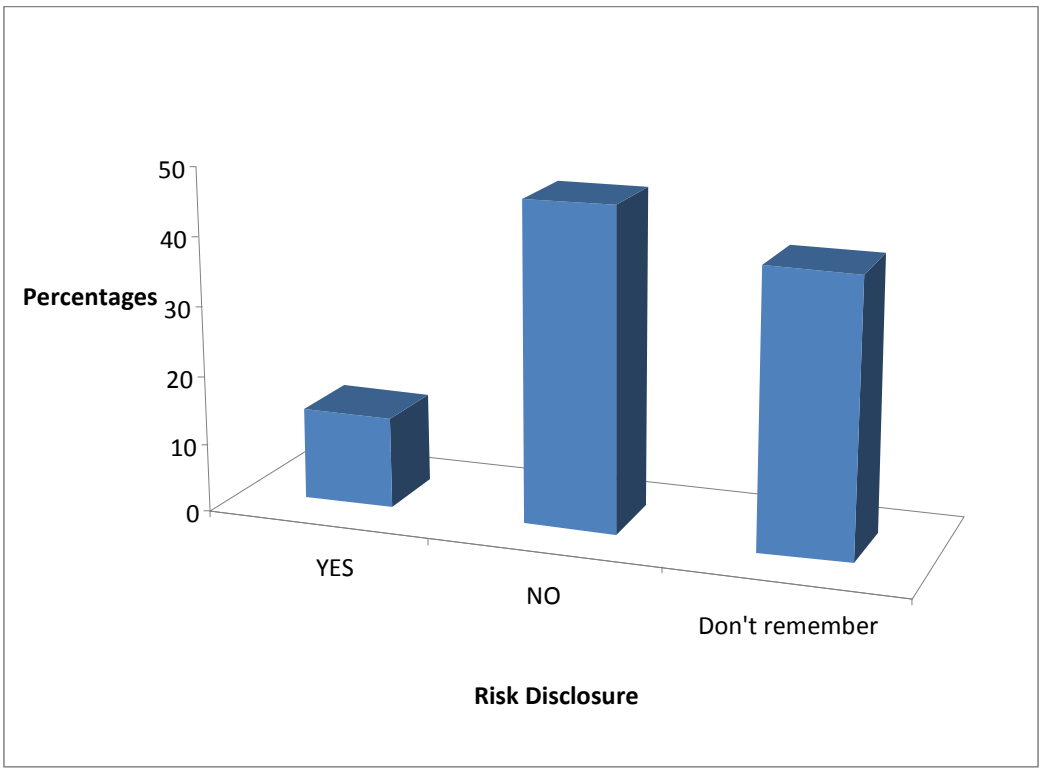

FIG. 4: DISCLOSURE OF RISKS TO PARTICIPANTS

Numerous respondents – 67(89.3%)– were not aware of any unforeseen risks, while 7 (9.3%) of the respondents knew there might be some unforeseen risks.

All the respondents –75 (100%)– knew they could withdraw at any point in the research without penalty and that people must be given the opportunity to choose whether or not to take part in the research before consent is given.

4.6. Knowledge and Perceptions of Research Participants about Clinical Trials

Despite the fact that these respondents participated in a clinical trial, the majority of them did not have knowledge on how medicines come to be known as being safe or effective. Only a few of them –3 (4.0%)– associated it with research/testing and only13 (19.7%) said efficacy and safety were determined when medicines are used by people who are ill. None of the respondents knew how new drugs are tested, while only 4 (5.3%) of the respondents knew that medicines are first tested on laboratory animals before they are tested on humans.

The majority of the participants –67 (89.3%)– did not know the kind of people used most often in medical research, 7 (9.3%) said no specific group is used whereas 1 (1.3%) said that white people are most often used in medical research.

The people who should be used for medical research, according to the respondents, are sick people –57 (76.0%), followed by volunteers –17 (22.7%), and those who trust doctors/scientists –1 (1.3%).

