Evaluation of an alternative informed consent procedure for clinical trials conducted in The Gambia

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Declaration

'I, AFOLABI Muhammed Olanrewaju, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.'

Abstract

Background: Comprehension of informed consent poses greater challenges to clinical trial participants in The Gambia because of low literacy and absence of standardised formats for writing the local languages. This thesis reports the development and evaluation of a locally developed informed consent tool that addresses these challenges.

Objectives: 1. Develop and validate an audio digitised tool for assessment of comprehension of informed consent.
2. Develop a multimedia consent tool for Gambian research participants.
3. Evaluate acceptability and ease of use of the multimedia tool.
4. Assess the effectiveness of the multimedia tool compared to 'standard' consent among participants in a clinical trial.

Methods: A 34-item questionnaire was developed and audio-recorded in three major Gambian languages. This was digitised and validated among clinical trial participants in Gambian urban and rural areas. The informed consent document of a malaria drug trial was developed into a multimedia tool which integrated video, animations and audio narrations in three major Gambian languages. Acceptability and ease of use of the tool were assessed using quantitative and qualitative methods. Participants in the drug trial were randomised to either receive consent information through the multimedia tool or 'standard' procedure. Participant comprehension was assessed using the digitised questionnaire at baseline and follow-up visits.

Results: The questionnaire was deemed to be valid and reliable (Cronbach's alpha: 0.73-0.79). Majority of the participants (70%) reported that the multimedia tool was clear and easy to understand. Participants in the intervention arm had significantly higher comprehension scores than those in the control arm at baseline and follow-up visits. Higher comprehension scores were associated with being a male participant (p=0.03), resident in a peri-urban area (p=0.02) and having basic formal education (p=0.005). Male participants (OR = 0.29, 95% CI: 0.12-0.70, p=0.006) and living in a peri-urban area (OR= 0.33, 95% CI: 0.13-0.82, p=0.017) were independent predictors of comprehension. Survival analysis showed that participants in the intervention arm took longer time to drop to 50% of the baseline comprehension scores than those in the control arm (hazard ratio=0.22, 95% CI: 0.16-0.31).

Conclusions: A customised multimedia tool was more effective in delivering consent information and sustaining participant comprehension than 'standard' consent procedure. Further research is needed to compare the tool with conventional consent method in other sub-Saharan Africa settings.

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Abbreviations

ACASI	Audio Computer Assisted Self Interview
ADOC	Audiovisual Documentation of Oral Consent
ASTMH	American Society of Tropical Medicine and Hygiene
BICEP	Brief Informed Consent Evaluation Protocol
DICCT	Deaconess Informed Consent Comprehension Test
DICCQ	Digitised Informed Consent Comprehension Questionnaire
DHAPQ	Dihydro artemisinin piperaquine
EDCTP	European and Developing Countries Clinical Trials Partnership
EPI	Expanded Programme on Immunisation
G6PD	Glucose-6-Phosphate dehydrogenase
IC	Informed consent
ICQ	Informed Consent Questionnaire
ICH-GCP	International Conference on Harmonisation for Good Clinical Practice
LSHTM	London School of Hygiene & Tropical Medicine
MICCA	Modular Informed Consent Comprehension Assessment
MRC	Medical Research Council Unit, The Gambia
OR	Odds Ratio
PQ	Primaquine
QuIC	Quality of Informed Consent
RCT	Randomised Controlled Trial
SCC	Scientific Coordinating Committee
TML	Technology Mediated Learning

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Selected publications and presentations at international meetings associated with this thesis

1. **Afolabi MO**, Okebe UJ, McGrath N, Larson JH, Bojang K, Chandramohan D. Informed consent comprehension in African settings: A systematic review. *Tropical Medicine and International Health.* 2014; 19(6):625-642

2. **Afolabi MO**, Bojang K, D'Alessandro U, Ota MOC, Imoukhuede EB, Ravinetto RM, Larson JH, McGrath N, Chandramohan D. Digitised audio questionnaire for assessment of informed consent comprehension in a low literacy African research population: development and psychometric evaluation. *BMJ Open.* 2014; 4:e004817.doi:10.1136/bmjopen-2014-004817

3. **Afolabi MO**, Bojang K, Imoukhuede EB, Ravinetto RM, Larson JH, McGrath N, Chandramohan D. Multimedia informed consent tool for a low literacy African research population: development and pilot-testing. *Journal of Clinical Research and Bioethics.* 2014;5(3):178.doi:10.4172/2155-9627.1000178

4. **Afolabi MO**, Bojang K, D'Alessandro U, Kampmann B, Imoukhuede EB, Ravinetto RM, Alexander N, Larson JH, McGrath N, Chandramohan D. Evaluation of effectiveness of a multimedia consent tool among low literacy participants in The Gambia: a randomised controlled trial. *Bulletin of WHO (Accepted)*

5. Ravinetto RM, **Afolabi MO**, Okebe J, Van-Nuil J, Lutumba P, Muhindo MH, Nahum A, Tinto H, Addissie A, D'Alessandro U, Grietens KP. Participation in medical research as a resource-seeking strategy in socio-economically vulnerable communities: A call for research and action. *Tropical Medicine and International Health.* 2015; 20(1):63-66

Presentations at international meetings:

1. Development and evaluation of a digitised audio questionnaire for assessment of informed consent comprehension in The Gambia. Oral presentation on 2nd July 2014 at Seventh EDCTP Forum, Berlin, Germany. http://www.edctpforum.org/2014/wp-content/uploads/2014/08/CO-29-Seventh_EDCTP_Forum_-_Muhammed_Afolabi.pdf

2. Development and evaluation of multimedia consent tool for a low-literacy African research population. Poster presentation on 4th November 2014 at 63rd ASTMH meeting, New Orleans, USA. Abstract Number 720. http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=52126352-c6f3-46f9-9c1f-c18e06fe67c4&cKey=0d776e23-2f50-4003-937a-8e43db396eb5&mKey=52ae2426-7f12-4d2b-9404-c0d0b5a8eb5a

Chapter One: Introduction and background

1.1: Introduction to the thesis

'Doctor, I prefer to take part in a single-blind study rather than a double-blind study. This is because in a single-blind study, there is a risk of losing ONE eye, but in a double-blind study, I may lose my TWO eyes....'

The above assertion came from a potential participant during an informed consent discussion of a malaria vaccine trial in The Gambia. The statement aptly describes the level of comprehension of an average clinical trial participant in most African communities (1-3). These communities are characterised by low literacy rates, high poverty rates and poor socio-economic status (2, 4). This disturbing phenomenon of poor comprehension calls for a closer scrutiny of how study information is delivered to the participants, with a view to addressing how participant comprehension can be improved.

This thesis reports on the methodology and findings of a three-stage study designed to evaluate the effectiveness of delivering study information to low literacy participants using a locally developed multimedia intervention in a randomised clinical trial conducted in an African country. The first stage of the study developed and validated an informed consent comprehension questionnaire for a Gambian research population. In the second stage, acceptability and ease of use of a locally customised multimedia consent tool was assessed among potential research participants. In the third stage, the effectiveness of the customised multimedia consent tool in enhancing comprehension of the consent information was compared with the 'conventional' written consent method among Gambian participants in a malaria drug trial.

I hypothesised that: 1) clinical trial information could be made more understandable to low literacy participants by using a locally appropriate multimedia tool rather than using

a ‘conventional’ written consent method; and, 2) the comprehension scores measured using a validated comprehension assessment questionnaire would be higher among participants exposed to multimedia informed consent tool than participants who underwent ‘conventional’ written consent.

Clinical trials are widely acknowledged as the design of choice for evaluating safety and effectiveness of new drugs and vaccines before they are licensed for human use (5, 6). Increasing numbers of these clinical trials take place in developing countries including Africa where potential study participants generally have poor comprehension, mainly because research concepts are not familiar (7). Also, owing to various poor socio-economic factors which make health care access inadequate, a substantial proportion of low literacy participants in Africa decide to enrol in clinical trials without adequately understanding the study (5). In addition to participant factors, other reasons underpinning poor comprehension of study information include the provider factor (e.g. communication skills and attitude of the person providing informed consent, difficulty with the consent procedure), the trial itself (e.g. study design, complexity) and system/organisational factors (e.g. organisation infrastructure, additional time required for consent requirements)(8).

Poor comprehension could greatly undermine the quality of data and negatively affect the findings of a clinical trial (9). Furthermore, decision to participate based on poor comprehension of study information could compromise the freedom of choice and protection of rights of the participants (10, 11).

Many interventions have been suggested to improve comprehension of participants (12, 13), but few of such interventions have been evaluated in Africa where the burden of miscomprehension of clinical trial information is fuelled by high illiteracy and high poverty rates (14). This leaves a clear scope for empirical research to determine effective interventions to improve participant comprehension of study information; and this could ultimately improve ethical conduct of clinical trials in Africa.

Systematic reviews (15, 16) of clinical research showed that participants in developed countries demonstrated relatively better comprehension of concepts of randomisation, placebo, and refusal to participate in or withdraw from a study, than their counterparts from sub-Saharan Africa (SSA). Quality of informed consent depends on the type and amount of study information disclosed, adequate comprehension of trial information, and voluntary decision to enrol in a clinical trial (16). Nevertheless, comprehension of trial information and consequently, decision to participate or not in a study, are largely influenced by the method through which the study information is delivered to the participants (17, 18).

Participant comprehension was selected as the primary endpoint for the studies reported in this thesis because I consider improving participant comprehension as a potentially effective way of improving the quality of informed consent especially among low and non-literate research participants. Furthermore, comprehension of trial information has a substantial impact on voluntary decision to enrol in a study. Also, there is evidence that some of the factors responsible for poor comprehension of study information are amenable to change (19).

Unlike in developed countries where literacy rate is high, refusal rates are usually low among low literacy research participants in SSA (16). The low refusal rates have been implicated on poor comprehension and misconceptions of clinical trial information, particularly regarding the concepts of refusal to participate or withdraw, randomisation, placebo, blinding (20). Given that the key issues which are central to informed consent are poorly understood, comprehension of informed consent information is the major focus of this thesis.

Comprehension of informed consent information was reviewed from the theoretical and empirical perspectives to determine the aspects of information that are important and relevant for comprehension in low or non-literate research settings in SSA. This was done with an aim to assess appropriate information delivery methods in the settings before developing the intervention for this study.

My assessment led to the recognition of the participant comprehension as fundamental to all elements of informed consent: 1) 'what participants need to know (study information); 2) how the information is conveyed to maximise understanding (disclosure); 3) the extent to which the participants understand the information conveyed (comprehension); and, 4) the extent to which the participant consent meets the criteria for decision making in this context – competence and voluntariness' (21). Comprehension is crucial for competence and voluntariness in decision making. This provided further justification for focussing on participant comprehension both in terms of the main study endpoint as a

potential way of improving quality of informed consent, and also in terms of the participants understanding their rights to participate or withdraw from a study.

The theoretical framework underpinning this thesis is synthesised from the seminal work of Faden and Beauchamp (22), Nishimura et al (13) and technology mediated learning postulated by Alavi and Leidner (23). According to Faden and Beauchamp (22), participant comprehension is considered the foundation for independent action, which remains an essential element of informed consent. Crucial aspects of understanding that are essential for informed consent could be expressed in a manner which makes a participant comprehends that he or she is being requested to take an informed decision about study participation (21). However, evaluation of comprehension of informed consent information is challenging in the absence of a standardised definition (24), and this has led to a lack of consensus in the approaches to its measurement.

Nishimura et al (13) in a recently published systematic review identified several effective strategies for improving informed consent process including enhanced consent forms, extended discussions and multimedia. The enhanced consent form involves the use of simplified paper consent document with revised layout, text styling, and sometimes with added pictures. In extended discussions, a study team member engages participants in additional discussions and; the multimedia approach involves a presentation of the study information through combined use of video, audio and animations (25). The usefulness of multimedia intervention among literate participants in developed countries is uncertain (26). Nevertheless, multimedia was chosen as the intervention tool for this study because:

i. substantial methodological flaws existed in the studies reporting limited usefulness of multimedia consent tool.

ii. report of limited usefulness of multimedia tool may not be applicable to low literacy research settings as these studies were conducted among literate participants in developed countries.

iii. availability and affordability of media-based technology in Africa is making multimedia tool an attractive approach to improve the delivery of informed consent information.

The literature appears to suggest that multimedia tool could promote retention of consent information longer than one week (13), but its effectiveness in improving comprehension of study information in randomised clinical trials conducted among low literacy participants in Africa is yet to be reported. This context led to the development of a culturally sensitive, locally appropriate yet ethically sound multimedia consent tool based on the informed consent document of a malaria drug trial. The choice of nesting the evaluation of the multimedia consent intervention among participants in the drug trial was made to avoid the limitations associated with findings of previous studies which were conducted in hypothetical trial situations (27-29).

Furthermore, there is inconclusive evidence suggesting that participants who have better comprehension of clinical trial information are more likely to enrol (30, 31). There are also concerns among some researchers that better comprehension of trial information by African participants may lead to higher refusal rates (32). In addition to the primary objectives, this thesis also aimed to address this knowledge gap on the association of

participant comprehension and acceptance/refusal rates in relation to randomised clinical trials in an African setting.

Another dimension to the studies reported in this thesis is the use of qualitative method to explore the 'actual understanding' of participants in the parent trial. This was intended to explore retention of study information and determine how it affects participant decision on whether to continue participation in or withdraw from the parent trial.

1.2: Outline of the thesis

The objectives of this thesis are as follows: (1) to develop and validate an audio digitised informed consent comprehension questionnaire for a Gambian research population ;(2) to develop a multimedia consent tool for a malaria drug trial and assess its acceptability and ease of use among low literacy research participants in The Gambia; and, (3) to evaluate the effectiveness of the multimedia tool in enhancing comprehension of informed consent information compared to 'conventional' written consent among participants in the malaria drug trial.

This thesis reports the processes involved in the development and validation of an informed consent assessment tool and how it was contextualised for a low literacy population where written translations of English versions of informed documents to local languages are heavily constrained by the absence of standardised writing formats.

Because of considerable overlaps on the concepts of informed consent, I describe the framework underpinning the objectives of this thesis in chapters two, three and four. Chapter two features the history and development of the principles of informed consent

in the context of biomedical research. Also in the chapter, I examine major international research ethics guidelines, local operational guidelines in The Gambia and how these formulations influence the close link between the principles of voluntary informed consent and participant comprehension of consent information. In chapter three, I report a systematic review of studies on informed consent comprehension among African study participants and discuss various methods of assessing comprehension of consent information. In chapter four, I examine various strategies and interventions developed to address the problem of poor comprehension of consent information.

The process of development and psychometric evaluation of an audio digitised questionnaire employed to assess comprehension of informed consent in this thesis are reported in chapter five. Chapter six describes the development and evaluation of a customised multimedia tool for delivering consent information to low literacy participants who were considering enrolment in a malaria drug trial. In chapter seven, I gave details of the methods used in comparing the effectiveness of the multimedia consent tool (intervention) with 'standard' consent procedure (control) in the malaria drug trial.

The results and interpretations of the observed comprehension scores of participants in the randomised groups, retention of information during the study visits are discussed in chapter eight. The study findings, limitations in the application of the results and main conclusions are discussed in chapter nine.

1.3: Background to the study

Before discussing the framework underpinning the objectives of this thesis, I will describe the context in relation to the conduct of clinical trials in The Gambia.

1.3.1: Study sites

The study was conducted at Basse and Jahaly sites of Medical Research Council Unit, The Gambia. The Gambia is one of the smallest West African countries with an estimated population of 1.79 million (33) . Basse is located in the Upper River Region of the country while Jahaly is in the Central River Region, about 370km and 275km respectively east of Banjul, the capital of The Gambia. According to a 2012 World Bank report, Gambia's total adult literacy rate was 45.3% while the adult literacy rate of female population, who constitutes a large majority of clinical trial participants, was 34.3% (34). With a gross national income of US$610 in 2011, 34% of Gambian population lived below the international poverty line of US$1.25 per day between 2006 and 2011 (34). As the country depends mainly on foreign aid, the global economic recess has contributed to a further decline in Gambia's economic situation. Three major ethno-linguistically distinct groups: Mandinka, Fula and Wolof populate the country. They have similar socio-cultural institutions such as extended family system and patrilineal inheritance. Health-seeking behaviour is governed by traditions rather than modern health care norms (35).

1.3.2: Profile of the Medical Research Council Unit, The Gambia

The Medical Research Council Unit in The Gambia is an institute established for research into tropical infectious diseases with key northern and southern linkages and a track record of achievements spanning over 67 years. The Unit gained its international reputation by hosting over 30 clinical trials in the last 15 years, and is working towards

becoming a coordinating centre for Africa regional multicentre trials, where translational research can be sustained in an enabling environment. Important recent and current trials include those on vaccines (e.g. the *Haemophilus influenzae* type B, the malaria RTS,S, pneumococcal and the Gambia Hepatitis Intervention study) and on preventive interventions (e.g. intermittent preventive treatment with sulfadoxine-pyrimethamine versus intermittent screening and treatment of malaria in pregnancy, a cluster-randomised controlled trial on indoor residual spraying plus long-lasting insecticide impregnated nets (LLIN) versus LLIN alone). The Unit has the mission of (1) delivering innovative, relevant research aimed at reducing the burden of morbidity and mortality in The Gambia, West African sub-region and beyond supported by an enabling, cost effective research environment; (2) transforming the outputs and outcomes of the Unit's research, using a variety of mechanisms, into changes in practice and policy that maximise the health and economic impact of research, particularly in low-income countries; (3) training and development in order to manage processes, people and resources effectively, and to increase local and international capacity in health research in the sub-region. The Unit has a large field capability, including three well-established field stations: Fajara, Keneba and Basse and numerous field sites located within rural and urban Gambian communities. Research activities are divided into four research themes, i.e. Disease Control and Elimination; Maternal, Neonatal and Child survival; Nutrition; and Vaccinology.

As highlighted above, several intervention trials have been conducted at MRC in the prevailing context of high morbidity and poverty at the rural and urban field sites. Basse and Jahaly are two of the rural field sites where this study was conducted. Apart from low literacy rates in most Gambian communities, the local languages are oral and do not have

standardised writing formats. This makes translations and back-translations of English versions of informed consent documents to local languages to be practically challenging. In 2010, the local Ethics Committee appraised the situation and recommended that field staff involved in informed consent process of clinical trials taking place in The Gambia should be trained on the correct oral interpretations of the information on the informed consent document (ICD) in English language. Furthermore, the field staff should demonstrate ability to interpret the contents orally in the local languages in role-plays and such training should be audio-recorded and archived (36). This development implies that delivery of consent information is inherently dependent on individual variations in communication skills. This becomes crucial because communication skill of a person conducting consent interview largely determines the comprehension of the information by a prospective study participant, which may ultimately undermine obtaining a truly informed consent based on consistent delivery of study information in comprehensible manner. This study therefore sought to address the situation by developing an appropriate and ethically acceptable informed consent procedure for conduct of clinical trials in The Gambia.

In the following chapter, I will examine what is already known and documented in the literature about informed consent comprehension. I will also investigate specific knowledge gaps in this subject.

Chapter Two: Part I of Literature Review-Informed Consent

2.1: Introduction to the literature review

I present this literature review in three major areas to underpin the justifications for this study. Significant overlaps exist across these areas, but it was important to examine them separately due to the extensive data available on them. Three separate literature reviews were conducted and these are presented as follows:

- Chapter 2 (Part 1 of literature review) – *Informed Consent: Historical background and International ethical guidelines*

- Chapter 3 (Part 2 of literature review) – *Systematic literature review on informed consent comprehension in African research settings* (*including key components and measurement);*

- Chapter 4 (Part 3 of literature review) – *Interventions to improve informed consent comprehension (with focus on use of multimedia consent tool in Africa).*

Major highlights of these three chapters are summarised towards the end of chapter four, leading to a statement of the aims and hypotheses for the study. The main theoretical background of the study is discussed in chapter two in relation to informed consent theory and concept of comprehension.

2.2: Informed Consent: Historical background and International ethical guidelines

There is a widespread agreement that informed consent is a fundamental requirement before any biomedical research is undertaken. There is however less agreement about the process and documentation which are appropriate in varying cultural and social contexts (37). Researchers therefore face major challenges in establishing informed consent procedures that are both ethically sound and culturally sensitive because these two requirements appear to be in conflict in many situations.

During the last century, some medical researches have been conducted without the knowledge or consent of those on whom the studies were conducted (38, 39). Following global criticism of such practices, it was internationally agreed and accepted that study participants should give informed consent before taking part in biomedical research. This need is recognised in international human rights regulations (40), as well as documented in international guidance on research ethics (41-43), and many countries developed national regulations consistent with these guidelines (44-47).

The need to obtain informed consent to conduct research with human participants is based on the fundamental ethical principles of 'respect for persons' and 'respect for human dignity' (42). These principles require utmost respect for the study participants' capacity to consider options, make informed choices, and act without coercion and undue influence from researchers. This follows that researchers should seek the participants' voluntary consent to participate in medical research.

Succinctly put, informed consent could be described as the process by which prospective participants indicate their willingness to take part in research and give permission for

researchers to conduct necessary study procedures on them (41). For such informed consent to be considered valid, it is generally accepted that the prospective participant must: i) be appropriately informed about the nature of the research in which s/he is to participate; ii) adequately understand the study information; iii) voluntarily decide to participate in the research; and iv) freely consent to participation (42).