The way the respondents thought about how people get involved or are chosen for medical research was similar across the various age ($p=0.941$), gender ($p=0.078$), educational status ($p=0.326$), religion ($p=0.427$), marital status ($p=0.326$), occupation ($p=0.103$), and ethnic groups ($p=0.797$).

The majority of the respondents – 73 (97.3%)– thought that it was fair to use human beings for research, 1 (1.3%) thought it was not fair, while 1 (1.3%) did not know if it was fair or not. The major reason they offered for the necessity of human research was that humans were the end users –70 (94.6%). The reason one of the respondents said it was not fair to use human beings was that animals should be used for research instead of human beings.

There was a significant relationship ($p=0.048$) between the age of the respondents and knowledge that new medicines found to be safe on animals need to be tested on humansbefore being sold to the public. None (0.0%) of the respondents in the following age groups knew: 25–29, 30–34, 34–39, ≥ 44 years, whereas some respondents in the following age groups knew: 15–19 years –2 (28.6%), 20–24 years – 1 (33.3%), and 35–39 years –2 (13.3%).

Only 10 (13.3%) of the respondents felt people were well treated during drug trials because their ailments were treated, medicines were efficacious and beneficial, and normality was restored, while the rest –65(86.7%)– did not know if people were well treated or abused.

One (1.3%) of the respondents thought that people's rights are abused by being neglected when medicines are tested on humans, while 11 (14.7%) thought that people's rights are protected. Others –63 (84.0%)– did not know if people's rights were protected or abused.

Two (2.7%) of the respondents knew of people who were harmed or disadvantaged because medicines were tested on them. However only 1(1.3%) of the respondents could report on the type of harm or disadvantage (stomach upset) experienced by a drug trial participant.

CHAPTER FIVE

DISCUSSION

The study set out to assess the understanding and voluntariness of informed consent of participants in a clinical trial. This aim was achieved through the determination of various factors that influenced the voluntariness of participants. Some key issues that were impediments to the comprehension of the informed consent documents of participants were also determined.

The results showed that one of the key issues that impede the comprehension of participants is the improper and inappropriate interpretation of terminologies used in clinical trials in a way that is not applicable to the local setting, such as randomisation which does not have a direct local interpretation and which explanation may not be culturally acceptable to the indigenes. There is also the need to use appropriate personnel during the informed consent process. They should have adequate knowledge of the clinical trial and also be able to communicate effectively with the participants. The participants should be allowed enough time to understand all the information and feel free to ask questions about everything that is unclear. Informed consent should be a process and not a once-off information session – participants should be allowed to grasp the essence of their participation through multiple information sessions (Fitzgerald, Marotte, Verdier, Johnson & Pape, 2002).

In this study, participants' understanding of the information given was well above average probably because the informed consent document was translated into the local language. There was however limited understanding of technical terms relating to the clinical trial itself, such as randomisation and compensation of research-related injury. There seemed to be a need to find a way of explaining these terminologies and concepts in the local language and with relevant examples. According to Fitzgerald et al. (2002) participants' comprehension improves when information is passed repeatedly through many information sessions through a counselor before consent is given. This would have significantly improved the comprehension of the participants, who are not quite literate in the study environment, in understanding concepts such as compensation after research-related injury, which is still a strange concept to many people in developing countries. In these countries, participants lack access to legal recourse and the issue of health insurance is still strange and not subscribed to in many rural communities.

Despite the translation of the consent document into the local language, there were still some terminologies that the participants found difficult to comprehend. This could probably have been mitigated if the participants were given more time for the informed consent process or were even allowed to go home with the document to discuss it with family members (Tindana, 2007). This probably would have improved their levels of understanding of the issues concerned or might even have resulted in informed refusal.

The fact that 98.7% of the respondents stated that they were not allowed to go home with the information leaflets, suggests that it was a rushed decision and the support they would have received from family members in terms of advice was lacking. These are some of the factors that could hamper or enhance informed consent (Roberts, 2002).

The fact that the majority of the participants claimed that the risks involved in participation were not disclosed to them, or that they could not remember, showed poor comprehension of the risks involved in participation. This was in contrast to the benefits of participation, which seemed to be the major focus of the participants and might also have been the major area of emphasis by the researchers during the consent process, in order to encourage participants to enroll. In this study, the major factor that determined participation was the benefits the participants stood to gain by their participation, irrespective of their level of comprehension of the informed consent document.

According to Appelbaum et al. (1987), certain elements must be made clear to a research participant before consenting to participate in research. One of these is the fact that it must be clear to the potential participant that he is being asked to participate in research. The patient must understand that his belief that his interest will be the main priority of the researcher can be inaccurate in such a context. In this study, the basis for volunteering to participate was trust, which was created from the inception of the research by the interaction of the research team with the local leaders and opinion leaders in the community which was evident in the way the people entrusted their health in the hands of the researchers. This gave the researchers access to the community. This is unlike the study of Barsdorf and Wassenaar (2005), who reported a problem with trust due to the experience of the Blacks (mostly) during the apartheid regime, which was still fresh in their memories. There was therefore impairment of perceived and experienced voluntariness of mostly the black South African participants. The Blacks in their study perceived volunteering as a form of passive

compliance rather than an active wish to participate. This was contrary to the experience in this study where voluntariness was based on trust.

Voluntariness was however also influenced by what a participant stood to gain from participation, such as better access to treatment of ailments as well as diagnosis of ailments which would not have been possible without their participation due to poor health infrastructures. Voluntariness was arguably however hampered because of the benefits the participants stood to gain as a result of their participation. Unlike in the study of Barsdorf and Wassenaar (2005), where it was noted that education influenced perceived voluntariness, it was noted in this study that education did not have any significant association with the decisions of the participants to participate in the clinical trial.

All the research participants in this study indicated that they were given the opportunity to choose whether or not to participate in the clinical trial as a precursor to their involvement. This was done in furtherance of the principle of informed consent in research, which according to Appelbaum et al. (2009), derives from a legal doctrine that calls for potential research participants to make meaningful choices.

Appelbaum et al. (2009) stated that informed consent comprises three elements: information, competence and voluntariness. In this study the first two requirements were complied with. The participants were given relevant information and were competent to make voluntary decisions, though some of them claimed that the risks involved in the study were not disclosed to them. The voluntariness requirement of Applebaum et al. (2009), however, seemed not to have been adhered to. Despite the fact that their decision to participate was not influenced by any individual, it was not truly voluntary because of other motivational factors. The factors centered on the belief that with participation their chances of receiving better treatment for their ailments and getting their ailments diagnosed, could increase. This is the case in most African countries where there is a dire need for health care because of inadequate public health systems (Lynoe, Hyder, Chowdbury & Ekstron, 2001).

These factors neither present coercion nor undue influence, but rather reflect the participants' dire need for treatment and their trust in the investigators. They believe that clinical treatment or research study will confer personal benefit or that a clinical researcher will always act in the best interests of the participants. These beliefs might result in a therapeutic misconception

(Roberts, 2002), which is the failure of the research participant to appreciate that he or she is being enrolled in a research study and not in standard clinical care.

The above-mentioned results are in line with Cahana and Hurst (2008), who stated that motivation for research participation was not based only on what the subjects feel they can benefit, but also on the altruism and trust the subjects have in the investigators. To show respect for the culture of the people, help the research team gain the trust of the people and make them receptive to the research activities (Cahana & Hurst, 2008; Kass, Sugarman, Faden & Schoch-Spana, 1996), the research team met the traditional head of the community and its council and fully explained the purpose of the research to them before the trial started.

One can thus argue that, although people voluntarily made a choice to participate, the level of voluntariness was diminished by the influence of symptoms of illness and pressures intrinsic to their setting (Glick, Mackay, Balasingam, Dolan &Casper-Isaac, 1998; Moreno, Caplan & Wolpe, 1998). Roberts (2002) identified that severe pain is one of the physical symptoms that arise as a result of illness and has a profound impact on voluntariness. This has been demonstrated in studies in which adequate pain control radically changed the consent decision of patients, including end-of-life-care preferences (Ganzini, Lee, Heintz & Bloom, 1993). The degree of physical dependence a person experiences – e.g. the inability to feed oneself or to attend to one's own hygiene – due to pain or debilitation also affects one's ability to make and insist upon choices (Pearlman et al., 1993). The informed consent decision of the participants is related to their state of health and the need to get treatment for their sickness and because of these needs, they consented to participation. These factors had a major influence on voluntariness.