While there has been a general agreement about the crucial need to meet these four conditions, there have been growing controversies over how such conditions can be best met. This is especially true in areas where a number of different cultures are represented; or in developing countries where there are marked differences in socio-cultural perspectives about health and research by participants and researchers (48, 49). Much of the controversy derives from an increasing awareness and acceptance of the need for cultural sensitivity when conducting biomedical research. However, the meaning of 'cultural sensitivity' is highly debatable, which invariably has implications for the implementation of informed consent procedures (50-52).

Furthermore some researchers argued that for informed consent to be ethically acceptable, researchers must go beyond the minimal requirements that ensure their legal protection (53-55). This implies that informed consent should be seen as more than a formal legal agreement, but as the outcome of an ongoing process whereby a prospective participant makes informed decision on whether it is in their best interest to take part in research (53).

2.2.1: Informed consent: guidance and regulations

The need for formal consent to participate in research arose in the context of human experimentation of prisoners, particularly during the Second World War. This was articulated in the Nuremberg Code (39). Such consent is only ethically acceptable if the participant decides about participation on the basis of knowledge and understanding of what the research will involve; this has developed into the concept of 'informed consent' (56).

For consent to participate in a study to be appropriately informed, participants need to receive adequate, relevant and accurate information to enable them make a genuine choice about participation (42). Various forms of international and national guidance and regulations specify elements of informed consent that prospective participants should be informed in detail.

The Declaration of Helsinki, adopted by the World Medical Association in 1964, sets out the ethical principles that must be observed in research on human participants. The Declaration has become the foundation on which many national and international guidelines are based. The 2013 revision (41) requires that each potential participant must be adequately informed about:

1. 'the aims of the study and methods to be used;
2. sources of funding and possible conflicts of interest;
3. institutional affiliations of the researchers;
4. anticipated benefits and potential risks of the study;
5. discomfort the study may entail;
6. post-study provisions and other relevant aspects of the study; and

7. the right to refuse to take part in the study, or to withdraw at any time, without reprisals' (41).

The second international guidance that covers the field of research ethics was published by the Council of International Organisations of Medical Sciences (CIOMS) in collaboration with the World Health Organisation (WHO)(42). A revision of its 1993 guidance was published in 2002 (42), and went further than the Declaration of Helsinki, by setting out 26 areas which participants must be adequately informed. These include:

1. 'that the individual is invited to participate in research, the reasons for considering the individual suitable for the research, and that participation is voluntary;
2. that the individual is free to refuse to participate and will be free to withdraw from the research at any time without penalty or loss of benefits to which he or she would otherwise be entitled;
3. the purpose of the research, the procedures to be carried out by the investigator and the subject, and an explanation of how the research differs from routine medical care;
4. for controlled trials, an explanation of features of the research design (e.g. randomisation, double-blinding), and that the subject will not be told of the assigned treatment until the study has been completed and the blind has been broken;
5. the expected duration of the individual's participation (including number and duration of visits to the research centre and the total time involved) and the possibility of early termination of the trial or of the individual's participation in it;

6. whether money or other forms of material goods will be provided in return for the individual's participation and, if so, the kind and amount;
7. that, after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status;
8. that subjects have the right of access to their data on demand, even if these data lack immediate clinical utility (unless the ethical review committee has approved temporary or permanent non-disclosure of data, in which case the subject should be informed of, and given the reasons for such non-disclosure);
9. any foreseeable risks, pain or discomfort, or inconvenience to the individual (or others) associated with participation in the research, including risks to the health or well-being of a subject's spouse or partner;
10. the direct benefits if any, expected to result to subjects from participating in the research
11. the expected benefits of the research to the community or to society at large, or contributions to scientific knowledge;
12. whether, when and how any products or interventions proven by the research to be safe and effective will be made available to subjects after they have completed their participation in the research, and whether they will be expected to pay for them;
13. any currently available alternative interventions or courses of treatment;
14. the provisions that will be made to ensure respect for the privacy of subject and for the confidentiality of records in which subjects are identified;

15. the limits, legal or other, to the investigators' ability to safeguard confidentiality, and the possible consequences of breaches of confidentiality;
16. policy with regard to the use of results of genetic tests and familial genetic information, and the precautions in place to prevent disclosure of the results of a subject's genetic tests to immediate family relatives or to others (e.g. insurance companies or employers) without the consent of the subject;
17. the sponsors of the research, the institutional affiliation of the investigators, and the nature and sources of funding for the research;
18. the possible research uses, direct or secondary, of the subject`s medical records and of biological specimens taken in the course of clinical care
19. whether it is planned that biological specimens collected in the research will be destroyed at its conclusion, and, if not, details about their storage (where, how, for how long, and final disposition) and possible future use, and that subjects have the right to decide about such future use, to refuse storage, and to have the material destroyed;
20. whether commercial products may be developed from biological specimens, and whether the participant will receive monetary or other benefits from the development of such products;
21. whether the investigator is serving only as an investigator or as both investigator and the subject`s physician;
22. the extent of the investigator's responsibility to provide medical services to the participant;
23. that treatment will be provided free of charge for specified types of research related injury or for complications associated with the research, the nature and

duration of such care, the name of the organisation or individual that will provide the treatment, and whether there is any uncertainty regarding funding of such treatment.

24. in what way, and by what organisation, the subject or the subject`s family or dependants will be compensated for disability or death resulting from such injury (or, when indicated, that there are no plans to provide such compensation);
25. whether or not, in the country in which the prospective subject is invited to participate in research, the right to compensation is legally guaranteed;
26. that an ethical review committee has approved or cleared the research protocol'(42).

Similar to CIOMS, the International Conference on Harmonisation of Good Clinical Practice (ICH-GCP) guidelines (57, 58) listed 20 areas in which thorough explanations are required to be provided to the participants during informed consent discussions. These include:

1. 'that the trial involves research.
2. the purpose of the trial.
3. the trial treatment(s) and the probability for random assignment to each treatment.
4. the trial procedures to be followed, including all invasive procedures.
5. the subject's responsibilities.
6. those aspects of the trial that are experimental.
7. the reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.

8. the reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
9. the alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
10. the compensation and/or treatment available to the subject in the event of trial-related injury.
11. the anticipated pro-rated payment, if any, to the subject for participating in the trial.
12. the anticipated expenses, if any, to the subject for participating in the trial.
13. that the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
14. that the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorising such access.
15. that records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publically available. If the results of the trial are published, the subject's identity will remain confidential.

16. that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
17. the person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
18. the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
19. the expected duration of the subject's participation in the trial.
20. the approximate number of subjects involved in the trial' (57).

2.2.2: Conditions for validity of informed consent

Considering the amount of information highlighted by these international guidelines, critics have argued that not all this information is required to engender comprehension in varying research contexts (37, 59, 60). A strong case was made for contextualisation in line with the information need and absorptive capacity of the individual participant (61-63). In view of this suggestion, I consider each of the four requirements necessary to ensure valid consent, taking into account the conditions that are likely to exist when research is being carried out in a developing country where literacy rate is low.

2.2.2.1: Providing appropriate and comprehensive information

A number of issues may arise when informing participants in developing countries, and/or from differing cultures, about research (64). Study information that may be considered necessary or desirable in formally educated urban populations may be of little relevance in less formally educated or rural populations, or vice versa (65, 66). For example, in a preventative HIV vaccine trial some populations may want highly technical

information about the nature of the vaccine (48), whereas other populations may prefer information about the social impact of participating in the trial, such as risk of discrimination by other members of the community (67).

There is also a need to balance the use of extensive and detailed consent forms (which reflect the desire of organisations to protect participants and/or limit legal liability for possible harm caused by research) against ensuring that communities with limited biomedical and/or legal knowledge understand information about research (32, 68).

To underscore this position, Haitian researchers (61) reported that consent forms are too lengthy and have become increasingly complicated over the past decades. They stated that "the documents seem to be more concerned about legal implications for sponsor agencies than for the welfare of the participants. The document could not be read to the participants because the complexity of the languages used was similar to legal documents. This development has changed the trusting relationship that existed between researchers and participants" (61).

It should also be remembered that in some cultures it might not be acceptable to provide certain forms of information, such as describing uncertainty about the effectiveness of the treatment being tested, or information about possible alternative treatments. In Vietnam, for example, it has been suggested that "it is unacceptable for a physician to openly express uncertainty with regard to what is the best treatment" (69).

The need for comprehensive information also raises complex procedural questions such as who should decide which information is appropriate; and who is best placed to provide it. Despite the significance placed on the content of study information provided to

prospective participants, the way in which that information is provided constitutes a greater importance. If consent is to be valid, information must not only be accurate, but must be provided in a culturally appropriate and understandable manner (2). The information may include unfamiliar concepts that are difficult to meaningfully translate in some languages, such as randomisation and placebos (10).

Researchers have adopted different approaches to these difficulties, ranging from abandoning randomisation in research when it is thought to be impossible to obtain valid informed consent, to continuing with research despite concerns that participants have not understood the implications of using placebos (35). In other situations, researchers have developed means of informing participants about unfamiliar concepts by using common examples, such as agricultural practices (14).

The most recent CIOMS/WHO guideline (42) spells out a detailed list of the responsibilities of investigators (Guideline 6), which includes seeking consent only after ensuring that the prospective participant has an adequate understanding of relevant information, and has had sufficient opportunity to consider whether to participate. But there are also understated factors, such as the need to behave in a socially acceptable manner ('social desirability'), which may complicate this process. For example, marked differences in the social status of researchers and participants may make it difficult for participants to ask questions from the researchers. This has led to the suggestion that researchers/clinicians and participants/patients might be 'paired' according to similar cultural and social values (70).

2.2.2.2: Understanding

The second condition for consent to be valid is that prospective participants must adequately understand essential aspects of the research. Providing comprehensive information is not, in itself, considered sufficient grounds for assuming that the person fully understands that information. Consent procedures, therefore, may require some form of test of understanding, most commonly short yes/no or multiple-choice tests of factual information or combination of both (71, 72).

However, procedures for assessing participant understanding have also been a subject of debate, particularly when research is conducted in less formally educated, culturally diverse or developing country contexts, where the use of formal tests of knowledge is less appropriate. Questions that have been raised include: what level of understanding should participants demonstrate in order to be considered adequately informed? Do current tests measure short-term memory rather than 'real understanding'? Does the fact that participants often fail to remember information provided raise questions about real understanding? Who is best placed to decide whether a person has adequate understanding? (53).

2.2.2.3: Voluntariness

The third condition that must be met for consent to be valid is that the person must freely consent to participate in the research (i.e. must not be subjected to undue influence or intimidation), and must be free to withdraw from the research at any stage without penalty. This represents the implementation of the core ethical principle of respect for persons, including respecting the participants' autonomy.

A number of aspects of the social and cultural context in which research is conducted may affect a person's ability to voluntarily consent to participate in research, or their subsequent decision to stay in or withdraw from the study. For example, where there is a significant difference in social status between researchers and prospective participants, the latter may be reluctant to ask questions, or even to refuse taking part in the recommended research. This may often be encountered in developing countries, where great respect is given to doctors and other healthcare workers.

Economic factors might also affect prospective participants' abilities to freely consent to research. Access to benefits that are provided for those taking part in research may act as a significant incentive to participate, especially in poorer areas where there is less likelihood of alternative access to healthcare (73). One Thai research participant stated: "The study staff gives good advice and when this project is over, I hope I can enrol in another study. For that matter, I hope there will be new studies for me to participate in all the time. If there would be no more studies, I don't know if I would have the strength to go on, as I would not know where to get drugs outside of clinical trials" (74).

2.2.2.4: Formal consent

The final condition for valid consent is that there should be evidence of explicit consent to participate, which is usually done through signing (or thumb-printing) a consent form, in the presence of an impartial witness in case of non-literate participants. While this requirement has been widely accepted, there has been intense debate about the appropriateness of 'first person' consent (i.e. requiring that the participant personally provides consent) in all cultural and social contexts.

In some cases, community consent or consultation with leader(s) of the community or family is considered necessary before individuals are asked to participate in research. One Nigerian researcher commented: "There are really two levels. One is community and the other is individual"(2). The need for community consultation or consent is explicitly recognised in some forms of national or international guidance, as a safeguard against the abuse of vulnerable populations, or as an expression of specific cultural approaches to decision-making.

Although such guidance also stresses the need for consent from each participant in research, in some communities sexual or marital partners or senior family or community members may be considered to have authority to provide consent on behalf of others. This is referred to as proxy consent (as opposed to first-person consent). For example in Uganda, an adult male is expected to obtain the consent of his father before entering into any obligation or contract, including participation in research (75). Some critics argue however, that such cultural practices are ethically unacceptable, because they conflict with the fundamental principle of respect for persons, and they carry the risk that participants will be enrolled in research against their will (43).

To strike a balance between the ethical principles of respect for persons and respect for cultures, some scholars suggest that in certain cultures it may be necessary to have multiple levels of forms of consent. For example, the consent of traditional leaders or community elders might be sought in order to enter a community or household (76), and the explicit consent of individuals obtained for participation in research. Another opinion is that prospective participants might voluntarily consider inviting family members or community members to be part of the consent process.

2.3: Conclusion

The importance of obtaining valid consent as an essential requirement for research is widely accepted and entrenched in national and international guidelines for medical research. However, determining appropriate consent procedures, especially in culturally diverse and poorer settings raises important and controversial issues.

The challenge for researchers is to establish procedures that are both ethically sound and culturally sensitive, although there may be times when these two requirements appear to be in conflict. Careful and sustained community involvement in research and involving communities as research partners may give some solutions to the apparent conflicts.

2.4: Development of principles of informed consent

Marshall and colleagues (2) conclude that, not only is voluntary informed consent universally accepted as a pre-condition for scientific research involving human beings, but also, national and international guidelines for ethical conduct in research stipulate specific conditions for obtaining such consent.

Considering the importance placed on the requirement of voluntary informed consent, it is crucial to examine what the principle of voluntary informed consent entails? This will further shed light on how the principles developed in the context of ethics and biomedical research as a whole. These are some of the questions that I shall seek to examine in this section of this chapter. In the section that follows, I shall also briefly consider the historical development of the doctrine of informed consent in the context of biomedical research, as well as the ethical background of the idea of informed consent. I will start by

re-examining the questions: what is informed consent? And why is the requirement of voluntary informed consent necessary in research involving human participants?

2.5: What is informed consent?

The principle of voluntary informed consent is an important principle in medical practice as well as research ethics. Here, I shall be concerned with the idea of informed consent in the context of research ethics. In this context, research refers to a process by which a potential study participant expresses his or her willingness to be part of a research involving human participants. The central concepts in these categorisations are "approve," "authorise," and "willingness"(42). The process of informed consent is "an opportunity to provide accurate and non-judgemental information regarding trial procedures and potential risks and benefits, correct any misconceptions and allay any unfounded fears, and provide sufficient time and resources to facilitate the thoughtful consideration necessary for the best possible personal decisions (77).

To be more specific, informed consent refers to the *knowledgeable* and *voluntary* agreement (or authorisation) by a prospective participant to undergo an intervention by a researcher and "one that is in harmony with the participants' values and preferences" (78). Consent is said to be informed and voluntary when a prospective participant willingly agrees to participate in a research study. The need to develop knowledge about human diseases and possible cures or treatments for them ultimately depends on medical scientists using people as 'experimental animals' (79). Furthermore, exposing individuals to risks in the name of science becomes legitimate only with their informed, voluntary consent (79). While recognising the value and importance of individual

decision-making, a crucial point needs to be stressed that the idea of informed consent also entails the possibility of "informed refusal" (80).

It is evident from the above that pursuing biomedical research should not only be a priority, but should also be undertaken in an ethically acceptable manner. According to the report of the Nuffield Council on Bioethics (43), the urgency of biomedical research is based not only on the need to promote scientific knowledge into research but also to deal with cases of harmful and serious diseases affecting those countries. This implies that "developing countries urgently need research to help address the enormous burden of existing diseases"(43). The Nuffield Council Report (43) lists the goals of biomedical research as including the followings: (1) the need to find new or improved medicines and vaccines to deal with life-threatening diseases; (2) the desire to find better ways of delivering existing products and services to those in the need. Indeed, the benefits to be derived from biomedical research cannot be over-emphasised. Apart from the scientific progress which biomedical research promotes, it also has the added advantage of promoting medical knowledge and human well-being. But as experts acknowledge, the use of human participants in research or the use of human beings as experimental subjects often comes at great costs to those who are involved. According to Leonardo De Castro, such uses of human beings as research subjects not only expose people to great risks, but also generate ethical concerns (81). The concerns range from the impact of research on values such as human life, autonomy, dignity, justice as well as happiness. To estimate the cost of research or experimentation on these core values of life, researchers and the public need to carefully assess not only the impact of interventions on persons

but also “the consequences arising from the procedures involved” in the interventions(81) .

In addition to the possibility of harm and inconveniences which have been highlighted above, human participants in research and clinical experimentations are also vulnerable to exploitation by some investigators who may deliberately hide information about some procedures. As Robert Young points out, the way in which information is framed determines its significance or value for the research participants to whom it is provided. If information is framed in such a way as to coerce or manipulate people, whatever ‘consent’ is given under this condition cannot be considered genuine authorisation or voluntary (82). This emphasises the notion that many research participants are not familiar with the technical details and complicated experimental procedures. For example, in resource-poor countries burdened with the problems of poverty, illiteracy and diseases, local participants are often ignorant about the basic concepts of scientific research. Given their vulnerabilities therefore, “human subjects of experimentation are more exposed than they are ordinarily to the possibility of exploitation’’ (81). In view of these reasons, bioethicists emphasise the need for researchers to ‘full’ and uninhibited disclosure of information about research protocols or procedures to enable individuals take reasonable decisions about matters involving their lives.

The importance of transparency by researchers with regard to the disclosure of information and obtaining consent from research participants is a crucial issue that experts have brought to limelight. However, given the importance of these matters, disclosure and consent, and considering the imperfection of human nature which

sometimes makes people act in doubtful and ethically inappropriate manner; the duty to disclose information and obtain the consent of the individual is not merely left to the will of investigators. Experts have unanimously agreed that leaving the matter in the hands of researchers to determine when voluntary consent has been given will undermine the significant importance and value of informed consent. Virtually all prominent research codes as well as international rules of ethics require that "investigators must obtain informed consent of participants prior to substantial intervention''(80). Thus the most important goal of the informed consent doctrine is to protect the autonomy or self-determination of research participants.

2.6: The historical development of the principle of informed consent

The principle of informed consent represents a unique paradigm shift in biomedical research. The global acceptance of informed consent is unique for two major reasons:

(1) it is a reminder that individuals have important roles to play in decisions that affect their own lives, and

(2) it is a rejection of the old idea of 'paternalism', which was encapsulated in the attitude that the clinical researcher 'knows the best'.

With regards to the second reason above, the paradigm shift against what is called 'paternalism' is due largely to incidents of "involving the perceived abuse of human participants in clinical research"(78). Paternalism is described as "the interference of a state or an individual with another person against their will, and justified by a claim that the person interfered with will be better off or protected from harm'' (83). Other scholars described paternalism as "the intentional overriding of one person's known preferences or action by another person, whether the person who overrides justifies the action by the

goal of benefiting or avoiding harm to the other person whose preferences or actions are overridden'' (80). Theoretically, paternalism derives from the analogy of a father acting (paternally) to "protect" or regulate the life of his children. The analogy with the father assumes two characteristics. One is that the father acts generously (that is, in accordance with his conception of the interests of his children). The other is that he makes decisions relating to the welfare of his children, rather than letting them make their own decisions (82). In the context of biomedical research, clinical researchers sometimes withhold information from a participant regarding his or her condition in order not to cause harm or worsen his/her condition. This attitude is often motivated by a desire by the clinical researchers to "do the best" for their patients but withholding information from patients not only denies them the opportunity of making informed choices about their lives, but also places "a person's interest in his/her health ahead of their interest in deciding what would be best for the individual, provided all factors are put into consideration'' (82)." Paternalism sometimes arises from the idea that a medical personnel has "superior" training, knowledge and insight and is therefore in an authoritative position to determine what is in a patient's interest (80). Nevertheless, paternalism needs to be rejected because it denies a competent person the right to make autonomous choice with regards to his/her welfare. The crucial question here is to ask if paternalism is always wrong or if there are occasions when it may be permissible to act paternalistically?

Gerald Dworkin lists four versions of paternalism: (i) 'hard' versus 'soft' paternalism, (ii) 'weak' versus 'strong' paternalism, (iii) 'pure' versus 'impure' paternalism and, (iv) 'moral' versus 'welfare' paternalism (83). Other authors acknowledge only two versions: weak (soft) and strong (hard) paternalism. In weak paternalism, an agent intervenes on

grounds of beneficence or non-malfeasance to protect persons against their own "substantially non-voluntary" conduct, that is, actions that are not adequately informed. Strong paternalism on the other hand, involves intervention intended to benefit a person, even when it is the case that "the person's risky choices and actions are informed, voluntarily, and autonomous (80)." The major distinction between the two forms of paternalism is that in the former, the paternalist's action was undertaken because a person's ability has been compromised one way or the other, whether by severe depression, addiction or sickness that makes rational decision difficult. In the latter, a person's wishes and choices are overridden even when his/her choices are substantially autonomous (80).