Some other factors, according to Roberts (2002), that could hamper or enhance voluntariness during decision-making are: (a) rushed timing of a complex or highly important health decision, for example, may threaten the person's ability to make a deliberate choice that is otherwise well informed and congruent with his or her life values (WMA, 1997); (b) a dialogue between a clinician and a patient who is suffering from chronic illness may provide an optimal situation for authentic decision-making (Lidz, 1984); (c) large financial incentives may cause an individual to subordinate his or her usual values and to take serious risks (Russell, Moralejo & Burgess (2000); (d) the presence of a supportive family member may improve the person's ability to identify and state his or her preferences (Rothchild, 1994); (e)

ill-defined but potential role conflicts, such as when a person enrolls in a study in which his or her personal clinician is also the principal investigator (Cattorini & Mordacci,1993).

LIMITATIONS

The generalisability of the current finding is limited by the relatively small sample size, which is as a result of the small number of people that are usually involved in clinical trials because the participants need to be monitored closely. Since those who took part in the study were volunteers who had initially volunteered in the clinical trial, the study was unable to capture enough reasons why people may not want to take part in clinical trials since the study did not have access to those who refused to take part in the clinical trial. The clinical trial enrolled participants from a large area and the remoteness made accessibility difficult. It also took a longer period of time to complete the study due to long travelling hours in heavy traffic. Finally, the time interval between the time consent was given for the clinical trial and this study could also have influenced what the participants were able to remember.

CHAPTER SIX

CONCLUSION AND RECOMMENDATIONS

CONCLUSION

In this study about the voluntariness and understanding of research participants in Nigeria, it was found that the level of participants' understanding of the informed consent documents was generally above average. The study did however identify the need to improve the process by giving enough time to participants for consultation with their family members and also ensure that the process is being carried out by trained personnel, which will increase the voluntariness of the participants.

This study showed that although informed consent was without the deliberate, specific influence of any individual, there were other factors that played major roles in the participants' decision to take part in the clinical trial. The results of this study showed that the state of health of the participants and the benefits of treatment they stood to gain through their participation, acted as motivational factors while other factors such as age, sex, education, marital status and ethnicity did not influence the participants' decision to take part in the clinical trial.

There is therefore a need for the protection of the vulnerability of participants in this regard. This could be in the form of allowing adequate time to enable the improvement of participants' understanding of the consent form, using innovative ways of explaining complex concepts such as randomisation, and providing the necessary support to facilitate participants' right to self-decision, except when they are incapable of consenting.

RECOMMENDATIONS

In this study, participants' willingness to participate in a clinical trial hinged on the benefits derived from such participation. This situation arises out of the lack of access people in developing countries have to adequate health care, except when involved in a clinical trial. This makes them vulnerable and has the consequence that people might participate in clinical trials without actually grasping the essence of their participation. There is therefore a need to further explore ways of achieving true voluntariness based on altruism.

There is also a need to evolve ways of describing and explaining some terminologies in clinical trials, such as randomisation, and what it means to be compensated for research-related injury. All these should be incorporated into ways of improving the understanding of participants during the informed consent process. This could be done by engaging trained counselors in the informed consent process and allowing the participants to be involved in multiple information sessions for adequate comprehension of the essence of participation and to facilitate the participants' right to self-decision without coercion, inducement or therapeutic misconception. There is also a need to allow participants time to discuss the proposed research with their relatives before giving their consent. This will enable the participants to gain the support and encouragement of the family members in the case of trials related to chronic illnesses. This could be necessary in a clinical trial that involves antiretroviral therapy which requires intensive chemotherapy and where compliance with the drug regimen is very crucial to prevent the development of drug resistance.