Addressing the question earlier raised on possible situations when acting paternalistically could be justified, an expert (84) submits that whether or not we can justify the overriding of a person's decision for the benefit of that person will depend on the case under consideration. It was argued that if the justification is 'consequentialist', i.e. respecting autonomy is seen as a means of creating good consequences; then there is a good justification for paternalism because the consequences of respecting a given autonomous choice will be unfavourable for the person in question. Conversely, if the justification for respecting autonomy is 'non-consequentialist', Holm says it will depend on the exact premises of the justification as to whether paternalism can be warranted or not (84). Other authors argued that beneficence sometimes provide justification for paternalism (80). They posit the following as conditions that may warrant or justify paternalism: (i) sometimes when physicians act not to aggravate a patient's situation,

(ii) when a patient is legally or cognitively incompetent, and (iii) when disclosure of a disease diagnosis could worsen a person's condition.

Above discussion on the issue of paternalism has focussed mainly in the context of clinical practice, with particular reference to patient-physician relationship. There is not much evidence in the literature on justification of paternalism in the context of research, that is, whether researchers or investigators can justifiably withhold information that will enable research participants make informed decision on whether or not to participate in a research procedure. As Pauwels postulates, ethics is about telling the truth; and truth itself is central to scientific integrity. Consequently, the quality of any research is only enhanced when it is carried out in compliance with fundamental ethical principles (85). "The measure of ethical sensitivity in a research proposal is directly related to the degree of honesty and truthfulness declared"(85). What all these opinions show is that paternalism is never justified except in special circumstances such as those highlighted above. By rejecting paternalism, patients and research participants affirm their rights to decision-making as autonomous individuals. This position is consistent with the submission of Edward and Wilson (86) on flaws inherent in prohibition of non-therapeutic research for reasons of equality of welfare. They argued that banning such studies was not only un-inspiring, but could also ethically overshadowed egalitarian concerns and might attract negative outcomes (86).

In summary, "the once unquestioned authority of physicians in clinical decision-making has declined as their scientifically grounded expertise has grown, to be replaced by

patients' and research participants' insistence on their rights to give an informed consent'' (78).

Having emphasised the impact of the principle of informed consent in health care and research practice, the issue still remains to trace its historical roots. In addressing this issue, Robert Young submits that although the doctrine of informed consent has featured prominently in legal cases over the last century, it nevertheless, "rests ultimately on a moral foundation" (82). The foundations of the principle of voluntary informed consent rest on the ideas of human dignity, freedom, self-determination, autonomy, or individual choice. The argument holds, for example, that a society that fosters or promotes "respect for persons as autonomous agents will be a more progressive and, on balance, a happier society because her citizens will have the opportunities to develop their capacities to act as rational, responsible moral agents." Taken together, autonomy is valuable primarily as a means to the creation of that which is intrinsically valuable, such as preference, satisfaction, pleasure, human welfare (84).

The principle of informed consent has become a central element in ethics of biomedical practice and research. A classic case involving *Schloendorff v. Society of New York Hospitals* in the USA was historically linked to the philosophical basis of the idea of informed consent. The legal argument focussed on whether surgical operation should be performed on a patient who had only given consent for an abdominal examination under anaesthesia but refused an operation. In legal parlance, this type of action could be described as assault or battery, and this attracts punishment under the law. The Judge unequivocally stated the rights of competent people to self-determination: 'Every human

being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without a patient's consent commits an assault' (84). Many other instances exist in history of non-disclosure of full information to patients by physicians about medical interventions. These were clear cases of abuse of the trust bestowed on physicians by their patients. These individual cases of abuse demonstrate the extreme of 'paternalism' which has been banned, especially in Western societies. While individual cases of abuse have featured prominently in the literature and in the development of the idea of informed consent, ethical reflection on the doctrine of informed consent has however been largely due to a number of highly publicised cases involving the abuse of human subjects or the inappropriate use of them in clinical research. The most well-known case of abuse occurred during World War II in Germany where Nazi physicians carried out horrific experiments on non-consenting prisoners (39).

Another horrendous cases of abuse occurred in the United States of America, in which 400 poor black labourers diagnosed with syphilis were recruited for Tuskegee study on the natural course of untreated syphilis (38). The participants were neither informed about the study nor agreed to be part of the study. Despite the availability of a proven treatment for syphilis during the course of the study, the participants were not treated but were kept under observation for four decades while many developed complications and died. Similar research was conducted in Guatemala from 1946 to 1948 where vulnerable people were deliberately infected with sexually transmitted diseases without their consent. The subjects included prisoners, soldiers from several parts of the army, mentally-ill patients and commercial sex workers (87).

The Milgram study focussed on obedience and human response to authority. The participants were deceived about the nature of the study that it was a teacher/learner experiment. The 'teachers' were instructed to give electric shock to the 'participants' for giving incorrect answers to a set of question items. Apart from not obtaining informed consent from the participant because of the deception, most participants were subjected to severe psychological stress (88).

According to Baruch Brody, "these cases illustrate the need for informed consent and for ensuring that the gains and benefits of clinical research were commensurate with the risks. It also illustrates the need to protect vulnerable study participants from abuse and exploitation. And, because the Tuskegee and Guatemala studies were more epidemiological than interventional, Brody says it also "illustrates the need for policies governing that type of human research" (89).

2.7: The need for ethical guidelines

A major factor that emerged in the development of the guidelines was the need to deal with ethical problems that arise in research involving human participants. This explains why cases of human abuse by Nazi physicians (90), the Guatemala (87) and Tuskegee syphilis studies (38) led to development of ethical codes or guidelines. However, it could be concluded that these guidelines are circumstance-driven than theory-driven. Several other cases of unethical conduct exist in history that shaped the theory of research ethics and made it mandatory to develop the ethical guidelines. The milestones surrounding the development of some of these guidelines are summarised in Figure 1. I cite three more of these examples to underscore the nature and magnitude of the problem.

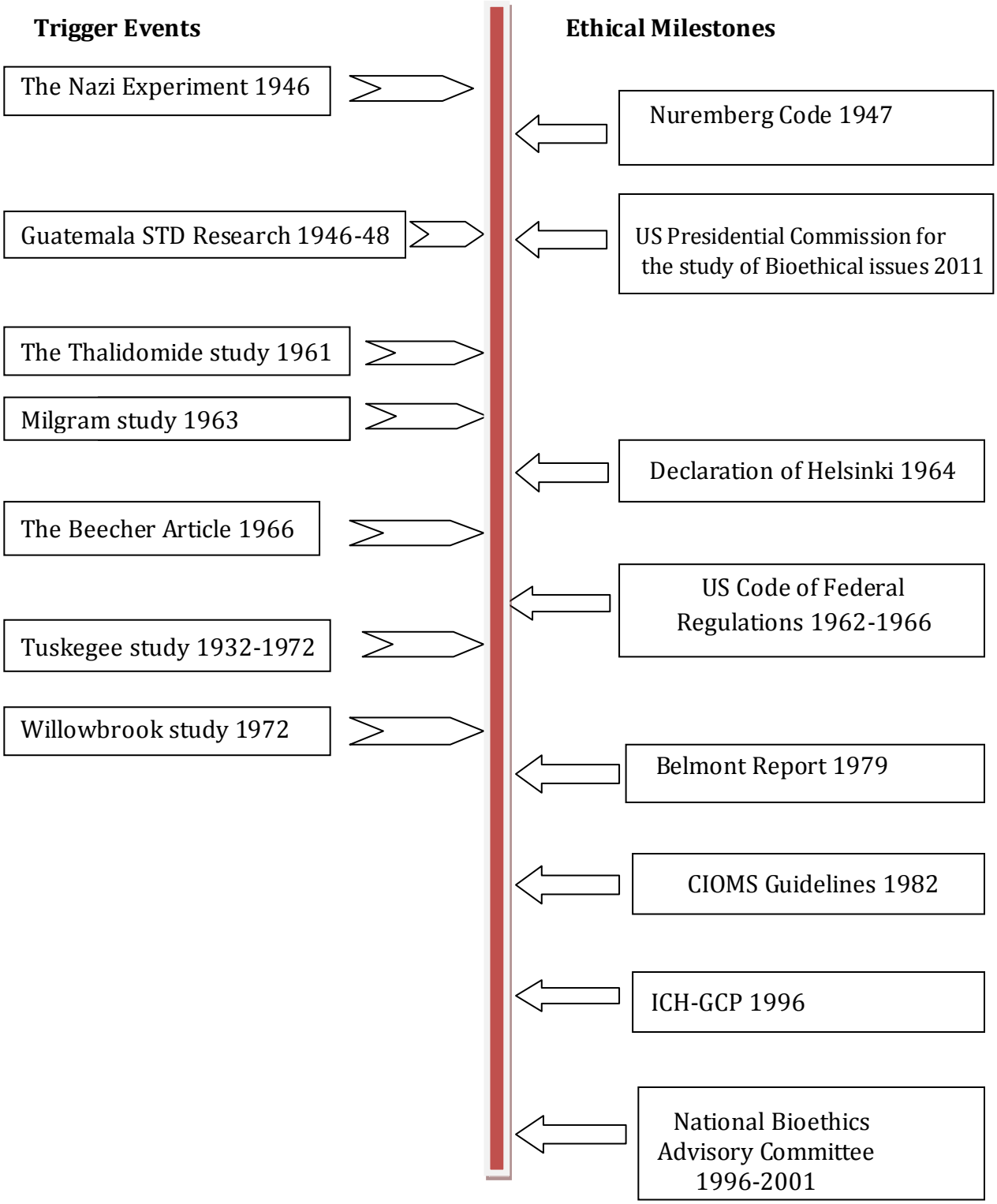
One study involved a placebo controlled trial of chloramphenicol treatment for typhoid fever at a time when the drug effectiveness in dealing with this condition had been established. Of the patients randomised to the 'placebo' treatment, 22.9% died compared to 7.9% of those who received the active drug. The data suggested that 23 patients who died during the study would have been alive if they had received specific therapy (91).

In Willowbrook hepatitis study, 800 cognitively impaired children were deliberately infected with hepatitis virus to determine the natural history of hepatitis and test the effects of gamma globulin (91). Similarly, live cancer cells were injected into human participants in another study to determine the rate of rejection. The patients were merely informed they would receive some "cells". The word "cancer" was completely left out in the information conveyed to them (91).

Sub-saharan Africa has recorded many similar unethical human experimentations and a well known example involved the use of Trovafloxacin during meningitis outbreak in the northern part of Nigeria. It was established that appropriate ethical approval was not obtained before the trial commenced and the parents of the study children were not informed that a new medication would be used to treat their sick children (92, 93).

In all examples mentioned above, not only were the participants unaware of the details of the studies, they were also conducted without the participants' consent. There are numerous unreported examples of other abuses of vulnerable participants in socially and economically disadvantaged countries (94). These situations underscore the need for appropriate standards for conducting research on human participants.

Figure 1: Research Ethics Milestones



In summary, the most crucial goal of informed consent is the need to promote individual informed choices and self-determination. Similarly, consent is said to be informed and voluntary if the following conditions are met:

i. If there is full disclosure of information to a research participant about the nature, risks and benefits of a proposed treatment or research;
ii. If the participant comprehends what is being disclosed;
iii. If the participant is aware of reasonable alternatives to the proposed intervention/investigation;
iv. If he/she is competent to give (or withhold) consent; and,
v. If he/she voluntarily decides (or declines) the said intervention or to be part of the research.

Taken together, an individual is said to have given an informed consent " if he or she is competent to act, receives a thorough disclosure, comprehends the disclosure, acts voluntarily, and consents to the intervention (80)." In the next section, I will examine the ethical guidelines in relation to the doctrine of informed consent.

2.8: Ethical guidelines on clinical research

Moreno et al (78) argue that, "in the context of biomedical ethical analysis, informed consent gives modern medical ethics its special character." Similarly, Robert Young emphasises that informed consent requirement existed largely as a result of various court judgments about the health care provided to specific patients, and through "the establishment of regulatory standards in connection with medical experimentation (82)." This establishment of regulatory standards to guide scientific experimentation will be the focus of discussion in this section.

There are currently many national and international guidelines on research (43, 46). The development of the guidelines or ethical reflection on them has been greatly influenced by documented evidences of the inappropriate use of human participants in research and scientific experimentation. Ethical guidelines are also sometimes called "official policies" or "ethical codes" on research. These guidelines have identified and developed "ethically informed responses to issues on human participation in research" (89). In the section below, I will focus on the aspects of the ethical guidelines that deal with research involving human participants. The following guidelines will be examined in detail:

(i) The Nuremberg Code (1947);

(ii) World Medical Association, Declaration of Helsinki (also known as The Helsinki Declaration) [latest revision, 2013];

(iii) Council of Europe, Recommendation Concerning Medical Research on Human Beings (1990);

(iv) Council for International Organizations of Medical Sciences (CIOMS), International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993); and

(v) Guidelines for scientists: Gambia Government/Medical Research Council Joint Ethics Committee. Banjul, May 2000 [latest revision, 2011].

The selection of the guidelines listed above is influenced by a number of reasons. First, the inclusion of the Nuremberg Code is based on its importance as a historical document and as the first major effort by the medical community to protect human beings against unethical experimentation as exemplified by Nazi physicians during the Second World War.

Second, the inclusion of the Helsinki Declaration is based on its global approval by researchers and medical professionals as the key set of guidelines on biomedical research. It was also the first major endeavour by the medical community to standardise research principles and process. Furthermore, the Helsinki Declaration introduced new principles that were not covered by the Nuremberg Code.

The European Union guideline is relevant as a transnational guideline, spanning across the national and international communities. It also represents the consensus of the European Community on the recommended conduct of scientific research involving human participants.

The guideline by Gambia Government/Medical Research Council Joint Ethics Committee is unique in its history and origin. It represents the position coming from a sub-Saharan Africa country on the need to conduct scientific research in an ethically responsible manner which acknowledges the rights and dignity of the human person. More important is the fact that the code is a legal document which has a binding force on all research efforts as well as on all researchers who wish to carry out scientific research in The Gambia.

2.8.1: The Nuremberg Code

The Nuremberg Code is a set of ten principles that were established in response to the unethical research conducted by Nazi physicians on prisoners during the Second World War. The Code states that certain human experimentations are acceptable provided they are kept within "reasonably well-defined bounds" of the ethics of the medical profession.

For research experimentation to be appropriate, adherence to the ten articles or "basic principles" in the Code is mandatory (39). Below are the summaries of some of the principles that are relevant to this thesis.

The first principle reads: "The voluntary consent of the human subject is absolutely essential" (39). The Code stipulates that this criterion must be satisfied before any biomedical research can be considered ethically appropriate. Researchers must mitigate the risks which participants are exposed. Also, the level of risk involved in any research should not outweigh the benefits of the outcomes of the research. Furthermore, research participants should always be free to withdraw from the research if he or she "has reached the physical or mental state where continuation of the experiment seems impossible'' (39).

The history and authority of the Code are unparallel. The Code was a strong expression that unethical conduct of human research is unacceptable. It was also a firm assertion that "respect for human rights must be considered at every stage of research''(95). The Nuremberg Code re-established public awareness not only in research but also in the way physicians provide care to their patients. The Code also contributed to the formulation of other guidelines such as the World Medical Association's Declaration at Helsinki. I will briefly summarise some of the important guidance in the Declaration.

2.8.2: World Medical Association Declaration of Helsinki

The World Medical Association's Declaration (popularly known as the *Helsinki Declaration*) on "Ethical Principles for Medical Research Involving Human Subjects (41) was adopted by the WMA General Assembly at Helsinki, Finland, in June 1964. Since then

it has undergone several amendments, the last of which was the adoption of 2013 amendment in Fortaleza, Brazil. The Helsinki Declaration is globally accepted as the cornerstone of research ethics because it was the first significant effort by the medical community to formulate ethical principles to regulate itself. The Declaration incorporated many of the principles expressed in the Nuremberg Code. It however added two important principles not covered in the Nuremberg Code. First, investigators must submit their research proposal to "an independent committee, for ethical consideration, comments and guidance." This recommendation led to the development of "institutional review board," which is a local ethical committee saddled with the responsibilities of reviewing research proposals to identify and resolve ethical problems (96).

The second development emanating from the Declaration is the ethical provisions for research on children and other individuals who are unable to consent if there are people who can give "proxy consent" on their behalf. This is a considerable improvement because the Nuremberg Code did not make provision for conduct of research on children who constitute an important population with special research needs (96). In addition to the uniqueness of the Helsinki document, the latest revision in the 26th article of the Declaration raises a very significant statement that is relevant to the objectives of this thesis. The statement reads: "Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information''. This emphasis on giving special consideration to the peculiar information needs of prospective participants with special attention to the methods of information delivery captures the essence of using appropriate informed consent procedures in varying social and cultural contexts.

This statement further underscores the justification to contextualise written consent information to an appropriate method for low literacy research participants. The Helsinki Declaration, like the Nuremberg Code preceding it, has had significant influence on theories of research ethics and official research policies (96). The two documents formed the basis of most subsequent documents on research ethics.

Another vital guidance that shared similarities with them is the World Health Organisation and the Council for International Organizations of Medical Sciences (CIOMS) guidelines (42) on research involving human subjects. I will briefly examine CIOMS guidelines below.

2.8.3: CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects (42)

The Council for International Organisations of Medical Sciences (CIOMS) was formed in collaboration with World Health Organisation and the United Nation Educational, Scientific, Cultural and Organisation (UNESCO) in 1949. The CIOMS guidelines (42) which were first adopted in 1982 have also undergone three revisions. The latest revision of 2002 contains 21 guidelines with commentaries on ethical review, informed consent, vulnerable groups and women as research participants. The opening statement of CIOMS document emphasises the conduct of research in strict adherence with the basic ethical principles: "All research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficence and justice." In particular, respect for persons is said to incorporate at least two ethical considerations, namely:

(a) respect for autonomy which requires that those who are capable of deciding on their personal choices should be treated with respect for their capacity for self-determination; (b) protection of persons with impaired or diminished autonomy which requires that those who are dependent or vulnerable be afforded security against harm or abuse (42).

The fundamental principle of respect for person is the direct practical application underpinning informed consent which strives to protect the rights and freedom of choice of potential participants without coercion, undue influence, inducement and intimidation(42).

Furthermore, two prominent guidelines in the CIOMS document are relevant to the objectives of this thesis. First, Guideline 4 states that investigators should provide prospective subjects with necessary information about research "in the language" that suits the individual's level of understanding"(42). This is particularly essential in view of the reality that in many rural and remote communities, prospective research participants may not be familiar with technical details or information about biomedical research or the vocabularies with which the research information is relayed. In sub-Saharan Africa, for example, due to high illiteracy rates, most rural dwellers will only understand the meaning of research if information is communicated in a local language by a native speaker who is also familiar with the indigenous culture and research concepts (97). The guideline further recommends that investigators should make provision for resources to ensure that informed consent can indeed be obtained legitimately within different linguistic and cultural settings.

Second, the guidelines accord special attention to "research involving participants in under-developed communities. The guidelines emphasise that investigators must ensure: (i) "persons in under-developed countries will not ordinarily be involved in research that could be carried out reasonably well in developed communities, and (ii) the research is responsive to the health needs and the priorities of the community in which it is to be carried out''(42). The two statements consolidate the foundation laid by previous ethical guidelines against the possibility of exploitation of vulnerable individuals from socially and economically disadvantaged communities.

The Nuffield Council on Bioethics (43) also underscores the need for researchers not to exploit research subjects from resource poor societies. In its 2002 report, "The Ethics of Research Related to Healthcare In Developing Countries," the Council states that in developing countries, the social, cultural as well as economic contexts in which research is conducted often differ from those of developed countries. Furthermore, it states that despite the differences in the two environments, researchers have a "duty not to exploit vulnerable" subjects who volunteer for research in developing societies (43).

2.8.4: Council of Europe, Recommendation Concerning Medical Research on Human Beings (98)

The European Union release guidelines on research ethics from time to time. Some are policies on the protection of animals used in experimental and other scientific purposes; scientific research on human gametes, embryos and foetuses and donation of human material; research on gene therapy, recommendation on genetic testing and screening for health care purposes (98).

The guideline lends credence to most of the ethical issues highlighted in the aforementioned guidelines in this thesis. It underscores the importance of seeking "informed, free, express and specific consent" of research subjects; their freedom to withdraw their consent at any stage in the research; the duty of investigators to protect the interests and well-being of subjects; the need to conduct research in ways that will minimise risks and produce benefits for those involved. However, Principle 13 of the guideline is of particular interest because of its requirement that research subjects should "not be offered any inducement which may compromise free consent." Although they may be compensated for "expenses," "financial loss" or "any inconveniences inherent" in research, they are not expected to derive any financial benefit for participating in a research. The statement against financial inducement is designed to guide against people volunteering to be part of a research merely for economic reasons and not out of comprehension of the study information or informed decision made following understanding the information. This implies that investigators must provide prospective research participants with study information in comprehensible manner to make an informed choice devoid of inducement or undue influence. Further supporting this position, some critics have argued that "the ability to be autonomous is likely to be restricted by a feeling of obligation to participate because of benefits received (99)."

2.8.5: Guidelines by the Gambia Government/Medical Research Council Joint Ethics Committee

I will now focus on the Gambia Government/Medical Research Council Joint Ethics Committee operational guidelines (44) for research scientists in The Gambia. The guidelines, which serves as code of research ethics, contains a set of statements that specify the norms and standards for the conduct of research on humans, including norms

and standards for conducting clinical trials with particular consideration for social and cultural contexts in research communities in The Gambia. This represents the joint efforts on the part of the Government of The Gambia and Medical Research Council Unit, The Gambia to regulate the conduct of biomedical research in the country and to ensure that research involving human beings is carried out in an ethically sound and socially acceptable manner. The unique private-public partnership in developing the guidelines that regulate research issues ensures that investigators and other important stakeholders adhere to the requirements of ethical conduct of research.

The guidelines are fashioned to reflect international agreed guidance with additional considerations of social and cultural issues that are prevalent in most research communities in The Gambia. The guidelines provide for a joint ethics committee comprising of fair representation of experienced scientists and lay persons from the MRC and Gambia Government. The guidelines contain statements on safeguarding the dignity of research participants, rights, safety and well-being of all actual and potential research participants. This includes the informed consent processes, risk-benefit ratios, distribution of burden and benefits, and provisions for appropriate compensations, volumes of blood required for different age groups of participants, HIV testing, participation in multiple projects. In evaluating risks and benefits, the guidelines consider only those risks and benefits that may result from the research, as distinguished from risks and benefits of diagnosis or therapy the individuals would receive even if not participating in the research. In addition, guidance is also provided on the use of biological specimens and data with regards to purpose and confidentiality.

The joint Ethics Committee (EC) is mandated to approve research proposals before the start of any study and to monitor the research throughout the study and after its completion. The EC reviews applications only after they have been approved by a recognised Gambian scientific committee such as MRC's Scientific Coordinating Committee (SCC). The main role of the scientific committee is to review the scientific feasibility, which includes the suitability of the investigator, facilities, methodology of proposed projects, and to offer advice on these. Amendments to ongoing, previously approved projects or changes in the informed consent are reviewed by the EC. Substantial amendments to projects need approval by the EC before they can be implemented. Minor changes need only approval by the chairperson in an expedited review process.

The progress of approved research projects is usually monitored by annual reports and a final report after completion of the project. If in the opinion of the EC, the research project involves higher risks on the safety of participants or otherwise, interim reports might be requested. If studies do not commence or are being terminated at premature stages, a final report will requested as well. Members of the EC can conduct audits on study sites whenever deemed necessary. Investigators in clinical trials are requested to provide reports on Serious Adverse Events (SAEs) that occurred in approved studies annually, if not otherwise agreed upon. SAEs that might be related to the study should be reported immediately.

Of particular relevance to this discourse are the challenges in complying with international recommendations of providing consent information in the language understandable by potential participants. In The Gambia, local languages exist only in oral or spoken forms. The languages are not formally taught in schools and do not have

standardised writing formats. Coupled with high level of illiteracy among potential participants, absence of acceptable writing methods makes written translation and back-translation of informed consent document to be practically challenging. In recognition of this contextual issue, the ethics committee reviewed various options available to deliver consent information to participants in comprehensible manner as stipulated by international guidelines. They recommend oral interpretation of the study information by a trained research staff who is a native speaker and is conversant with the prevailing social and cultural contexts in the research communities. The committee further recommends audio recording of the evidence that the field assistant could provide accurate research information to the participants and archive it for future reference (36).

The local guidance is not without its limitations. It potentially gives rooms for variation in oral delivery of crucial research information to participants. This becomes relevant due to the general belief that comprehension of information depends largely on the communication skills of the person providing the information. There is thus a vital need to improve delivery of consent information in a way that will remove the obvious limitations of the current informed consent procedure in The Gambia and optimise the comprehension of the participants.

2.9: Ethical perspectives of informed consent

I will examine the informed consent process from both ethical and practical perspectives; to determine its key components, and specifically to examine the role of comprehension and highlight effective methods for assessing informed consent. To complete this discussion, I will review the strategies and interventions aimed at improving informed consent process in the following chapter.

Informed consent should be an autonomous action, and participant comprehension of consent information is central to it. As highlighted in the earlier part of this thesis, informed consent is a complex concept, but at an elemental level, it comprises at least four domains:

- What a participant needs to know [or understand about a study] (*information*)
- How the study information is relayed to the participant [to maximise comprehension] (*disclosure*)
- The level at which the participant comprehends the disseminated information (*comprehension*)
- The level at which the participant's agreement to join the study satisfies the criteria for decision-making within the purview of competence and voluntariness [given that comprehension of study information is crucial for competence and voluntariness].

Apart from these four key elements, Beauchamp and Childress added a fifth element in their seminal work (80). This was described as 'decision-making' and has been frequently cited in the literature. Similarly, other experts were of the opinion that informed consent encompasses more than the elements highlighted above (100, 101). Greater emphasis is placed on the circumstances and settings where the informed consent takes place (100). Given the central role of 'respect for autonomy' of study participants, the importance and values underpinning informed consent are firmly embedded within the society and in the realities of inter-personal relationships (101). For example, to protect the privacy of potential participants, ethics committees in Western societies sometimes request that the participants should be approached through their physicians.

This is similar to the common practice in Africa where community heads form an important channel to pass study information to potential participants.

Furthermore, experts identified three criteria for evaluating validity of informed consent (102). First, relevant study information must be disclosed to the potential participants to make them understand and arrive at an informed decision without coercion. Second, participant must freely and voluntarily decide to participate. Third, the participant must be legally and mentally competent to give consent. These sets of conditions generate important questions such as: What amount of and which types of information are crucial for informed consent? What does coercion entails? Who should assess the competence of an individual and what is the best way to do the assessment? (102). I will draw on guidance from the literature to address these questions, although many of the aspects are still under intense debate.

2.10: Ethical and legal background to informed consent

2.10.1: Ethical background

Informed consent is the ethical foundation of biomedical research. The idea of informed consent came into existence in the early part of 19th century and criticised the paternalistic notion described in the Hippocratic Oath (103). Following a legal judgement described in chapter two, informed consent became accepted as a concept in medicine in the mid-twentieth century (22).

As extensively discussed in this chapter, ethical principles were developed to guide researchers on the safety and well-being of study participants. Informed consent was a

fundamental aspect of these guidelines. I have chronicled the incidents that led to the establishment of Nuremberg Codes and Helsinki Declaration, each of which specifies the elements of study information which need to be conveyed and understood by participants. But, critics have argued that the volume of information outlined by each guideline may be too much for participants to truly understand them.

2.10.2: Legal position for informed consent

The legal perspective on informed consent has been primarily focussed on informed consent in clinical practice, rather than clinical research. As described in section 2.6, it became operationalised following an introduction of a new judicial guideline in 1972 in the United States. The guideline stipulated that "the decision about whether a patient should have been informed of a risk is based on whether a reasonable person in that patient's position would want to be informed"(104). Before the introduction of this regulation, medical personnel were requested to give opinion on whether standard procedures were followed. These two standards are adopted to varying extent in developed countries (104). Regarding clinical research, the international guidelines discussed in this chapter have largely shaped the legal formulations in many developed and developing countries with some slight variations depending on the social and cultural contexts. As also highlighted above, informed consent has become an integral entity of most national regulations in most countries (102).

2.11: Conceptual framework of Informed Consent

2.11.1: Introduction

The conceptual framework of informed consent originated mainly from bioethics, and especially research ethics (105). Legal and moral approaches of conceptual framework

of informed consent were popularised by Faden and Beauchamp (22). As highlighted above, the legal position focussed entirely on informed consent in clinical practice settings while the moral approach informed most of the guidelines and guidance in clinical trials. In view of the significant relevance of a moral approach in shaping the ethical framework of informed consent, I will focus on this approach in subsequent discussion in this section.

A systematic framework of informed consent has been hinged on three universal ethical principles, which includes respect for autonomy, beneficence and justice (22). Faden and Beauchamp stated that these principles contained adequate information to enable a logical and methodical analysis of the concept of informed consent (22). However, differences of opinion exist among experts about the applications and interpretations of these ethical principles. For example, it is not entirely clear whether autonomy is the main justification for the requirements of informed consent. The general principle has been that when such differences of opinion occur, it is recommended that a logical conclusion should be based by assessing the relative importance of the two conflicting situations (22). Presenting another viewpoint, O'Neill (106) submitted that study participants should be empowered to discern information that are useful to make them arrive at informed decision on participation and also be able to withdraw the consent without having concerns for consequences of their actions. Though seemingly different from widely held consensus, this opinion represents a further application of autonomy.

2.11.2: Autonomy

Generally, respect for person's autonomy is regarded as the basis for right to self-determination, independence, liberty and choice. The practical application of the principle is informed consent. As highlighted above, various meanings have been given

to the concept, the most popular view holds that rights to privacy and principle of truthfulness are embedded within the concept of informed consent (107).

Most researchers place a significant importance on the concept of 'an autonomous individual' who has the competence to act independently to take personal decision on varying options, based on past experiences, values and beliefs. 'Autonomous actions' are however considered to be more fundamental than the person making the decision (107). I will briefly draw some examples to highlight the differences between autonomous individual and autonomous action.

2.11.2.1: Autonomous actions

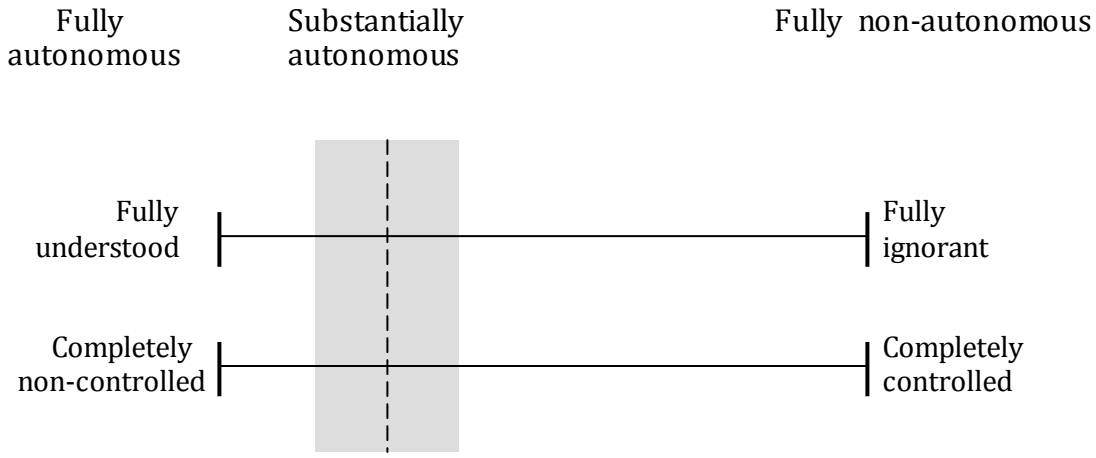
It is crucial to differentiate between autonomous persons and autonomous actions. According to Faden and Beauchamp (107), informed consent is described as "acts of autonomous authorising"; where autonomous actions are usually taken by autonomous persons but can also be taken by non-autonomous persons. Furthermore, ' informed consent and informed refusal' are considered coordinated actions that are targeted at the goal of ensuring that potential participants take these actions in line with the established requirements. This implies that participants could make 'substantially autonomous choices' on whether or not to consent to a research involvement".

An autonomous person is further described as having the capacity for, and often demonstrates, autonomous action which encompasses refusal to align with desirable social norms that operationalise compulsion, and downplay reflective thinking, comprehension and insight. For example, a typical autonomous participant may endorse a consent form without reading the content in a relaxed atmosphere. The same participant may be psychologically disturbed after receiving life-threatening news, and

therefore not be able to take autonomous actions. This implies that being able to take autonomous action in different circumstances is more important than describing an individual as autonomous.

Three conditions have been identified as central to taking autonomous actions (107). These include intentionality, understanding, and non-control. 'Non-control' is defined as voluntariness by some authorities while others simply described it as 'without controlling influences' (107). Rational distinctions exist among these conditions. Regarding 'intentionality', participant actions could either be described as intentional or non-intentional, thus existing as a dichotomous variable. On the other hand, 'understanding' and 'non-control' are continuous variables. A graphical illustration of Faden and Beauchamp's continuum highlights 'understanding and non-control' in the context of autonomous actions (Figure 2).

Figure 2: Degrees of autonomy of intentional actions (107)



'Fully autonomous' is a perfect condition but this is not often encountered in real life settings while fully non-autonomous does not conform to ethical standards. Challenges of interpretation exist in the area regarded as 'substantially autonomous'. Therefore,

'substantially autonomous' would be a realistic balance between the two extremes. No agreed criteria is available to guide on what is considered 'substantially autonomous'. However, clinical and social contexts will dictate the acceptable level of understanding and non-control (voluntariness). To satisfy the three conditions, understanding is central if the participant's decision is to be intentional and voluntary. Therefore, the concept of 'understanding' needs to be critically reviewed.

2.11.3: Understanding

As cited in various parts of this thesis, understanding is a central requirement to take autonomous actions. This underscores the importance of making it the primary endpoint of this study. Nevertheless, critics have argued that 'disclosure' of study information deserves a greater importance than 'understanding'(108). Reason for this is attributed to the difficulties in ensuring the participants' understanding especially the concept of randomisation, placebo, risks and benefits. As full understanding may not be realistically possible in view of varying social and cultural contexts in which clinical trials take place, a substantial level of understanding is needed for participant to make autonomous decision.

Experts have also suggested that meeting the understanding requirement of informed consent is an important step to satisfying the conditions of intentionality and authorisation (107). It is also established that the chance of taking autonomous action is increased with better understanding of study information by a participant (107). Harmonising the views expressed above, it could be concluded that 'substantial autonomous action' is dependent on the condition of 'substantial understanding'.

It will be relevant at this juncture to highlight what 'substantial understanding' represents and what process can be used to achieve it? According to Faden and Beauchamp (107) 'substantial understanding' entails articulation of *important* descriptions that are essential to the participants' decision from their point of views. This may not be exclusive of *all relevant* or *possible* descriptions. 'Relevant descriptions' involve presentation of information in any form that captures the true picture of the context. This implies that a participant could still give consent despite demonstrating a complete lack of knowledge about a relatively minor but relevant requirement of a clinical trial. The concept of understanding is complex, and three main types have been identified (107):

1) Understanding *how* to do something is equated with knowing how;

2) Understanding *that* something is true: This is a statement of idea that understanding could be broken down to the analysis of participant knowledge. For example, understanding that a participant demonstrates when he/she is being requested to give consent to enrol in a trial; and

3) Understanding *what* has been said; for example, what the trial entails.

Therefore, the crucial aspects of understanding that are central to informed consent include understanding *that* a potential participant is being requested to decide participating in a trial, and understanding *what* is communicated about the trial. Experts (107) suggest that the best way to achieve 'substantial understanding' is through disclosure of factual study information after which, more individualised discussions could be held on what the participant requires or desires to know. The disclosure of factual information is influenced largely by regulatory requirements and usually includes: key information that is considered important for decision-making on trial participation; what the experts consider important; and information about the

purpose of obtaining consent as an act of authorisation (107).

Given the central role of individual autonomy in decision-making, the possibility of participants holding or expressing erroneous views has considerable impact and demands that researchers make concerted efforts to correct the misconceptions. In situations where participant understanding is based on false beliefs, then understanding will be 'less than correct', and the action (for example, to consent to a trial) cannot be autonomous (107). Challenges could arise in assessing the veracity or otherwise of participant belief. However, Faden and Beauchamp proposed the use of ' justified' belief standard which encompasses the natural conception of rational belief and declaration that defines common social engagements about what is truthful (107). This suggestion is limited in applicability because of divergent opinions on what constitutes a 'justified' belief.

2.11.4: Non-control or Voluntariness

Non-control is an essential component of theory of autonomous action. This implies that a participant performs an action independently, with no external controls on his/her action. In the literature, non-control has been largely associated with voluntariness, which is also discussed within the context of autonomy. In view of wide interpretations, caution is advised on the usage of voluntariness. Also factors which could influence control need to be identified and evaluated objectively as challenges exist in establishing the level of non-control required for autonomous action (107).

2.11.5: Competence

Competence is a crucial requirement to take autonomous action, and this consequently applies to informed consent. Competence is also described as 'capacity to consent' or 'decision-making capacity' and evaluation of competence has been extensively discussed in literature. Competence is also suggested to cover a wide spectrum, from incompetent to fully competent (107). A reference range is required to determine the point where a participant demonstrates sufficient competence to accept or decline a trial. Thus, for a participant to be competent to make decision about participation, he/she needs to comprehend the study information and its consequences.

Measurement of competence is a challenging exercise. Because of its importance, evaluation of competence is crucial to determine whether a person is considered competent to make the decision about clinical trial participation. The current dominant approach towards decisional capacity is cognitive and rational (109). This implies that participants make choices based on systems of logical assessment. Four criteria of evaluating decision-making capacity were identified as follows: "the capacity to make a choice; the capacity to understand relevant information; the capacity to evaluate the character of the situation and possible consequences; and the capacity to handle information rationally (109)." Other likely approaches include relevance of emotion and mood, meaningfulness to the patient, and promoting the researcher-participant interaction to discuss values (109).

2.12: Other relevant ethical principles

2.12.1: Beneficence

The principle of beneficence is an important principle of research ethics, and focusses on ensuring well-being of study participants. It encompasses four elements namely:
(1) ''one ought not to inflict evil or harm; (2) one ought to prevent evil or harm; (3) one ought to remove evil or harm; and (4) one ought to do or promote good" (107).

Researchers should employ this principle regarding consent to participation in a clinical trial and this extends to prospective participants and the entire community. This implies that participants should be adequately informed and understood the risks and benefits associated with the trials.

2.12.2: Justice

The principle of research ethics stipulates that study participants should receive fair and equal distribution of risks and benefits. This is further underscored by Faden and Beauchamp when they asserted that "a person should be treated according to what is fair, due or owed" (107). The principle of justice should not be ignored even when there is substantial evidence that beneficence and respect for person's autonomy have been met. The special consideration given to justice reinforces the importance of social context when involving vulnerable populations in clinical research. This will be further explained in the next section.

2.12.3: Balancing the principles in informed consent

Before the advent of informed consent, the driving force in research and clinical practice was beneficence model. This changed following introduction of informed consent, with

participant right to self-determination and principle of autonomy taking centre stage. Of all ethical principles, autonomy is regarded as the most important, and should not be undermined irrespective of the contexts or circumstances (110). This position runs contrary to Faden and Beauchamp views. While acknowledging autonomous choice as central to achieving genuine informed consent, they do not support that it should take precedence over other ethical principles (22). They however advocate careful balancing of the principles depending on the prevailing social and cultural contexts in which the clinical research is operating.

Conveying crucial research information to study participants requires considerable communication skills. In most instances, researchers tend to wonder why study participants do not understand research information, but the researchers usually do not ask whether they communicate the information well to the participants. It is to this important aspect that I turn to examine the relationship between informed consent and ethics of communication.

2.13: Informed consent and ethics of communication

Following on Faden and Beauchamp's argument, Manson and colleague (100) also challenged the conventional thinking that the principle of autonomy is the most important requirement for informed consent. They stated that informed consent should be conceptualised as an integral part of ethics of communication. They identified eight crucial aspects of communication that they considered could be easily neglected due to overriding views in the use and transfer of information on informed consent concepts. The eight key aspects recommend that informing should be:

(1) "context-dependent - statements frequently depend on shared knowledge

(2) norm-dependent - relies on acceptable ethical standards

(3) propositional - an invitation to action

(4) rationally evaluable - a communicator can be asked legitimately to explain why the statement made is true

(5) referentially opaque - full meaning may depend on prior knowledge and worldview

(6) inferentially fertile - a simple statement may convey more than words

(7) a type of rational action - most communication is intention-driven

(8) audience-specific'' (100), (p41).

Manson et al (100) used the model of 'conduit' and 'container' to further explain the above aspects of informing. The 'conduit' refers to the medium in which the content of information is conveyed while the 'container' suggests where the information is contained, for example, in the human mind, email, or text. It is possible to transmit information available in one 'container' to another. If this argument holds, there is a chance that some elements of information and communication, such as knowledge, will take precedence over many significant features of communication that rely on medium of transfer of information, such as context and relationships. (100), (p48).

The "medium" aspect of communication presents a platform for acknowledging the interactive or transactional nature of successful communication. This ensures that communication and action of the two parties involved are properly recognised (100), (p61). This model is considered to engender a more realistic and comprehensive justification of informed consent than autonomy-based justifications which focus mainly on disclosure for decision-making. Consequently, informed consent is regarded as a communicative transaction between a researcher and a participant. Based on this

conclusion, informed consent transactions must be guided by the required norms for successful communication: intelligible, relevant, accuracy and truth/truthfulness (100), (p85).

In certain situations, participant decisions may be influenced by his/her background knowledge. This suggests that "certain kinds of communicative action, or reason-giving or forms of respectful behaviour" have occurred; and this is not based entirely on the content of the informed consent disclosure (100), (p32). This proposition agrees with the work of Buccini et al (24) where understanding of informed consent information is said to occur when:

- ''there is evidence that a potential participant has integrated his/her background knowledge with the consent information;
- the evidence occurs at a time when potential research participant decides whether or not to take part in the study; and
- at a minimum, the integrated consent information includes the consent requirements stipulated by national and international ethics regulations'' (24).