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APPENDICES

Appendix 1

[1]QUESTIONNAIRE: **Assessing Participants' Understanding and Voluntariness of Informed Consent in a Clinical Trial in Nigeria**

SECTION 1: DEMOGRAPHICS

(Introductory comment) "This is just to collect some basic background information. None of this personal information will be available to anyone other than the researcher."

Age: 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69

Gender: male, female

Marital Status: **Single**
Married
Divorced
Widowed

Occupation: .....

Education: Illiterate
Primary
Secondary
Post-Secondary

What is your ethnic group: …….

What is your religion: **Christianity**
Islam
Traditional religion
Atheist
Others ……

SECTION 2:

(Introductory comment) "These are some general questions about medical and health research as different people have different information and ideas about medical research."

1. How do certain medicines (e.g. Panado, Alabukun, Lailaetc) come to be known by the people as medicines that work and are safe?
   a Read package insert
   b Tradition/word of mouth/reputation

[1]Adapted from Barsdorf and Wassenaar, 2005

c Research/testing
d. Advertising
e Other……

2. Do you know how new medications are tested?
   YES NO

   If YES, How?.....

3. Do you know that most new medicines are first tested on animals in a laboratory?
   YES NO

4. Do you know that after new medicines are found to be safe on laboratory animals, they need to be tested on people before they can be sold or used by the public?
   YES NO

SECTION 3:

(Introductory comment) "This section asks you for some of your opinions on medical research. There are no right or wrong answers - we are just interested in your own opinions and ideas."

5. Do you think that people have been treated well or abused when medications are tested on humans?
   WELL/ABUSED
   Give reasons for your answer:.....

6. Do you know of any people who have been harmed or disadvantaged because medicines were tested on them?
   YES/NO
   If yes, describe what you know/heard:…….....

7. Do you think that, in general, people's rights are or have been abused or protected when medicines are tested on humans?
   ABUSED/PROTECTED
   Give reasons for your answer:.....

8. What kind of people do you think get used most often in medical research?
   White Black Indian Coloured No specific group Don't know
   Give reasons for you answer…….....

9. How do you think people get involved or chosen for medical research?
   Do you think people get chosen for medical research because:

   (Tick what respondent gives, then ask about others)

a. They are poor
b. They are ill
c. They think they cannot refuse
d. They cannot understand what researchers want them to do
e. They are illiterate
f. They are asked to volunteer to help their community
g. They trust the doctors/scientists and do not want to offend them
h. They will be offered better medical care if they volunteer
i. They hope that they will be offered jobs/employment by the researchers/scientists
j. They will feel respected by the doctors/scientists/researchers
k. They want future generations to be protected against illness
l. They are bribed
m. They are offered fair payment for their time and effort
n. Other reasons:…….....
.....

10. Which people do you think should be used in medical research?

(Tick what respondent gives, then ask about others)

a. People who are poor
b. People who are ill
c. People who think they cannot refuse
d. People who want to help their community
e. People who trust doctors and scientists
f. People who are looking for jobs/employment
g. People who want the benefits of the treatment being tested
h. People who are bribed
i. People who are offered fair payment for their time and effort
j. People who want to feel good about helping future generations
k. Any people who wish to volunteer
l. Other types of people:…….
m. Any reasons for your answer?…….

SECTION 4

11. Do you know that you are taking part in a research procedure? Y/N

12. Did you consent to take part before you were recruited to take part? Y/N

13. How was the informed consent carried out?
    a. Written
    b. Verbal

c. Audio visual
d. a and b
e. a, b, and c.

14. Were you given information leaflet? Y/N

15. Did you consent immediately you were given the information? Y/N

16 Did you have enough time to think about the issues? Y/N

17. Who carried out the informed consent process?

a. My physician
b. Investigator
c. Nurse
d. Health educator
e. I don't know

18. Did you understand all the information given you during the informed consent procedure? Y / N

19. Did you have the opportunity to ask questions before consenting? Y/N

20. Were you allowed to go home with the informed consent document?

1. Yes
2. No
3. Not applicable

21. Did you consult anybody outside the medical personnel before you consented? Y/N

22. If yes, whom did you consult? ……

23. Why did you consent to take part in the research?

…….