These two models underscore the need to make participants have sense of belonging, and to guide their expectations rather than directly influencing their decisions. Faden and Beauchamp (22), (p307) also stressed the need to concentrate on the communication aspect of the relationship between researcher and participant as this will shape the information needs and concerns of the participants. This will consequently create an enabling environment to optimise participant understanding of study information (22), (p307).

Another critical perspective compared the application of principle of autonomy in informed consent to an 'empty ethics' model in which the context or research environment is downplayed and the informed consent process becomes a rational choice model of action (105). The author asserted that informed choices, based on an adequate understanding of the clinical trial information, and consideration of the potential benefits and risks could be practically challenging to achieve, due to social importance attached to the disease of research, participant anxiety and expectations from and trust on the treatment. This is however possible if individual factors are put into consideration when developing the trial information (105).

The above concepts suggest that a good blend of autonomous actions, communicative transactions and individual context is required to engender understanding of research information during an informed consent process. Understanding is also influenced by other components of autonomous actions which include non-control (voluntariness) and competence to consent (decision-making capacity).

As discussed in the early part of this thesis, informed consent theory is predicated on four elements namely: information, disclosure, understanding and decision making. I did not review the theory under these distinct terms in order not to digress from the focus of this thesis which primary endpoint is participant understanding of informed consent information. After providing the historical and theoretical background, I will discuss next the association among the four elements and understanding.

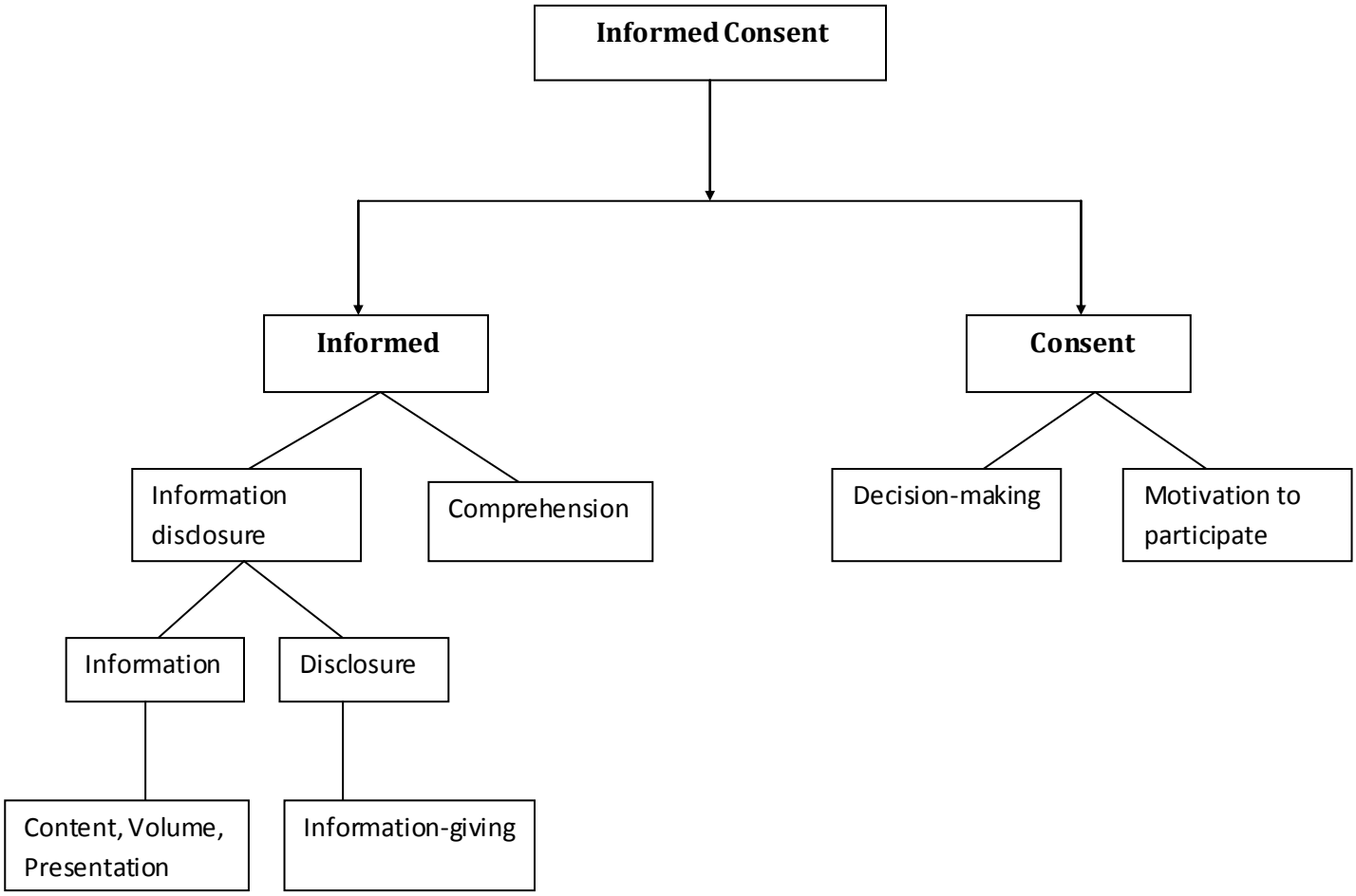
Clearly, the foundation for 'understanding' element is ''understanding" itself. This is also related to the 'information' element, regarding understanding of 'what' is important and relevant (e.g. randomisation, equipoise, voluntariness of consent), and also the 'disclosure' dimension, since factors such as the medium and clinician/participant interaction can have a positive or negative effect on the participant's understanding of the information disclosed. The other requirements for autonomous actions: non-control (voluntariness) and competence (capacity) to consent also demand that participant understands and are central to the *decision making* dimension. Further empirical evidence will now be provided to establish the link between the four elements and theory of informed consent.

2.14: Empirical evidence linking elements and theory of informed consent

2.14.1: Introduction

I will draw much of the evidence from the model proposed by Verheggen et al (111) in their review of informed consent in clinical trials (Figure 3). Two key domains: *informed* and *consent* were the main focus. In the Verheggen model, within the *informed domain*, information disclosure is further divided into two sub-domains: 'information', including content, volume and presentation, and 'disclosure', the information-giving process. Comprehension (understanding) is the third component of the *informed* domain. The *consent* domain consists of decision-making and motivation to participate (Figure 3). To make the model resonates with the four key elements of informed consent, I combine 'decision-making' and 'motivation to participate'.

Figure 3: Informed consent model [adapted from Verheggen et al (111)]



The practical application of this model shows that participants must receive appropriate information that they can understand, to enable them make decisions about whether or not to take part in a clinical trial (111).

Based on the above model, different forms of strategies have been designed and evaluated to aid understanding of informed consent. These interventions were targeted at improving different aspects of the process, with the majority focussing on the information-giving process or on increasing participant understanding. I will discuss the interventions in relation to the model described above.

2.14.2: Information

The sub-domain of information emphasises that content, volume, and presentation are crucial in maximising the participants' understanding of informed consent procedures. The content of participant information in clinical trials is guided by international regulations (41, 42, 58). Apart from the core components of informed consent discussed, and what the researchers consider important, special attention is required for the specific information needs of the individual participant, to ensure all necessary issues are covered during informed consent discussion (22). As highlighted in the earlier parts of this thesis, empirical evidence showed that clinical trial participants had problems in understanding the concepts of randomisation (16, 77, 112, 113), placebo (63), right of refusal (114, 115) , right to withdraw (67, 116) , clinical equipoise (117, 118).

Divergent opinions exist on the amount of information needed to engender comprehension of information among clinical trial participants. The majority of the studies showed that participants expressed satisfaction with the amount of information

they were given (119). Another author (103) reported appreciable level of information about 'side-effects' in the amount that was neither too much nor too little. Participants demonstrated better retention of abridged, simplified versions of informed consent document than those who had the standard, complex versions (120). Similar finding was reported in a US study in which better comprehension occurred among participants with lower literacy (121).

Readability of clinical trial consent forms has also been extensively investigated among participants who reported difficulty in understanding the consent documents written above eighth grade level (122-125). The findings of the studies raised concerns about the need to address the miscomprehension arising from the complex and lengthy informed consent documents.

Researchers have made efforts to present study information in various ways that made the documents easier to read and understand. Linguistic analysis accompanied by revisions of information leaflets led to improvement in readability and comprehension among participants in a Danish trial (126). Higher levels of understanding and increased possibility of giving consent were reported among participants following re-writing the study information in a manner that highlighted positive aspects of the study (127). Tailoring information to specific situations, participant groups, individual preferences or requirements have also been reported to be effective in aiding participant understanding (32, 128). I will discuss further the impact of contextualising study information in chapter four of this thesis, with emphasis on multimedia intervention used in this study.

General awareness of people living in a community about clinical trials has been identified to be of great impact on participant understanding of informed consent (103, 129-132).

Many studies in developed and developing countries have reported poor public knowledge about clinical trials (2, 35, 130, 132). Given that knowledge can be strengthened with prior communication, raising public awareness about clinical trials can improve research communication and ultimately the understanding of crucial research information. There is also evidence that participants with previous knowledge about clinical trials tend to cope better with informed consent procedures than those who are not (103).

2.14.3 Randomisation

Randomisation means that trial participants have an equal chance of receiving any one of the treatment arms in a clinical trial. Randomisation is widely accepted as most favourable in experimental design for assessing efficacy or effectiveness in clinical trials. The concept is however often misconstrued by participants in developed and developing countries (16, 112, 133, 134). In few instances when participants demonstrated some degree of understanding about randomisation, they failed to accept the rationale behind it (77, 112, 118).

In view of the poor understanding and acceptance of this concept, researchers have made efforts to provide more explicit information to improve participant understanding of randomisation (135, 136). Similar efforts have been documented in African settings where supporting materials were employed in communicating the concept of randomisation (14, 137).

These interventions become crucial as there are concerns that inadequate comprehension of the concept of randomisation implies that participants consent to trial participation

without accurate understanding of what the study entails. Extensive studies have been conducted in recent times using a combination of qualitative and quantitative tools to find a better way of communicating the concept of randomisation to participants (138, 139).

2.14.4: Equipoise

The scientific rationale for randomisation is built on an important ethical concept called 'equipoise'. In participant information leaflets, equipoise is usually expressed in terms of uncertainty about which treatment allocation is most beneficial, or about the benefits of a new treatment, drug or vaccine. The concept of equipoise is central to the conduct of an ethically sound clinical trial (140, 141). A mix of qualitative and quantitative methods has been used to explore participant awareness of uncertainty (142). Due to the technical connotation ascribed to 'equipoise', a simplified word 'indifference' was suggested as an alternative term (143, 144). Thus, a participant may exhibit indifference on the inclination towards the expected benefit or risk of a treatment allocation. Also, researchers may not be sure of certain scientific evidence, and yet be unequivocal that participants may favour one treatment over another (144).

Various forms of equipoise have been described in literature. These include: scientific equipoise, also referred to as theoretical equipoise (145), clinical equipoise (143, 146), individual clinician equipoise (144), and patient-centred equipoise (140) , also referred to as individual subject indifference (143).

For scientific equipoise to occur, researchers must be uncertain about which treatment has best efficacy. This differs from clinical equipoise which depends on clinicians'

assessment of efficacy and side-effects of available treatment options and perception of the study participants' suitability for the treatment (144).

Clinical equipoise is generally considered to be of scientific and ethical value, but there were huge concerns that the equipoise is not applicable in most settings. Because a clinical researcher may find it very challenging to be impartial in matters relating to treatment options, participants should be empowered to make objective assessment of treatment options that they consider morally appropriate (144). This is referred to as patient-centered equipoise (140, 143, 144).

2.14.5: Therapeutic misconception

Therapeutic misconception arises when participants believe that every aspect of a clinical trial was designed solely for their benefits (147). It could also result from rejection of clinical equipoise (when participants think that the clinician knows what is best for them) and randomisation (participants think the clinician will select a treatment for them) (142). Therapeutic misconception is very common among participants in developing countries because of inadequate access to healthcare and participants assume that they are allocated to a particular treatment based on their individual medical needs (2, 50, 51, 108, 148). Improving participant understanding to enable acceptance of randomisation and clinical equipoise has been suggested as an appropriate method of correcting therapeutic misconception (32, 149).

2.14.6: Placebo and blinding

A 'placebo' is an inactive treatment that appears like the real study treatment except they do not contain the active ingredient. Using placebo minimises bias in randomised

clinical trials by "blinding" participants and/or investigators on whether a participant receives active or placebo treatment. Several studies in developed and developing countries have reported that participants demonstrate poor understanding of placebo and blinding (15, 16, 63, 115).

2.15: Disclosure

According to Verheggen model illustrated in Figure 3 above, information and disclosure are closely associated. Disclosure is considered an information-giving process which largely depends on the content and volume of information (111). The timing of the process, coupled with the time given to participants to consider and understand the study information before making decision on participation is a crucial factor in clinical trials. Studies have reported that participants require different amount of time to make an autonomous decision about participation. Low-literacy and older participants are known to need more time to take decision, whereas, about 70% of other age groups who had formal education believed that they had adequate time to make decision (113). Another study reported better understanding among participants who took informed consent document home (150). This probably allowed them sufficient time to consider participation and discuss with family members before making decision.

In African settings where communal decision-making is a norm, there is a consensus that family members and significant others should be involved in the information process, although great caution needs to be exercised so that the participants' final decision is not negatively influenced by the misconceptions held by the family members (2, 64, 65).

2.15.1: Medium

The medium of conveying information is vital for participant understanding. Studies have been conducted on a range of methods for delivering study information in different contexts (25, 26, 151-154). A review of 10 systematic reviews and 30 randomised controlled trials conducted in developed countries showed that communication tools in most formats (written, verbal, video, provider-delivered and computer-based) increase participant understanding, but are more likely to do so if structured, tailored and/or interactive (155). As highlighted in chapter one of this thesis, Nishimura et al (13) in a meta-analysis of 22 out of 54 interventions identified enhanced consent forms, extended discussions and multimedia as effective strategies for improving informed consent comprehension. Of all interventions, multimedia tool was considered a promising agent in low literacy settings that needs to be fully explored to establish its effectiveness (156-158). As the intervention of choice in this thesis, multimedia tools will form the focus of discussion in the next chapter.

2.15.2: Interaction

The behaviour and communication skills of the researchers have been reported to be a major driving force in engendering meaningful interactions between participants and investigators (159-161). Participants in an oncology study preferred physical face-to-face discussion of the contents of informed consent document. They also placed a high importance on 'reflective, patient-centered, supportive and responsive' behaviour from the clinical investigators (159).

Similar findings were reported by other authors (160, 161). Despite extensive data existing on the valuable impact of interactive communication, Albrecht and colleagues

reported that many clinical investigators could not engage in effective communication with their patients or research participants (160). Comprehension of information is largely influenced by the skills of the person communicating it. However, researchers usually express concerns over participants' poor understanding of study information, without ascertaining whether they have communicated the information well to the participants.

To address this challenge, the use of a multimedia tool like video was suggested to allow consistency in the communication process. Other interventions have been designed to improve the doctor-patient interaction in clinical trial settings. Most of the communication skill guidance and training have focused on physicians involved in communicating informed consent information to the participants (136, 162-164).

Furthermore, a set of 'communication strategies' based on ethical, linguistic and psychological theories was developed to facilitate discussions with research participants (165). Important and relevant thematic areas were incorporated and described in detail. These included shared decision making (at the participant's preferred level of involvement); sequence of participant's movement during the consultation (including the order of provision of information, the packaging of participant and doctor inputs to promote understanding, ensuring fairness in treatment allocation); type and clarity of the information provided (for example, avoiding jargon, using familiar analogies and summaries); disclosure of controversial and potentially coercive information (such as information that is often not revealed, for example, financial incentives for doctors) (165). Evaluation of these strategies showed an improvement among the

doctors as they used less coercive words and engaged more in shared decision making (166).

There is a scarcity of studies focusing on participant understanding as a primary outcome following intervention on the communication skills of investigators. A Finnish study examined the impact of a one-day communication skills training course on the quality of the informed consent process among physicians and research nurses. The primary outcomes were assessed by administering the Quality of Informed Consent (QuIC) questionnaire to the patients that were being treated by these physicians and nurses and the patients demonstrated significant improvement in satisfaction and understanding (164).

Given the severity of disease and complexity of the available treatments for cancer , a number of practical guidelines were developed to improve the communication skills of oncologists (162, 167). Similarly, Jenkin et al (136) evaluated an intensive training programme using video and interactive exercises among 33 clinicians and 68 research nurses practising in the UK. A video recording of the communication with professional actors and participants was done before and after the interactive exercises. Following the interventions, the participants reported an improvement in their confidence and ability to communicate the research information to their colleagues.

2.16: Comprehension/Understanding

According to Faden and Beauchamp (22) (p301), 'comprehension' could sometimes be referred to as 'understanding' and the words have been used interchangeably in literature. 'Comprehension' or 'understanding' is a difficult concept to define, and this

contributed to a lack of clarity in the use of the two terms and their relationship with 'knowledge'. This is further complicated as empirical studies (15, 63, 116, 133, 168) showed that researchers used terms like 'knowledge', 'remembering', 'retention', 'recall, 'awareness' or 'recognition' extensively in place of 'understanding' or 'comprehension'.

As no clear differences exist in literature among these terms, it may be helpful to examine the definition available in the dictionary. According to Oxford English Reference Dictionary (169), comprehension is defined as 'ability to understand something while 'understanding' is 'the power of abstract thought and intellect' or 'an individual perception or judgment of a situation'. 'Knowledge' on the other hand is described as facts, information or skill acquired through experience or education; and represents a theoretical or practical understanding of a subject.

These literal definitions show that 'understanding' forms part of 'knowledge' and 'comprehension'. Therefore, if 'knowledge' is conceptualised as a 'theoretical or practical understanding of information about randomised clinical trials', the two terms may be accepted to have same meaning. However, the 'ability' component in the definition of 'comprehension' makes it to have greater nuance than 'understanding' or 'knowledge'. Furthermore, the context in which these terms are used could offer more insights into establishing appropriate meaning to the concept. Faden and Beauchamp's theory of informed consent states that "understanding *that* you are being asked to decide about taking part in a trial; and understanding *what* is communicated about the trial, are the key parts of understanding that are important (107).

Consistent with this theory of understanding *that* and understanding *what*, is the position expressed by Minnies et al (170) that 'comprehension' consists of two key components: 'recall' and 'understanding'. And, recall is described as "the function of the access one has to the stored memory of an event and it can be influenced by the salience of information and the passage of time''(171).

Because of the context in which the study reported in this thesis was conducted using quantitative and qualitative approaches to measure 'comprehension' as the primary outcome, I adopt Minnies et al (170) definition of comprehension as comprising of 'recall' and 'understanding' where 'recall' is described as the ability to give correct answers to close-ended and multiple choice questions while 'understanding' is considered as the correct responses given to open-ended questions. This definition will shape subsequent discussions in this thesis.

2.16.1: Interventions to improve comprehension: Extensive work has been conducted on the need to improve comprehension of clinical trial participants on difficult concepts like randomisation, equipoise, placebo and therapeutic misconception (25, 112, 113, 134, 165, 172, 173). As highlighted above, divergence of opinions exist in the definition of 'comprehension and understanding'. As a result of which no uniform definition is available to form the basis of developing a measure of comprehension (174, 175).

Nevertheless, important factors that shape comprehension of informed consent concepts have been documented. Ageing and low education were associated with reduced comprehension of study information (176). Furthermore, participants with advanced diseases tended to remember less information about risk and adverse events of medications than their counterparts who were less ill (177). Participants in phase I clinical trials were also observed to demonstrate poor comprehension (178).

An array of interventions has been developed to improve comprehension of trial participants. These included national guidance and pre-testing information sheets (179), audio-visual patient information (71, 137, 153, 180), telephone based interventions (181), corrected feedback (182), simplified consent forms (183, 184), informed decision making checklists (111) and communication skills training for health care professionals (164).

Despite evidence of improvements in participant comprehension demonstrated by studies cited above, it is inconclusive that a single approach could be sustainable (174, 181). This

will be further discussed in chapter four under various interventions and strategies that have been developed to improve participant's comprehension of informed consent.

2.17: Decision making

2.17.1 Decision making in the context of informed consent

Given that the participant comprehension of study information and decision-making in the context of informed consent to clinical trials require voluntariness and competence to consent, both of these will be discussed in this section.

The evaluation of informed consent to clinical trials is underpinned by the assumption that research participants adhere to the basic principles of rational choice (171). Rationality is defined as "decision-making consistent with the principles of probabilities", where a rational choice is "one in which the option with the highest expected utility is selected"(185). Situating these definitions to clinical trial context, participants are expected to understand the required trial information, consider its benefits and risks, and make the decision about participation based on the best expected value of outcomes (186). However, participant decision-making may be influenced by heuristics and biases rather than their personal values (185). Also, different behavioural and socio-cultural factors are known to shape rational choice model. For example, information obtained from sources outside formal health facilities tend to be laced with cultural and emotional nuances which may alter rational decision-making (185).

The nature and severity of diseases in a clinical trial may influence the participants' decision-making process and information retention. For example, decision-making after a patient receives a diagnosis of life-threatening disease like cancer may adversely affect

information retention and rational decision-making. The time required to make the decision could also be short considering the need to start the treatment for the disease. The quality of decision-making in this context is usually not optimal and decision aids have been suggested to support participants in such situations (187).