……

……

24. What influenced your decision to take part in the research?

…….

…….

…….

25. Did you get additional information from other sources about the clinical trial? Y/N

26. If yes, what are the sources?
    i. Books and Newspapers
    ii. Other physicians / health professionals
    iii. Internet
    iv. Other patients
    v. Others

27. Have you participated in a clinical trial before?
    i. Yes
    ii. No
    iii. Don't Know

28. Is the research of any benefit to you?
    i. Yes
    ii. No
    iii. Don't Know

29. If yes, what are the benefits?

……

……

…….

30. Are you being paid for your participation in this clinical trial?
    i. Yes
    ii. No

31. Do you believe participants should be paid?
    i. Yes
    ii. No

32. If yes, How much is acceptable payment?.....

33. Do you think payment will influence your decision to participate in the trial?
    i. Yes
    ii. No
    iii. Don't Know

34. If yes, explain

……
……
……
……
……
……

35. Were you told the risk involved in taking part in the research? Y/N

36. If yes, what are the risks involved?

……..

……...

……

……..

37. Are you aware that there are some unforeseen risks? Y/N

38. Do you know that you can withdraw at any point in the research without any penalty? Y/N

39. Do you think that people must give signed permission before research can be done on them? Y/N

40. Do you think that people are put into research without being given much choice? Y/N

41. Do you think that it is fair to use human beings for medical research ? Y/N

Give reasons for your answer:.....

42. How easy or difficult did you find the decision to participate in clinical trial?

a. very easy
b. easy
c. neither easy nor difficult
d. difficult
e. very difficult

43. Why?

……
……..
……
……..
……
……..
……
……
……..

“Thank you for your time and effort in cooperating with this survey.”

Appendix 2

FORCED-CHOICE CHECKLIST

(Lindegger et al., 2006)

Asks whether statements about trial participation are true or false.

This is according to the method of Lindegger et al.(2006) in assessing the understanding of the participants on seven important components that are essential for participants to understand concerning trial. Only six of these are of relevance in the present study. The participants are expected to answer True or False to the statements concerning the important components pertaining to the trial. Each answer to the statement will be graded 1 or 0

True = 1

False = 0

All the points will be added together as percentage. The Percentage score of each participant on this determine the level of understanding e.g if a participant gets all the questions correctly, then that is 100%.

Below are the components:

Trial aim; Eligibility to participate; Increasing ones risk 47ntimala (false sense of security); Methodologic considerations such as placebo and blinding; Compensation for research related injury; and right to withdraw.

1. The aim of the trial was to evaluate the efficacy and safety of new antimalaria drug. T/F
2. You must have malaria parasite for you to be eligible to participate in the trial. T/F
3. The drug given you will prevent you from having malaria. T/F
4. Do you know that there were two groups fro the treatment and you were randomly selected to either one. T/F
5. Do you know that if you were injured during the trial you are entitle to compensation. T/F
6. Do you know that you have a right to withdraw from the trial without any penalty? T/F

SELF REPORT

(Lindegger et al., 2006)

Estimate your level of understanding of the following components of the trial based on the following gradings:

Little or no understanding = 0

Good enough understanding = 1

1. Do you understand the trial aim?
2. Do you understand the eligibility criteria?
3. Do you understand that the drug given you will cure malaria?
4. Do you understand how you were grouped into two?
5. Do you understand that you could be compensated if you were injured during research?
6. Do you understand that you could withdraw from the study without any penalty?

The gradings will be added up as above and graded as percentage of the total of the six components that are applicable to this study.

Appendix 3

INFORMED CONSENT DOCUMENT

TITLE OF STUDY: Assessing Participants' Understanding and Voluntariness of Informed Consent in a Clinical Trial in Nigeria

Dear Participant,

You are invited to take part in a research study. Before you decide whether or not you wish to participate, we will want you to fully understand why the study is being done and what your participation entails. Please if you have any questions that this document does not fully explain, please do not hesitate to ask the investigator.