2.17.2: Decision aids

Decision aids are interventions developed to assist individuals arrive at a deliberate choice among various treatment options (187, 188). The aids are usually made of simple graphical illustrations of evidence-based information about the trial, to help participants assess the benefits and risks of the trials in the context of their personal values before making the decision about participation (187, 189). The mechanism of actions of decision aids is not entirely known, but their effectiveness is thought to be due to either the facilitation of cognitive strategies or changes to emotional processes (188).

Studies have documented various benefits of decision aids to include less decisional conflict, better comprehension scores, more active involvement of participants in decision making, greater satisfaction with the decision-making process and the decision itself (187, 190, 191).

2.17.3: Shared decision-making

In developed world and some parts of developing countries, the concept of shared decision making has gained ground in randomised clinical trials. This has led to greater involvement of participants in the process of decision-making. A document containing patient information on a cancer trial was compared with a video recording containing information about treatment decision-making. Participants who watched the video

recording demonstrated greater readiness to discuss their treatment preferences and reasons for their choices than those who did not watch the video (192).

Some authorities have argued that shared decision-making is similar to informed consent (80),(p 77-78). This position was criticised by Holmes-Rovner and Wills who stated that equating the two concepts had the potential of legitimising coercive tendencies among researchers (185). Consequently, it was agreed that informed consent should not replace shared decision-making but researchers could adopt it as a method to identify and discuss treatment preferences in the context of participant values (193).

2.18: Voluntariness

As discussed in section 2.10 of this thesis, 'voluntariness' is also referred to as 'non-control' (22). Also, 'voluntariness' is closely used with 'competence' as a requirement for informed consent (p80),(80). Evidence from literature also suggests that 'voluntariness' could be perceived as 'self-control'(194). Various factors could also endanger 'voluntariness' of prospective participants. These include reduced capacity which may arise from poor socio-economic status, family dominance, imbalance in the power of researchers and participants (194). Comprehension of study information as well as its contextual meaning is crucial for potential participants to achieve competence to consent and consequently make a voluntary decision on study participation.

2.18.1 Consent capacity/competence to consent

'Consent capacity' is also described as 'competence to consent' or 'decision-making capacity to consent' in literature. This concept requires potential participants to possess certain qualities to make a valid informed consent. This set of qualities includes the capability:

1) "to understand the research in question

2) to appreciate how the research applies to one's own situation

3) to make a voluntary decision whether to enrol in the study in light of this understanding" (195).

A review of instruments developed to evaluate decisional capacity for clinical research was conducted by Dunn et al (196). This review identified MacArthur Competence Assessment Tools (MacCAT) as a potential tool for such evaluation. It consists of six domains on targeted understanding of disclosed information, and 11 domains on understanding, appreciation, reasoning and expression of a choice. The tool exhibited good psychometric properties with appreciable degree of standardisation of disclosures, flexibility of item content, format, and scoring procedures. However, the tool's main drawback was a lack of generalisability across clinical research contexts (196). Another dimension was added by Robinson et al (142) who identified a potentially important aspect which was not addressed in previous development of MacCAT procedure (197). Robinson et al (142) argued that exploring participant understanding about *why* the trial is being conducted in a particular way (e.g randomisation) could afford the participant the opportunity to express his/her interpretations of the research concepts.

Evaluation of 'capacity to consent' is crucial but empirical evidence has shown that participants who have 'capacity to consent' do not usually give valid consent, hence, it was recommended that evaluation of actual consent should take a higher precedence over assessment of 'capacity to consent' (195). It was further advocated that the best way to determine whether a prospective participant has the capacity to comprehend research information, and to give voluntary consent, is to determine after adequate explanation,

whether they do actually understand and give voluntary consent (195). This argument further supports the rationale for assessing participant comprehension, not competence/capacity to consent in the study reported in this thesis.

2.19: Summary of Part I of the literature review - Informed Consent

Informed consent can be considered as comprising four main dimensions, where participant comprehension is central to:

i. What the participants need to know [or understand] (information)

ii. How that information is conveyed [to maximise understanding] (disclosure)

iii. The extent to which the participant understands the information conveyed (understanding)

iv. The extent to which the participant's consent meets the criteria for decision-making in this context – competence and voluntariness [understanding is essential for competence and voluntariness] (decision making).

2.20: Conclusions from the literature

2.20.1: Conclusion 1

Informed consent is an autonomous choice and requires participant comprehension along with voluntariness and competence. Participant comprehension is considered as understanding *that* one is being asked to take part in a clinical trial, and understanding *what* is communicated about the trial.

2.20.1.1: Study implications

- Participant comprehension is the primary endpoint in the study.
- Apart from comprehension, 'voluntariness' and 'competence' are also assessed through an audio digitised questionnaire. Question items include voluntariness of the participation decision (understanding *that*), understanding of freedom to withdraw from the study, and understanding about what happens if they refuse to participate in the clinical trial.
- Understanding *what* includes concepts identified in the literature as particularly difficult to explain to participants, such as understanding of randomisation, placebo, therapeutic misconception etc.

2.20.2: Conclusion 2

'Substantial comprehension' is essential for autonomous actions, and requires that participants receive and comprehend core disclosure of key facts, as well as important information from their own perspectives.

2.20.2.1: Study implications

- The standard written informed consent document of the parent trial in which the study reported in this thesis was nested, already addresses core information about the trial, according to internationally agreed guidelines and regulatory requirements, before the initiation of the trial.
- The multimedia tool was developed based on the key generic and trial specific information contained in informed consent document of the parent trial.

- The multimedia tool was pilot-tested among potential participants giving them the opportunity to be involved in the development.

COVER SHEET FOR THE PUBLISHED SYSTEMATIC REVIEW INCLUDED IN THIS THESIS

1. For a 'research paper' already published

1.1. Where was the work published? **Tropical Medicine and International Health**

1.2. When was the work published? **June 2014**

1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion: **Not applicable**

1.3. Was the work subject to academic peer review? **Yes**

1.4. Have you retained the copyright for the work? **No, the re-use of the article by author is permitted by the journal and a grant licence for re-use is attached in the appendix**

If yes, please attach evidence of retention. **Not applicable**

If no, or if the work is being included in its published format, please attach evidence of permission from copyright holder (publisher or other author) to include work: **Not applicable**

2. For a 'research paper' prepared for publication but not yet published

2.1. Where is the work intended to be published? : **Not applicable**

2.2. Please list the paper's authors in the intended authorship order: **Not applicable**

2.3. Stage of publication – Not yet submitted / Submitted / Undergoing revision from peer reviewers' comments /In press: **Not applicable**

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

Following my PhD upgrading assessment in October 2012, I realised the potential value of a systematic literature review to my study. Prof Daniel Chandramohan and Dr Emily Webb gave me substantial advice on search methodologies and appropriate rigor. I designed the search criteria in consultation with a colleague who has published many Cochrane reviews. I carried out all of the searches. The colleague, Dr Joseph Okebe double-screened the abstracts and articles as described in the eligibility criteria. I wrote the first draft of the article. All co-authors provided comments on the draft article, many of which I incorporated during revisions to the article. I further revised the article substantially in line with the reviewers' comments

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SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above) ……

Chapter three: Part II-Systematic literature review on informed consent comprehension in African research settings

3.1: Introduction to the chapter

In the foregoing chapter, I established the significance of comprehension as an important component of a valid informed consent. Comprehension of informed consent in various clinical research settings in developed countries was also highlighted. Because the study reported in this thesis focuses on the improvement of informed consent comprehension in a low literacy research setting in a sub-Saharan African country, I will dedicate this chapter to examining informed consent comprehension in African research settings with a particular focus on what African research participants understand about study information, with a view to identifying elements of informed consent which are better or less understood in these settings. This is important to informing the selection of an appropriate intervention which may be tailored to the information need of research participants in low literacy research settings in Africa (198).

3.2: Introduction to the systematic review

International ethical guidelines stipulate that informed consent must be given in a comprehensible manner to a competent person who freely decides to participate after understanding the information (11, 42, 199). However, the amount and quality of study information required to engender comprehension of a potential participant is unclear. There are divergent opinions among researchers on the level of comprehension a potential participant should reach to be able to freely decide (200, 201). In most African settings, the majority of research participants have low literacy, but informed consent documents are designed and delivered in a complex, lengthy manner that makes

comprehension very challenging for the participants (59, 202, 203). In such settings, what constitutes 'satisfactory or adequate' comprehension of informed consent is vague (108, 204). This phenomenon has raised concerns about the quality and ethics of data generated from the increasing number of clinical trials being conducted in these low literacy communities (6).

A previous review of studies conducted in developed countries reported a lack of consensus definition of comprehension and an absence of a standardised tool to measure objectively the adequacy of participant comprehension (15). The authors concluded that a contextual definition of comprehension and systematic design of an instrument could guarantee adequate measurement of participant comprehension (15, 16). This underscores the need to contextualise the definition of comprehension of informed consent information for different research settings as this may inform the development of a locally acceptable, culturally sensitive measure of informed consent comprehension.

I undertook this review to examine how participant comprehension of informed consent information has been defined and measured in clinical studies conducted in sub-Saharan Africa (SSA). This will be a major step toward reaching a consensus definition of informed consent comprehension in African research settings, which in turn will help to design improved informed consent procedures.

3.3: Methods

3.3.1: Literature search strategy: I searched five electronic databases for empirical studies on comprehension levels of different domains of informed consent among participants in SSA. The databases were Embase (1947-2010), Medline (1960-2010),

Global Health (1960-2010), EthxWeb and Bioethics Literature Database (BELIT). To complement these databases, I also searched African Index Medicus (AIM) and Google Scholar for relevant bibliographies and grey literature. The last search was conducted on October 11, 2013. Studies were included if they satisfied the following three criteria:

i. assessed or evaluated participant comprehension of informed consent information;
ii. involved participants who were in clinical studies rather than hypothetical trials;
iii. were conducted in a sub-Saharan Africa country.

The initial search was conducted on Ovid MEDLINE using a combination of medical subject headings (MeSH) and text-words, and then translated into the terms appropriate to Ovid Embase, Ovid Global Health, EthxWeb and BELIT. The African Index Medicus and Google scholar databases were also searched using text-words. The search terms included (*informed consent* OR *consent* OR *informed decision)* AND (*understanding* OR *comprehension* OR *retention* OR *knowledge* OR *awareness* OR *recall)* AND (*clinical trials* OR *clinical research OR randomi*ed clinical trials).* 'Sub-Saharan Africa' was searched using *Africa south of Sahara* OR *developing countries* OR *low-income countries* OR *vulnerable population* OR *underserved population*. To ensure all relevant countries were included in the review, sub-Saharan African countries listed in World RePORT database of global research (205) was used as a guide. Furthermore, to ensure the search was not limited to English language studies, specific Francophone and Lusophone country names like Angola, Burkina Faso, Cape Verde, Cote d'Ivoire, Gabon, Guinea-Bissau, Mali, Mozambique, Sao Tome and Principe and Senegal were also included in the search terms. Specific search algorithms used in each database are presented in Table 1.

Duplicate results from the searches were removed and thereafter, the abstracts of retrieved articles were reviewed for relevance prior to accessing the full paper. I excluded letters or responses to published articles, commentaries and editorials. Conference abstracts that had not been published as full papers were included where the abstracts could be retrieved, provided that the abstracts had sufficient information for either qualitative or quantitative analysis. In situations where a conference abstract has been published as a full paper, the paper was retrieved and the conference abstract excluded. I contacted authors of conference abstracts whose full paper publications could not be accessed to ask if the abstract had been published as a full paper and if not, to seek more information about the study. Of five authors contacted, only one responded by providing the full text paper of the conference abstract. However, the published article provided by the author (20) did not meet the eligibility criteria and was not included in the final analysis.

3.3.2: Data extraction: 245 articles were obtained from the primary search and 64 articles from African Index Medicus and Google scholar. Consistent with PRISMA guidelines (206), an independent reviewer and I screened the searches and applied the eligibility criteria. Of these 309 articles, 192 were removed because they were duplicates. Further 88 articles were sequentially excluded for reasons of ineligibility. Twenty-nine studies satisfied the three inclusion criteria and were reviewed in detail. Figure 4 illustrates the inclusion process. Twenty-three of the studies were conducted in Anglophone countries (14, 32, 48, 63, 114, 115, 137, 150, 168, 170, 207-219); five were in Francophone countries (1, 116, 133, 220, 221) and one in a Lusophone country (222). Similarly, 12 of these studies were conducted in West Africa (1, 63, 114, 116, 133, 150, 168, 207, 215, 219-221), eight in East Africa (32, 115, 137, 208-210, 214, 217) and nine

in Southern Africa (14, 48, 170, 211-213, 216, 218, 222). Despite adoption of official languages of former colonial masters, countries in each sub-region share similar socio-cultural factors that may influence informed consent comprehension (5, 6). Therefore, this review focussed on a regional comparison rather than the adopted official languages.

We (the independent reviewer and I) extracted information on the types and sites of the studies, the sample size, definition of understanding/comprehension as provided by the authors, method and timing of evaluation of the participants' comprehension. Also retrieved were data on participant understanding/comprehension of study information including key concepts of informed consent: study nature and purpose, blinding, placebo, randomisation, voluntariness, rights of withdrawal, benefits/risks and adverse events. We performed a detailed descriptive analysis and head-to-head comparison of study design, timing of informed consent, categories of participants recruited, instruments used for assessments and domains of informed consent assessed in each study (see Table 2).

Because only three authors provided a full questionnaire in their papers (116, 133, 170), we did not analyse the few questionnaires for data extraction. We based our comparison on results provided in the papers included in this review.

3.3.3: Meta-analysis: We conducted meta-analyses of summary statistics from 21 studies (14, 48, 114-116, 133, 137, 150, 168, 170, 207, 208, 210-216, 218, 220) which provided comprehension or understanding levels of participants on different domains of informed consent. Studies which used qualitative methods for assessments of comprehension (n=7) (1, 32, 63, 209, 217, 219, 221) and one with insufficient information (222) were excluded from the meta-analysis. Owing to differences in methods of outcome assessments (understanding scores or percentages of participants

who demonstrated understanding), we generated the proportions of participants who had 'understanding' and 95% confidence intervals (95% CI) for each domain of informed consent. Random effects meta-analysis was used to pool the estimates of proportions across the studies because heterogeneity of study participants, study designs and assessment tools was envisaged. We estimated heterogeneity statistically using I squared statistics, which is the proportion of true heterogeneity that could be explained by chance (223). Expectedly, I squared statistics revealed a substantial heterogeneity in all domains of informed consent assessed (I^2 = 98-99%, $p<0.0001$).

Tables 3 and 4 summarise the meta-analytic results. The meta-analysis was conducted using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Table 1: Search strategy for the systematic review

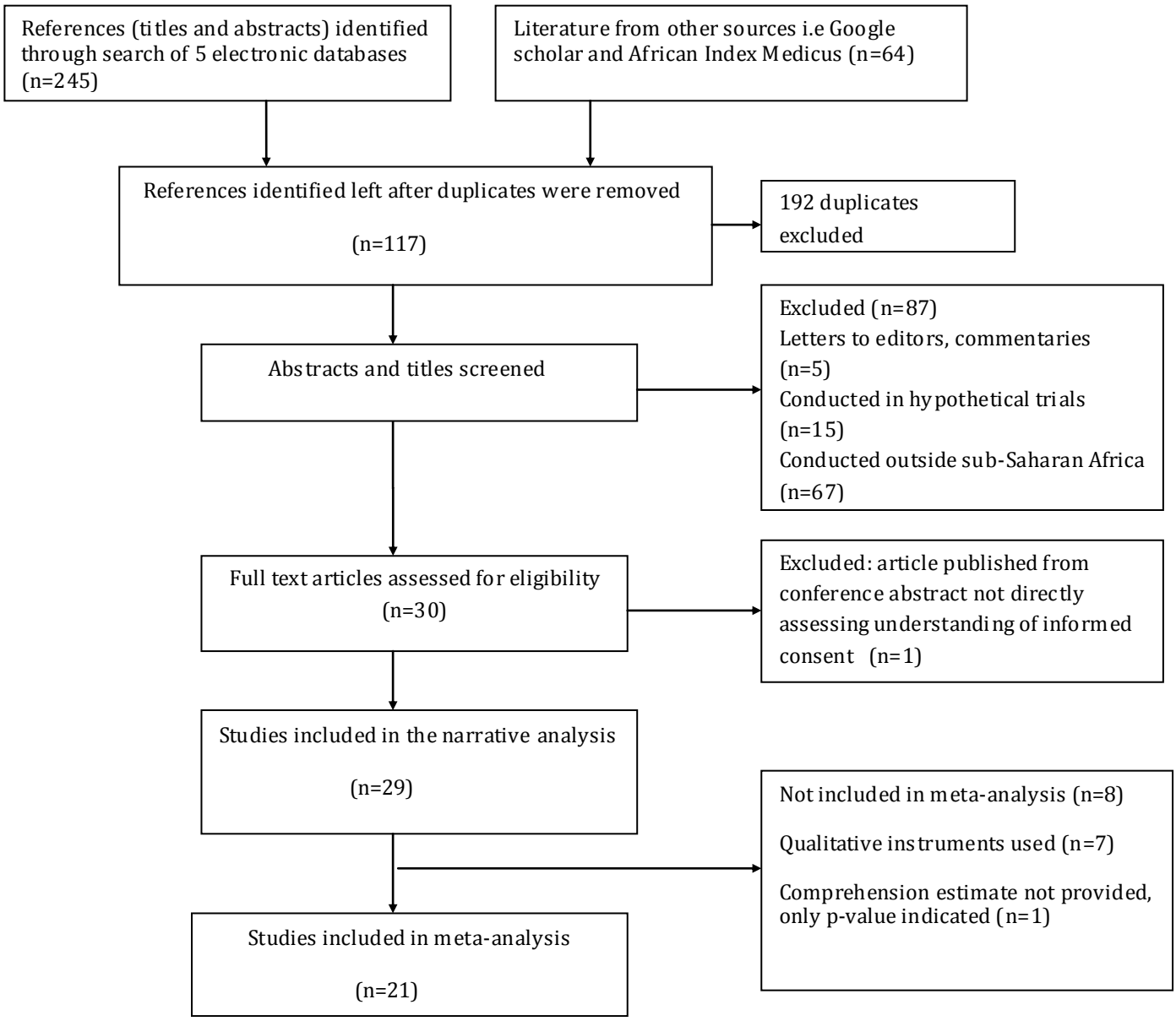
Concept	Search terms	EMBASE via Ovid (1947-2013)	Global Health via Ovid (1910-2013)	Medline via Ovid (1946-2013)	EthxWeb	BELIT via DRZE (1850-2013)
Informed consent	**#1:** (informed consent OR consent OR informed decision). mp.	319882	10179	164307	22586	59923
Comprehension	**#2:** (understanding OR comprehension OR retention OR knowledge OR awareness OR recall). mp.	1318519	158692	662692	880	9630
Clinical research	**#3:** (biomedical research OR clinical research OR clinical trials OR randomi*ed controlled clinical trials OR random allocation trials OR intervention trials). mp.	275353	25182	363991	50885	117927
sub-Saharan Africa	**#4:** (Africa south of Sahara OR low-income countr* OR developing countr* OR vulnerable populations OR disadvantaged populations OR underserved populations).mp. exp Angola/ OR exp Burkina Faso/ OR exp Cape Verde/ OR exp Cote d'Ivoire/OR exp Gabon/ OR exp Guinea-Bissau/OR exp Mali Mozambique/ OR exp Sao Tome and Principe/ OR exp Senegal. mp.	107234	610100	103689	189847	373209
All	**#1 AND #2 AND #3 AND #4**	74	27	104	36	4

Key:

BELIT- Bioethics Literature Database: extensive bibliographic directory of literature in the area of bioethics, containing monographs, academic dissertations, collective works, reference works, books , journal articles, newspaper articles, legal documents , gr ey literature, and electronic document.

EthxWeb- Bioethics Research Library at Georgetown University, USA,
Medline mp: [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier],
Embase mp: [mp=title, subject headings, heading word, drug name, original title, device manufacturer, drug manufactu rer, device trade name, keyword

Figure 4: PRISMA flow chart showing inclusion process of papers for the review



3.4: Results

3.4.1: Study characteristics and design: Twenty-nine studies conducted in 20 countries from sub-Saharan Africa (SSA) examined participant comprehension of informed consent information in clinical research on vaccines, tuberculosis treatment in HIV infected patients, HIV prevention trials, male circumcision scale-up, oral health, Vitamin A supplementation, immune correlates in paediatric age-group and genetic studies of hypertension (Table 2). The number of study participants in the studies ranged from 36 to 5755. Of the studies, 17 interviewed participants close to the time of consent (32, 35, 48, 63, 115, 116, 133, 170, 207, 209, 210, 214, 215, 221, 222, 224, 225); interviews were conducted 1-14 months after participants gave consent in six studies (14, 63, 137, 216, 218, 220) and longer than 14 months in two studies (168, 211); pre- and post-assessments were done in two studies (1, 208) while baseline and repeated assessments of understanding were done in another two studies (211, 226). Six studies interviewed the mothers of study children (1, 168, 170, 207, 208, 219); nine studies interviewed adult male and female participants (32, 63, 137, 150, 212, 213, 216, 218, 220), seven interviewed only female participants(14, 48, 137, 214, 218, 221, 222), two interviewed only male participants (212, 213) and five studies interviewed both parents and adult participants (115, 116, 133, 209, 217).

3.4.2: Measurement tools: Sixteen studies used questionnaires to assess participant comprehension (14, 48, 114, 116, 133, 168, 170, 207, 208, 210, 211, 214, 216, 218, 220, 222); six employed in-depth qualitative interviews (32, 63, 115, 217, 219, 221) and five used both qualitative and quantitative methods (137, 150, 212, 213, 215) and two used community group discussions (1, 209). The majority of the questionnaires used closed-ended response formats. The questionnaires varied significantly in the number of items

and the domains addressed by these items. The authors indicated the number of question items in eight studies (116, 133, 150, 170, 211-213, 216); the number ranged from 3 to 20-item quiz. The items in the questionnaire could be classified into two broad domains: generic and trial-specific questions (227). The generic questions focused on general aspects of research like confidentiality, compensation, rights of withdrawal or refusal (Table 3) while the trial-specific questions focused on individual research related domains like study purpose, study rationale, study procedures, medications, risks, and adverse events (Table 4). A complete questionnaire was included in the appendix in three papers (116, 133, 170). Participants were assessed on several domains of informed consent while two studies (32, 137) focussed only on participant understanding of therapeutic misconception. The format adopted in the semi-structured or in-depth interviews was not clearly discussed in most of the papers except one study (137) which used a standardised interview guide.

3.4.3: Development of measurement tools: Only four manuscripts (14, 116, 137, 222) provided an account of how the measurement instrument was developed. One study (215) mentioned that the questionnaire was adapted from previously developed questionnaires such as Quality of Informed Consent and Deaconess Informed Consent Comprehension Questionnaire. Another study (222) adapted and validated its questionnaire from the Wide Range Achievement test. Ten reported that they translated and back-translated the questionnaires from foreign languages to participants' local languages (14, 115, 116, 150, 168, 210, 211, 216, 218, 222). Significant linguistic diversity made it costly and logistically challenging to translate informed consent documents from

English, French or Portuguese into effective written versions of several local languages of participants in each country (1, 14, 32, 211, 222).

In three studies, participant comprehension was measured by the proportion of correct responses to the question items (116, 133, 168) while other studies assessed proportions of participants who gave correct responses to questionnaires and interviews (150, 216, 218, 220). Additionally, terms like 'understanding', 'comprehension', 'knowledge', 'remembering', 'retention', 'recall, 'awareness' or 'recognition' were used interchangeably without clear definitions. Only one study (170) defined the outcome variables: recall as "success in selecting the correct answers in the question items" and understanding as "correctness of interpretation of statements presented in the question items". There was also no consensus on the time-points to measure comprehension as participants in the studies (15, 115, 116, 150, 212, 213) were evaluated at different times.

3.4.4: Comprehension of informed consent information: This section focuses on the meta-analytic results on 21 studies (14, 48, 114-116, 133, 137, 150, 168, 170, 207, 208, 210-216, 218, 220) and complementary narrative comparison of all eligible studies.

3.4.4.1:Study purpose: Meta-analytic results showed that 65% of a total of 12382 participants in 17 studies (14, 48, 114-116, 133, 150, 170, 207, 208, 211-215, 218, 220) understood purpose of the studies they were involved (95%CI 34.9-89.4%). Furthermore on descriptive comparison, comprehension of study purpose assessed in 18 studies (1, 48, 63, 114-116, 150, 207, 210, 211, 215-222) was markedly high among participants in southern Africa (170, 211-213). This ranged from 88 to 98.7%; while East and West African participants had comprehension rates between 8-47% (210, 215, 217, 218). Most participants in countries with poorer comprehension had a low level of education.

Endemicity of the conditions studied also explained the disparities in the observed responses. For instance, there were marked differences in comprehension of the causes, routes of transmission and prevention of HIV by pregnant women in Cote d'Ivoire and South Africa, with most participants in Cote d'Ivoire demonstrating poor understanding of the study rationale (220, 221). Similar low comprehension was observed in participants enrolled in an oral health study in Nigeria (215).

3.4.4.2: Voluntary participation: About 80% of 3679 participants across eight studies (48, 116, 168, 210, 211, 215, 216, 218) demonstrated comprehension about voluntariness towards participation 95% CI 39.0-98.5%), with perceived medical benefit cited as a main determinant (115, 168, 219). Inadequate access to health care and other poor socio-economic factors in developing countries were reported as strong motives for joining clinical trials (1, 219). Severity of diseases also contributed to the sense of compulsion to participate. In a Kenyan study, only 4% of mothers of seriously-ill children agreed that participation was voluntary; while most participants believed that they would have been chased away if they refused to join the study (217). In contrast, 97% of mothers whose children were less seriously sick in the same study reported voluntary participation during admission; 14% spontaneously reported this on discharge and 59% after prompting (217).

3.4.4.3: Rights of withdrawal*:* Of 4183 participants across 13 studies (48, 114-116, 133, 150, 168, 170, 207, 212, 216, 218, 220), 57% understood right of withdrawal (95% CI 33.3-78.6%) Further descriptive comparison of findings in seven studies (48, 114-116, 133, 168, 220) showed that understanding of right to withdraw from a study was low among most study participants across West African sub-region. In a Malian trial (116), participants believed that leaving before the end of the study would be disrespectful to

the investigators who might consequently deny them medical benefits associated with participation. Their counterparts from a South African (48) study showed better comprehension of their rights to stop participation. Similar trends were observed for rights of refusal to participate. Taiwo et al (215) reported that social status in the study community might positively influence a participant to enrol in a study. One example was cited of a highly educated community officer who enrolled in a trial so as not to discourage other community members from joining the trial. Participants in a Gambian study (219) also expressed the fear of serious, unknown side effects of an experimental vaccine as a major reason for declining to enrol in the study.

3.4.4.4: Confidentiality*:* Meta-analytic results showed that 55% of a total of 1775 participants in four studies (168, 170, 207, 215) did not understand the concept of confidentiality. However, descriptive comparison showed a high level of comprehension in two studies (170, 207) , but in other two studies (210, 215), participants were not aware of how their research records would be kept.

3.4.4.5: Compensation: Across three studies (116, 168, 211) involving 2428 participants, 76% understood compensation (95% CI 39.0-98.5%). Understanding of compensation associated with participation was largely dependent on how the questions were framed and presented to the participants, who generally considered personal benefit a high priority. Reimbursement of transport fares was misunderstood by the participants in two studies (168, 211) as payment for study participation.

3.4.4.6: Risks: About 51% of 3419 participants understood risks involved in study participation (95% CI=32.1-70.2%) in ten studies (114-116, 133, 170, 210, 211, 215, 217, 219). This was found to be better among participants from Southern Africa (170, 211) than their counterparts in West African studies (116, 215).

3.4.4.7: Therapeutic misconception: Only 30% of 753 participants across five studies (114, 116, 215, 216, 220) understood the concept of therapeutic misconception**.** This occurs when participants believe that the study is solely aimed at providing health care rather than generating research data. It featured prominently among West African participants (114, 116, 215, 220) while a South African study (216) reported that a significant proportion of participants recognised they were participating in a research as opposed to seeking medical care.

3.4.4.8: Randomisation and placebo: Of 1633 participants in four studies (115, 116, 133, 216), 47% demonstrated understanding about randomisation (95% CI=13.9-80.9%). Similarly, 48% of 3946 participants in six studies (14, 114, 115, 137, 211, 216) had understanding of placebo (95% CI 0.19.0-77.5%). Descriptive comparison showed that methods employed in explaining the concepts of randomisation and use of placebo during informed consent process influenced participant understanding. Malawian participants (14) demonstrated good understanding of randomisation when a locally designed narrative was used to illustrate the research terms. About 75-78% of these participants comprehended randomisation and placebo; while 10-19% of East and West African participants demonstrated good understanding about the concepts (63, 115, 219).

3.4.4.9: Autonomy/decision-making: Seven studies (116, 212, 213, 217, 219-221) assessed this concept**.** Ninety-nine percent of Gambian participants (219) submitted that parents and village leaders were involved in decision-making. Similar patterns were reported in East and other West African studies (116, 217, 220) while individual decision-making was common in Southern African countries (212, 213).

3.4.5: Predictors of comprehension: In most studies reviewed (14, 168, 210, 211, 215), demographic variables like age and literacy did not show statistical significance but

male sex was reported as the only independent predictor of higher comprehension scores in one study (133). Conversely, primary education and residence in urban areas were predictors of understanding among women (63). Similarly, another study (116) reported higher comprehension scores in most urban participants than their rural counterparts. Among Mozambican participants, numeracy level was significantly associated with comprehension of study purpose and this was independent of respondent's age, income, distance from the hospital and the language of survey administration (222). Moodley et al (216) also reported a positive linear correlation between participants' comprehension scores and their mini-mental state examination scores.

3.5: Discussion

This is the first comparison of participant comprehension of informed consent information in studies conducted across SSA. Previous reviews have either concentrated on informed consent comprehension in developed countries(15) or compared the quality of informed consent between Western and developing countries in Africa and Asia (16).

This review reveals that the methods used for assessing participant comprehension differed significantly. Such variations in methodology limited comparison of findings and raise challenges about how to measure comprehension of informed consent information. Very few studies (14, 222) described the format and justifications for deciding to use a set of question items. A sizeable proportion of the tools were developed ad-hoc for each study without following standard guidelines of instrument development and validation.

The review also identified a lack of a uniform definition of comprehension as studies in the review used the term 'comprehension' to mean 'understanding' or 'recall' or

'retention' or 'knowledge'. It is important to establish a distinction between these terms as it would help in developing a uniform definition for the concept. This review aims to provide an acceptable method for determining how an instrument can be constructed, implemented, interpreted and applied to measure the concept (228).

The domains of informed consent assessed by the studies also vary considerably with little regard to the crucial information that could engender comprehension. There is a need to develop guidelines that define most crucial information relevant for comprehension of informed consent in African research settings as well as the best way this information should be communicated.

Most study participants in this review did not understand the distinction between research participation and seeking medical care. This concept of therapeutic misconception has been documented among participants in resource-poor settings where inadequate access to health care exists (229). This is due to a mix of heavy burden of disease, poor access to health care, poor education, low literacy levels and the overriding impact of illness, suffering, and poverty on decision-making. A National Bioethics Advisory Commission reported that therapeutic misconception does not imply that participants will most likely get adequate clinical care during research, but subsists when participants believe that the sole aim of clinical trials is to provide treatment rather than collect data (11). Consequently, African researchers should strive to harmonise the research of essential medicines with the ethical requirements of making them accessible. Improved access to such care could reduce vulnerability and ultimately improve comprehension of African participants

The time interval between informed consent process and assessment of comprehension in most of the studies were long, some more than 14 months after the trials have ended. Given the background of low literacy among participants, and not being familiar with research terms, it is very unlikely that reliable inferences can be drawn from assessments done after such long periods. There are no existing guidelines on the timing of such assessments as these are likely to be study or context specific.

Availability of the questionnaires in local languages was reported to aid participant understanding in few countries (14, 211). However, this is not always possible as some African languages are spoken and do not have standardised writing formats. Translations and back-translation of informed consent documents are practically challenging in The Gambia for this reason.

A major strength of this review is the combination of meta-analytic results with the narrative comparison of the findings. This provided a robust summary of the findings on informed consent comprehension despite significant disparities in methodologies and heterogeneity of the data. Further contributing to this, participants in hypothetical studies were excluded so that the findings could reflect true clinical research situations as much as possible. Also, studies where participants were legally and cognitively competent were included in this review to remove factors which might confound the findings.

3.5.1: Limitations: Very few of the studies included in this review provided adequate information on the instruments employed to assess comprehension of informed consent.

This did not permit analysis of wordings of the questionnaires to establish what the authors actually explored in their studies. Such analysis could have provided useful insights that could have further contributed to the interpretations of findings of the studies.

Also, findings of this review need to be cautiously interpreted because the majority of the quantitative instruments used in this review contained closed-ended questionnaires, which are known to be an imperfect method of assessing comprehension, because respondents could guess answers correctly or provide socially desirable responses. This could have over-estimated the comprehension levels, thereby leading to inaccuracies in our findings. Studies (14, 230) have shown that requesting participants to explain, using their own words, their comprehension of study information may truly manifest what participants understand.

It could also be inferred that studies in this review examined the "performance" of participants, but apparently did not evaluate the communication skills of the researchers administering the consent; and this plays a key role for comprehension. This may represent an asymmetry, where researchers ask "why participants do not comprehend" but do not ask "why are we not good at explaining crucial information to our participants?" Nevertheless, the representativeness of studies in this review provides a reasonable knowledge base for setting research agenda and plans.

3.5.2: Conclusions: This review confirmed the findings of previous reviews that comprehension of informed consent in Africa settings varies from country to country

with relatively better comprehension among participants in Southern Africa. Tools for measuring participant comprehension are neither validated nor standardised. To overcome weaknesses in the effectiveness of conventional informed consent procedures in African research settings, it is crucial to design adequate tools for improving informed consent comprehension and genuine voluntariness among participants in clinical trials. Such tools should translate the respect for fundamental ethical principles, by taking into consideration local cultural values and constraints.

Furthermore, due to wide linguistic variability that made effective translations of informed consent documents to local languages challenging, appropriately developed tools using orally interpreted procedure with non-verbal support like video and animations, may improve the comprehensibility of unfamiliar research concepts among African participants. Experts who are familiar with the local context and influence of communication and demographic factors on informed consent process need to be involved in the design. This multi-disciplinary approach should harmonise local contextual and behavioural factors, including the expectations of the community, in developing comprehensible consent tools.

Table 2: Summary of studies on comprehension of informed consent information among research participants in sub-Saharan Africa

Authors	Country	Type of clinical research	Sample size	Method of evaluation	Outcome measures	Domains of IC comprehension targeted
Studies in Anglophone countries						
Saidu et al, 2013[207]	The Gambia	Pneumoprotein vaccine trial	1200 mothers of Study infants	Closed-ended study quiz	Comprehension measured by percentage of study mothers who demonstrated understanding	Study purpose, study procedure, Voluntary participation, confidentiality
Oria et al, 2013[208]	Kenya	Knowledge assessment to seasonal influenza vaccination	5284 parents for pre-assessment and 5755 parents for post-assessment	Pre- and post-assessment questionnaires; focus group discussions	Percentage of respondents who had knowledge of the vaccination	Reason for influenza vaccination
Vreeman et al, 2012[209]	Kenya	Community perspectives on informed consent and research participation	108 community members	Community group discussions	Proportions of respondents who demonstrated knowledge	Knowledge, attitude, community consent
Ndebele *et al*, 2012[14]	Malawi	Microbicide trial	36 women	Structured interviews with a questionnaire 8 months after completion of parent trial	Understanding measured by percentage of correct responses to the questionnaire	Randomization, blinding, placebo
Kiguba *et al*, 2012[210]	Uganda	8 clinical trials and 7 observational studies	600 men and women	Semi-structured interviewer-administered questionnaires	Satisfaction with informed consent process measured on a visual analogue scale (0 to 10 arbitrary scores)	Study purpose, study procedures, discomfort/risk, potential benefit, confidentiality, compensation, voluntary participation

Chaisson *et al*, 2011[211]	Botswana	Isoniazid prevention therapy trial	1995 men and women	20-item true/false quiz administered at enrolment, 2 years after enrolment and at subsequent 6 month visits.	Passing scores of ≥ 16 correct responses out of 20 questions	Study purpose, study procedures, randomization, placebo, adverse events, blinding, compensation, voluntariness, risks
Friedland *et al*, 2011[213]	Swaziland	Male circumcision scale-up	953 men	10-item questionnaire prior to surgery; qualitative interviews 1 week post-surgery	Comprehension about key informed consent measured by percentage of correct answers to true/false question items	Study procedure, motivating factor for undergoing the procedure, decision-making, post-operative care and complication
Friedland *et al*, 2011[212]	Zambia	Male circumcision scale-up	290 men	10-item questionnaire prior to surgery; qualitative interviews 1 week post-surgery	Comprehension about key informed consent measured by percentage of correct answers to true/false question items	Study procedure, motivating factor for undergoing the procedure, decision-making, post-operative care and complication
Hussein et al, 2011[214]	Ethiopia	HIV voluntary and counseling testing for PMTCT	422 pregnant Women	Pre and post-test questionnaire adapted from UNAID tool	Comprehension about VCT and PTMCT by percentage of participants who reported understanding	Comprehension and satisfaction about VCT and PTMCT

Vallely *et al*, 2010[137]	Tanzania	Placebo controlled microbicide trial	1146 women had comprehension assessment through checklist while a sub-sample of 99 women completed in-depth interviews	Comprehension checklist administered at screening, enrolment, 12, 24, 40 and 50 week follow-up visits during the trial. In-depth interviews conducted immediately with a semi-structured standardized interview guide after 4, 24 and 52 week follow-up visits	Comprehension and retention of key messages evaluated through the participants' internalisation of the messages and how understanding was incorporated into their beliefs, perceptions, risks and hopes of effectiveness of the gel	Understanding of 3 key messages were examined: i. therapeutic misconception i.e the microbicide gel may not protect against HIV acquisition, ii. that consistent condom use would prevent HIV infection; iii. discontinuation of microbicide gel in the event of pregnancy.
Taiwo *et al*, 2009[215]	Nigeria	Oral health research	113 men and women	Qualitative and quantitative instruments:	Understanding of key informed consent concepts measured by proportion of participants who gave correct responses	Involvement in research, benefits, contacts, confidentiality and voluntariness.
Tekola et al, 2009[32]	Ethiopia	Pilot study to develop appropriate Informed consent Procedure	27 men and 19 women	Qualitative instrument: in-depth interview and focus group discussion	Community understanding of participation in research	Therapeutic misconception
Oduro *et al*, 2008[168]	Ghana	Paediatric trials evaluating immune correlates of protection against malaria	270 mothers	Semi-structured questionnaire administered at the end of the study	Comprehension meas percentage of correct question items	Understanding about selection criteria, stud rights of withdrawal,

Hill *et al*, 2008 [63]	Ghana	Vitamin A supplementation trial	1971 men and women	60 semi-structured interviews and 12 FGDs after consent. Survey done to explore knowledge of treatment allocation.	Participant perception and knowledge of the trial evaluated by correct description of study purpose and whether they received active medication or placebo	Knowledge about study purpose and placebo used in the trial.
Minnies *et al*, 2008[170]	South Africa	Paediatric case-control trial of immune correlates of childhood TB	192 mothers	9-item questionnaire on 'recall' and 8-item questionnaire on 'understanding' administered within 1 hour of consent.	'Recall' measured by success in selecting the correct answers in the question items on voluntary participation, confidentiality, risks/benefits. 'Understanding' evaluated as correctness of interpretation of statements presented in the question items	Question items covered voluntary participation, confidentiality, risks and benefits
Manafa *et al*, 2007[114]	Nigeria	Anti-retroviral trial	88 men and women	Questionnaire with structured and unstructured items	Understanding assessed by selecting correct responses to the question items	Study purpose, participant eligibility, risks/benefits, rights of refusal, right of withdrawal

Marshall *et al,* 2006[150]	Nigeria	Genetic studies of hypertension	307 men and women	3-item survey questionnaire and in-depth interviews at variable time after consent	Understanding of study purpose and voluntary participation measured by the participants' responses to question items in the survey questionnaire and responses by participants at in-depth interviews.	Question items covered study purpose and voluntary participation
Moodley *et al*, 2005 [216]	South Africa	Influenza vaccine trial	334 men and women	6-item semi-structured questionnaire administered. 4-12 months post- trial. Separate questionnaires for treatment and placebo group.	Understanding and perception measured by the participants' correct responses to the question items.	Therapeutic misconception, study purpose, voluntary participation, right to withdraw, randomization, placebo and compensation
Pace *et al*, 2005[115]	Uganda	Paediatric malaria treatment study	347 parents	In-person interview immediately after consent. 60-item questionnaire covering 6 key domains of IC	Comprehension of study information measured by correct responses to question items.	Study purpose, study risks, number of clinic visits, ways treatment were assigned, option of quitting the study

Molyneux *et al*, 2004[217]	Kenya	1 field-based and 2 hospital-based studies involving blood sampling	30 patients admitted to paediatric ward and 1,600 adults and children in the field	Semi-structured interviews, informal interviews and structured observation of the consent process	Perceptions and understanding explored through participant responses	Reasons for collecting blood samples, therapeutic misconception, risks/benefits
Joubert *et* al, 2003 [218]	South Africa	Vitamin A trial for prevention; of mother to child HIV transmission	92 women	Interviewer administered structured questionnaire at a median of 14 months after consent	Knowledge and perceptions regarding the trial measured by proportions of participants who gave correct responses at the interview.	Medications used in the trial, reasons for administering medications, duration of follow-up visits, perceptions about HIV counseling and trial participation
Leach *et al*, 1999 [219]	The Gambia	Paediatric trial of *Haemophilus influenza* type B conjugate vaccine	137 mothers who gave consent and 52 mothers who declined consent	Semi-structured interview conducted in local languages within a week of consent. Interview about recall took place 1 week of joining the study.	Knowledge/understanding and motive for joining the study were evaluated by participantresponses at the interview	Study purpose, risks/benefit, placebo, motives for participation, people involved in decision making were explored at the interviews