Purpose of the Study

As a result of the disadvantaged position of the citizens of developing countries because of their needs for medical care and nutrition there is the need to assess participants' perception of understanding and willingness to participate in clinical trials with a view of identifying factors that influence their participation in clinical trials as well as suggesting ways of improving the process of informed consent which is rooted in the principle of respect for persons.

You as a participant in the study are a very important source of information for this study because of your recent experience as a participant in a clinical trial in this community.

Explanation of Procedures to be followed:

This study involves the administration of questionnaires to ask you questions on your recent experience as a participant in a clinical trial. We will ask questions on your knowledge about how a tablet is being tested, why you decided to be part of such test and what influenced your decision to be part of such study. We will test your perceived understanding by asking you if certain statements about the trial are true or false.

Risk and Discomfort involved

There are no risks in participating in the study except that you will need to spend sometime to answer the questions in the questionnaire that will be asked. If any of the questions make you feel uncomfortable, you may not answer such question.

Although, you may not benefit directly from the study, the results of the study will enable ways of improving the informed consent process for participants of clinical trials in the future.

What are your rights as a participant?

Your participation in this study is entirely voluntary. You are free to refuse participation or withdraw from participating at any time during the study without any consequence.

Has the study received ethical approval?

This study has been reviewed and received ethical approval from the Research Ethics Committees of the University of KwaZulu-Natal and the Nigerian Institute of Medical Research. Copies of approval letters are available if you wish to have one.

Information and Contact Person

The contact person for the study is:

Dr B. Adewale
Public Health Division
Nigerian Institute of Medical Research
6, Edmond Crescent Yaba, Lagos. Nigeria.
Cell: 08072775897

Compensation

Your participation in this study is voluntary and there is no compensation for participation but you may be given an incentive for the time you spent in answering the questions.

Confidentiality

All information you give in the course of your interview will be kept confidential. Once we have analysed the information no one will be able to identify you. Research reports and articles in scientific journals will not include any information that may identify you.

CONSENT TO PARTICIPATE IN THIS STUDY

I confirm that the person asking my consent to take part in this study has told me about nature, process, risks, discomforts and benefits of the study. I have also received, read and understood the above written information (Information leaflet and Informed Consent) regarding the study. I am aware that the results of the study, including personal details, will be anonymously processed into research reports. I am participating willingly. I have had time to ask questions and have no objection to participate in the study. I understand that there is no penalty should I wish to discontinue with the study and my withdrawal will not affect my access to health care in any way.

I have received a signed copy of this informed consent agreement.

Participant'sname ……..

Participant's signature: …… Date …….

Investigator's name ……

Investigator's signature …… Date ……..

Witness's Name ……

Witness's signature …… Date …….

VERBAL INFORMED CONSENT

I, the undersigned, have read and have fully explained the participant information leaflet, which explains the nature, process, risks, discomforts and benefits of the study to the participant whom I have asked to participate in the study.

The participant indicates that s/he understands that the results of the study, including personal details regarding the interview will be anonymously processed into a research report. The participant indicates that s/he has had time to ask questions and has no objection to participate in the interview. S/he understands that there is no penalty should s/he wish to discontinue with the study and his/her withdrawal will not affect access to medical care in any way. I hereby certify that the client has agreed to participate in this study.

Participant's Name ……

Person seeking consent …….

Signature …….. Date …….

Witness's name ……

Signature …… Date …….

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18 May 2010

Dr B Adewale
[redacted]

[redacted]

PROTOCOL: Assessing Participants' Understanding and Voluntariness of Informed Consent in Clinical Trial in Nigeria
ETHICAL APPROVAL NUMBER: HSS/0247/2010 M: Faculty of Humanities, Development and Social Science

In response to your application dated 13 May 2010, Student Number: **209502339** the Humanities & Social Sciences Ethics Committee has considered the abovementioned application and the protocol has been given **FULL APPROVAL.**

PLEASE NOTE: Research data should be securely stored in the school/department for a period of 5 years.

[redacted]

Yours faithfully

[redacted]

cc: Dr. T Rossouw
cc: Dr. L Schoeman
cc: Ms. B Jacobsen

INSTITUTIONAL REVIEW BOARD

NIGERIAN INSTITUTE OF MEDICAL RESEARCH

6, Edmond Crescent Off Murtala Muhammed Way, P. M. B. 2013 Yaba, Lagos.
Tel: 01-4823123, 01-7744723, 08050254484, 08033460947 Fax: 01-4823123, 234-1-3425171
E-mail: nimr_irb@yahoo.com *Website:* www.nimr-nig.org
Secretariat: Room 207, Biochemistry Division, Research Block, NIMR

22nd June, 2010

PROJECT TITLE:
ASSESSING PARTICIPANTS' UNDERSTANDING AND VOLUNTARINESS OF INFORMED CONSENT IN A CLINICAL TRIAL IN NIGERIA

APPROVAL LETTER

The above named proposal has been adequately reviewed; the protocol and safety guidelines satisfy the conditions of NIMR IRB, policies regarding experiments that use human subjects.

Therefore the study under its reviewed state is hereby approved by Institutional Review Board, NIMR.

INSTITUTIONAL REVIEW BOARD Research Block N.I.M.R. Signature & Date Nigerian Institute of Medical Research

DR. P. U. AGOMO 12/08/10
Name of vice IRB chairman *Signature & Date of IRB vice Chairman*

DR. A.A.ADEIGA 12/8/10
Name of IRB Member *Signature & Date of IRB Member*

This approval is given with the investigator's Declaration as stated below;
By signing below I agree/certify that:

1. I have reviewed this protocol submission in its entirety and that I am fully cognizant of, and in agreement with, all submitted statements.
2. I will conduct this research study in strict accordance with all submitted statements except where a change may be necessary to eliminate an apparent immediate hazard to a given research subject.
   - I will notify the IRB promptly of any change in the research procedures necessitated in the interest of the safety of a given research subject.
   - I will request and obtain IRB approval of any proposed modification to the research protocol or informed consent document(s) prior to implementing such modifications.

3. I will ensure that all co-investigators and other personnel assisting in the conduct of this research study have been provided a copy of the entire current version of the research protocol and are fully informed of the current (a) study procedures (including procedure modifications); (b) informed consent requirements and process; (c) potential risks associated with the study participation and the steps to be taken to prevent or minimize these potential risks; (d) adverse event reporting requirements; (e) data and record-keeping; and (f) the current IRB approval status of the research study.

4. I will respond promptly to all requests for information or materials solicited by the IRB or IRB Office.

5. I will submit the research study in a timely manner for IRB renewal approval.

6. I will not enroll any individual into this research study until such time that I obtain his/her written informed consent, or, if applicable, the written informed consent of his /her authorized representative (i.e., unless the IRB has granted a waiver of the requirement to obtain written informed consent).

7. I will employ and oversee an informed consent process that ensures that potential research subjects understand fully the purpose of the research study, the nature of the research procedures they are being asked to undergo, the potential risks of these research procedures, and their rights as a research study volunteer.

8. I will ensure that research subjects are kept fully informed of any new information that may affect their willingness to continue to participate in the research study.

9. I will maintain adequate, current, and accurate records of research data, outcomes, and adverse events to permit an ongoing assessment of the risks/benefit ratio of research study participation.

10. I am cognizant of, and will comply with, current federal regulations and IRB requirements governing human subject research including adverse event reporting requirements.

11. I will make a reasonable effort to ensure that subjects who have suffered an adverse event associated with research participation receive adequate care to correct or alleviate the consequences of the adverse event to the extent possible.

12. I will ensure that the conduct of this research study adheres to Good Clinical Practice guidelines.

DR. B ADEWALE
Principal Investigator Name

11/08/2010
Principal Investigator signature and Date