Abdool Karim *et al*,1998[48]	South Africa	Peri-natal HIV transmission trial	Evaluation group: 56 women; control group:56 women	Questionnaire administered before and after HIV counseling and consent	Knowledge and voluntariness of participation were measured by participant responses to the question items	Perception about study purpose, implications of positive HIV test result, voluntary participation, rights of withdrawal
Studies in Francophone countries						
Ellis *et al*, 2010[133]	Mali	Phase I malaria vaccine trial	89 men and women; 700 parents	9-item questionnaire administered before consent	Understanding measured by percentage of correct responses to the question items	The questionnaire focused on study design, study procedures, risk, benefit, right of withdrawal, randomisation.
Krosin *et al,* 2006[116]	Mali	Paediatric malaria vaccine trial	163 parents	9-item questionnaire administered within 48 hrs after consent.	Comprehension and recall of key messages were measured by correct responses to the question items	Question items covered study purpose, voluntary participation, compensation, rights of withdrawal, randomization, risks/benefits,

Ekouevi *et al*, 2004[220]	Cote d'Ivoire	Prevention of mother to child transmission trial	55 men and women	Interviewer administered questionnaire at a median of 136 days after consent	Perception and understanding measured by proportions of participants who gave correct responses to the questionnaire.	Rights of withdrawal, knowledge of informed consent process e.g receiving, understanding consent information ,
Coulibaly-Traore et al, 2003[221]	Cote d'Ivoire	Prevention of mother to child transmission of HIV	57 women	In-depth interviews and structured interviews	Percentages of women who showed understanding	Study purpose, randomization, placebo, motivation for participation
Preziosi et al, 1997[1]	Senegal	Pertusis vaccine trial	2071 mothers	Group consensus meetings	Refusal rates before and after introduction of individual informed consent	Study rationale, blinding, adverse events
Study in a Lusophone country						
Ciampa et al, 2012[222]	Mozambique	Association of HIV knowledge with literacy and numeracy levels of rural women	3557 women	Validated measure of literacy and numeracy	Participant scores assessed by correct responses to the validated test	Knowledge of HIV testing, prenatal care, PTMCT

Table 3: Meta-analytic results of studies examining comprehension of 'generic' domains of informed consent

Domain	Studies	Total sample size	Proportion (%)	95% CI
Compensation (n=3)	Chaisson et al, 2011 Oduro et al, 2008 Krosin et al, 2006	2428	76.2	39.0-98.5
Voluntariness (n=8)	Chaisson et al, 2011 Oduro et al, 2008 Krosin et al, 2006 Taiwo et al, 2009 Kiguba et al, 2012 Moodley et al, 2005 Joubert et al, 2003 AbdoolKarim et al, 1998	3679	78.6	63.1-90.8
Right of withdrawal (n=13)	Ekhuoevi et al, 2004 Oduro et al, 2008 Saidu et al, 2013 Krosin et al, 2006 Ellis et al, 2010 Abdool Karim et al, 1998 Manafa et al, 2007 Marshall et al, 2006 Minnies et al, 2008 Pace et al, 2005 Joubert et al, 2003 Friedland et al, 2011 Moodley et al, 2005	4183	56.7	33.3-78.6

Right of refusal (n=6)	Ekhuoevi et al, 2004 Manafa et al, 2007 Kiguba et al, 2012 Moodley et al, 2005 Minnies et al, 2008 Taiwo et al, 2009	1382	48.6	25.6-71.9
Therapeutic misconception (n=5)	Ekhuoevi et al, 2004 Krosin et al, 2006 Taiwo et al, 2009 Moodley et al, 2005 Manafa et al, 2007	753	30.1	4.6-66.7
Confidentiality (n=4)	Oduro et al, 2008 Minnies et al, 2008 Saidu et al, 2013 Taiwo et al, 2009	1775	55.4	11.1-94.7

Table 3 shows that about 80% of study participants across the studies understood compensation and voluntariness while only 30% understood therapeutic misconception, 55% understood confidentiality and less than 60% understood right to withdraw.

Table 4: Meta-analytic results of studies examining comprehension of 'trial-specific' domains of informed consent

Domains	Studies	Total sample size	Proportion (%)	95% CI
Risks (n=10)	Minnies et al, 2008 AbdoolKarim et al, 1998 Oduro et al, 2008 Pace et al, 2005 Krosin et al, 2006 Vallely et al, 2010 Ellis et al, 2010 Taiwo et al, 2009 Marshall et al, 2006 Ndebele et al, 2012	3419	51.3	32.1-70.2
Benefits (n=5)	Oduro et al, 2008 Taiwo et al, 2009 Pace et al, 2005 Vallely et al, 2010 Friedland et al,2011	2829	72.1	42.0-94.0
Placebo (n=6)	Moodley et al, 2005 Vallely et al, 2010 Chaisson et al, 2011 Pace et al, 2005 Ndebele et al, 2012 Manafa et al, 2007	3946	47.9	19.0-77.5
Blinding (n=4)	Chaisson et al, 2011 Ndebele et al, 2012 Pace et al, 2005 Vallely et al, 2010	3524	68.8	55.7-80.6
Randomisation (n=4)	Ellis et al, 2010 Krosin et al, 2006 Moodley et al, 2005 Pace et al, 2005	1633	46.6	13.9-80.9
Study purpose	Saidu et al, 2013 Minnies et al, 2008	12382	64.8	34.9-89.4

(n=17)	AbdoolKarim et al, 1998 Pace et al, 2005 Marshall et al, 2006 Taiwo et al, 2009 Krosin et al, 2006 Joubert et al, 2003 Ekhouevi et al, 2004 Ndebele et al, 2012 Friedland et al, 2011 Friedland et al, 2011 Ellis et al, 2010 Manafa et al, 2007 Chaisson et al, 2011 Hussein et al, 2011 Oria et al, 2013			
Study procedure (n=13)	Chaisson et al, 2011 Saidu et al, 2013 Oduro et al, 2008 Ellis et al, 2010 Manafa et al, 2007 Taiwo et al, 2009 Kiguba et al, 2012 Pace et al, 2005 Friedland et al, 2011 Friedland et al, 2011 AbdoolKarim et al, 1998 Minnies et al,2008 Joubert et al, 2003	6985	72.9	55.2-87.4

Table 4 shows that about 50% of participants across various studies understood placebo, randomisation and risks while higher proportions (about 70%) understood benefits, blinding and study procedure.

3.6: Summary of Part II of the literature review: Informed consent comprehension

Considerable challenges exist regarding definition of informed consent comprehension and its various elements. These challenges result in lack of uniformity in measuring and evaluating it in practice. Nevertheless, participant comprehension is central to most approaches of measuring informed consent. Different strategies are available to measure participant comprehension but none specifically address the issue in low literacy settings in Africa.

3.6.1: Study implications:

Participant comprehension is used as the primary measure of evaluation of informed consent in this thesis. There is no consensus in the literature about what constitutes participant 'knowledge' and 'comprehension'. No clear distinction was made and researchers used various terms interchangeably.

i. For the purpose of the study reported in this thesis, I adopt the definition which encapsulates 'recall' and 'understanding' as key components of 'comprehension'. This definition informs the development of the audio digitised questionnaire which encompasses 'recall' as ability to give correct answers to closed-ended and multiple choice questions and 'understanding' as the correct responses given to open-ended questions.

Chapter four: Literature review on interventions developed to improve informed consent comprehension

4.1: Introduction to the chapter

In chapters two and three, the challenges of poor comprehension of informed consent were discussed in varying social and cultural contexts. I also highlighted many strategies that have been suggested to improve participant comprehension of study information. These interventions have concentrated on modifying the content of informed consent documents. For example, expressing the information in lay language, increasing the font sizes of the letters to make it more legible, shortening the length of informed consent documents or supporting the process with learning materials such as decision aids and simulations (e.g. vignettes or case studies) (25, 71). In this chapter, I will provide further empirical evidence on the development and application of various interventions designed to improve comprehension of informed consent.

Systematic reviews on the interventions designed to improve informed consent comprehension was pioneered by Flory and Emmanuel (25). In the systematic review, hypothetical or simulated studies were included, with the main outcome of interest being improved understanding. A total of 42 studies were included: 12 reporting multimedia interventions; 15 on enhanced consent forms; five on extended discussion; five on test/feedback interventions (where participants were tested on the information they received and received feedback on incorrect answers); and another five were classified in a miscellaneous category (25).

Three of the 12 trials (25%) on multimedia interventions and six of 15 trials (40%) on enhanced consent forms showed significant improvement in the study participant understanding. Of five trials on extended discussion, three (60%) showed significant improvement in understanding (all $p<0.001$) and the remaining two (40%) showed trends toward improvement ($p=0.054$ and $p=0.08$ respectively). All five trials using test/feedback interventions showed significant improvement in understanding. Similarly, the trials categorised under miscellaneous interventions had varying impact on understanding.

Major concerns were raised about the quality of five of the six trials that used enhanced consent forms thereby limiting their practical relevance. Also, the trials which adopted test/feedback intervention were flawed because of the possibility that the authors might have reported repetitive memorisation for improvement in understanding (25). Because all studies included in the review were simulated scenarios with unknown relevance to a real situation, the authors recommended that further studies should avoid using hypothetical scenarios (25).

Improved participant understanding has been linked to increase in recruitment or participation rate in some clinical trials. For example, McCaid et al (231) in a systematic review of interventions to increase participation of cancer patients in randomised controlled trials identified eight studies that assessed interventions for improvement of different aspects of the informed consent process and its effect on study participation. In one of the studies included in the review, Donovan et al (232) used qualitative method to

successfully increase recruitment (from 40% - 70%) in a prostate cancer treatment trial by changing the nature and emphasis of information and presentation to patients.
In-depth interviews were conducted to explore patient interpretation and understanding of study information, and tape-recorded recruitment appointments to enable scrutiny of content and presentation of study information by the researchers.

Analysis of the qualitative data showed that recruiters had difficulty discussing 'equipoise' and presenting treatments equally. They unknowingly used terminology that was misinterpreted by the participants. This information was then used to determine changes to content and presentation of information, namely order of presenting treatments to encourage emphasis on equivalence, avoidance of misinterpreted terms, redefining of the non-radical arm, and a more convincing presentation of randomisation and clinical equipoise (231).

To avoid coercion, the authors (231) concluded that research involving interventions targeted at improving informed consent process as a means of increasing trial participation should not be considered in isolation from the quality of the informed consent process.

In a recently published systematic review, Nishimura et al (13) identified 54 interventions from 39 articles. Meta-analysis was conducted on 22 of the interventions. These were classified into multimedia, enhanced form, and extended discussion categories. Meta-analysis of multimedia approaches was associated with a non-significant increase in understanding scores (Standardised Median Difference [SMD] = 0.30), 95% CI:

-0.23- 0.84); enhanced consent form, with significant increase (SMD= 1.73, 95% CI: 0.99 - 2.47); and extended discussion, with significant increase (SMD= 0.53, 95% CI: 0.21- 0.84). From the review, 31% of multimedia interventions showed significant improvement in understanding; 41% for enhanced consent form; 50% for extended discussion; 33% for test/feedback; and 29% for miscellaneous interventions. Multiple sources of variation existed among included studies, namely control processes, the presence of a human proctor, real versus simulated protocol, and assessment formats (13).

The authors concluded that enhanced consent forms and extended discussions were most effective in improving participant understanding; although, multimedia has potential of achieving similar result if the methodological variations in the included studies are addressed (13).

4.2: Introduction to multimedia consent tool

Multimedia was identified in the previous chapters of this thesis as a valuable option that needs to be further explored for enhancing comprehension of informed consent in low literacy clinical trial settings. This section will provide more detailed information about multimedia tool and give insights into the rationale for using it as the intervention in this thesis.

Multimedia intervention falls under the category of audio-visual methods which have been used extensively in clinical care as a tool to educate patients for improved medication adherence, and also to assist patients in decision- making.

The impact of this intervention has been investigated in many studies (157, 233). Most of these examined knowledge/understanding, patient satisfaction, quality of life, management of symptoms and side-effects, anxiety levels, compliance, behaviour, and the effect on the decision as outcome measures (152, 157, 234-236).

For the purpose of this thesis, I will highlight different types of multimedia, their content and presentation of information, and their use as a tool to improve comprehension and to achieve more genuine informed consent in clinical trial settings. Limitations of previous research in this area will also be discussed prior to summarising the relevant literature.

4.3: Types of multimedia

4.3.1: Format

Multimedia includes a variety of formats for the delivery of research information to participants. The most extensively used and studied is video, although there is evidence in literature involving use of CD-ROM, DVD, interactive computer programmes and other multimedia packages. Other novel approaches include power-point slide shows to enhance understanding of trial information among cognitively impaired participants (237). In another study, a complex surgical procedure involving flexible sigmoidoscopy was illustrated with visual aids to enhance public understanding of the need for cancer screening (238).

The rapidly growing information technology has made it possible for the various multimedia packages to be interactive and customised for the needs of research participants. Example included a nutrition programme that was computerised and

customised for a group of company workers (239). Despite the enhanced understanding achieved through the use of interactive computer systems and web based packages, considerable financial and logistical constraints have limited its general applicability (240).

4.3.2: Comparison of approaches

Different multimedia approaches have been evaluated to determine the impacts on participant knowledge, understanding, behaviour and decision making. In a randomised controlled trial , 226 patients were randomised to receive research information on prostate cancer testing either through video or an internet-based format (241). Significant increase in knowledge was demonstrated by participants in both groups but those in video group were more likely to refuse participation (241).

Among 60 patients preparing to undergo dental extraction, Ader et al (242) compared the effects of interactive video disc, video tape and surgical information only on patient knowledge and satisfaction. Those in video tape group had more knowledge about the procedure while those who watched the information through video disc were more satisfied with the amount of preparation before the surgical procedure (242).

Similarly, Emmett et al (243) in a longitudinal study compared a decision analysis tool with the combination of written and video patient information in newly diagnosed hypertensive patients. After three years follow-up, no significant difference was observed in the blood pressure control and medication adherence of the two groups. This implies that video patient information may not sustain study information for a long period.

Knowledge about study information was assessed by comparing four methods of presentation namely standard written consent, video, computer program and booklet among three groups of 441 participants. The findings showed that participants in computer and video groups demonstrated better understanding compared with those in booklet and standard consent procedures. Furthermore, video was reported to elicit better comprehension than the computer format (19).

Furthermore, the effectiveness of video presentation was investigated among three groups of 90 medical students. All students had a verbal presentation about cataract surgery and one group received additional information through a video and the other group received schematic drawings on the surgical procedure. The results showed that the students who received additional video information demonstrated better knowledge and understanding of the facts and risks of cataract surgery (244). Similar improvement in knowledge and understanding was reported in a non-randomised trial on the use of audio-visual patient information among patients with end-stage renal disease (245).

Despite overwhelming evidence highlighted above on the effectiveness of multimedia delivery of research information to participants, critics have argued that the method is particularly more expensive and time-consuming to produce than the written method. Low-cost educative video using digital imagery was reported to improve patient comprehension on radiotherapy in similar way as the computer-based video production that required more time and cost to produce. It is generally believed that video and CD-ROM are cheaper and more flexible to produce than interactive computer packages (246).

Among non-literate populations of Guarani Indians, audiovisual documentation of oral consent was successfully obtained in a genetic study and had subsequently become a standard practice for clinical research carried out within the illiterate population(153). This finding underscores the key benefit of audio-visual patient information among low and non-literacy populations, for whom crucial research information can be simplified using graphical illustrations that are sensitive to social and cultural contexts. Other studies have also supported the clear benefits of video in improving comprehension of and satisfaction with study information among low literacy and minority groups. Thomas et al (247, 248) reported that oncology patients who belonged to minority ethnic groups demonstrated better understanding with satisfaction and less anxiety/depression after watching additional video information on the treatment modalities available for them. Similarly, culturally appropriate video intervention was reported to improve the understanding and uptake of colorectal screening among low-income, less acculturated minority group of female Chinese Americans (249).

A randomised controlled trial involving 1653 black and Hispanic residents in New York evaluated the impact of video information on knowledge, attitudes and behaviour toward uptake and use of condoms. Participants were randomised to receive study information either through video viewing or video viewing plus an interactive group session. Both video groups demonstrated improved knowledge, attitudes and behaviour with higher rates of condom acquisition while the group receiving the interactive group session in addition to the video had higher levels than the video alone group(250). Similar findings were reported in another study among 3348 African American and Hispanic patients (251).

Apart from the benefits documented in clinical research, multimedia patient information, particularly video has also been shown to be effective in a variety of areas in health care, most notably in health promotion, screening, surgery and rehabilitation. For example, video information has been used as a decision aid in cardiology (252), oncology (165), screening (235, 253), surgery (254) and general practice for hypertension and benign prostatic hypertrophy (255), eliciting benefits and improvements in knowledge.

The effectiveness of video intervention has been extensively investigated in cancer settings. Many of the studies underscored the importance and benefits of tailoring the video to the information needs of the participants (256-258). McPherson et al (259) conducted a systematic review of randomised controlled trials of effective methods of information delivery to oncology patients and their families. Ten studies which evaluated methods of information-giving where the intervention was aimed primarily at educating were included. Outcomes directly related to the intervention were objective measures of knowledge acquisition, recall and understanding, and the use of educational resources. The greatest improvements were seen in relation to knowledge and understanding. The review was limited in that it focused on studies that included patients with heterogeneous cancer types and excluded studies focussing on just one type of cancer (259).

Gysels and Higginson (258) also reviewed the literature to examine the impact of interactive technologies and videotapes on patient education in cancer care. They included nine randomised controlled trials from America, Australia, Canada and UK These studies evaluated interventions providing patient education to improve knowledge, satisfaction, decision making, treatment choice or care management by using videotapes or computer programmes in cancer care. Hypothetical choices,

informed consent to take part in a trial, screening for cancer prevention, and paediatrics cases were excluded. Three of these studies involved video and six involved computer technologies. Of the three video studies, two involved consent to a procedure (247, 260), while the other was designed to promote shared treatment decision-making (165). The review supports the use of video as a communication aid for patient education in cancer care (258).

In summary, substantial evidence exists in the literature on the usefulness of multimedia delivery of study information, although, these studies are few or almost non-existent in Africa where the need is high. With the advent of rapidly growing digital technology, video, CD-ROM and DVD have become cheaper to produce, readily available and more manageable even in Africa. This development has made evaluation of the effectiveness of a multimedia informed consent tool to be increasingly crucial in low literacy research settings in Africa.

4.4: Content of multimedia tool

Adaptation of multimedia information to suit specific social and cultural contexts is a crucial aspect of using the tool. The benefits of this will be discussed below.

4.4.1 Tailoring information

Evidence exists that customising study information to the specific needs of participant groups or interventions is helpful. However, nature of study and characteristics of participants require varying levels of contextualisation of the information, thereby making comparison of results challenging.

A meta-analysis of 20 studies evaluating the efficacy of tailored interventions reported that, in half of the studies, tailored interventions were more effective in promoting health behaviour than standard interventions (261). The tailored intervention was further assessed among 2831 American factory workers and the intervention was reported to increase their hearing protection (262).

Similarly, 10 systematic reviews of randomised controlled trials and 30 additional clinical trials reported that communication tools in written, verbal or multimedia formats were more likely to increase patient understanding if they were structured, tailored and/or interactive (155).

A personally tailored colorectal cancer screening programme (interactive multimedia via computer) was compared with a non-tailored 'electronic leaflet' (also available as an interactive multimedia programme via computer). Increased self-efficacy, less perceived barriers, and a greater state of readiness for screening were reported among participants in the tailored group (263).

Petty et al (264) recruited chest physicians from 49 exercise segments, and selected three different intervention times for their patients receiving customised video on pulmonary rehabilitation. This group of patients was compared with another group who received a standard (non-customised) video, and a control group who received routine care from their physicians. Patients in the customised video group demonstrated an improvement in quality of life, reduction in fatigue, and an increase in exercise compliance compared with the other two groups. Patients in the standard video

group showed an improvement in exercise compliance compared with the control group(264).

Contrary findings were reported in a study evaluating the effect of a customised and non-customised audiotape on radiotherapy in breast cancer management. Although, participants generally preferred the customised tape, there was no significant difference in the knowledge and perception about the information between the two groups of patients (265).

4.4.2: Framing information

The impact of framing information contained in multimedia is not clear, although unequivocal evidence exists for framing and manipulating written information (232). Empirical evidence from in-depth interviews showed an almost two-fold increase in consent rates in a hard-to-recruit prostate cancer trial. This included modification of the format of presentation of clinical trial information, avoidance of misinterpreted terms and changes to the sequence of treatments (232).

In another study, Lewis et al (266) reported that framing the information for mammography screening had no effect, but that the video was effective in all groups in correcting misconceptions and improving knowledge. This finding was corroborated by Llewellyn-Thomas et al (267) who also showed no effect of framing in the patients' reported preferences for participating in treatment decision-making and for trial entry.

However, inconsistencies were observed in patient views following framing of trial information on hormone replacement therapy (HRT) (268). Two different videos were

evaluated. In the first video, information was framed to emphasise the current state of uncertainty about the costs and benefits of HRT; and the same information was framed to offer explicit numerical detail about currently known facts in the second video. Participants receiving information from the second video were more likely to hold stronger views about whether or not they would take HRT, and were more likely to refuse entry to the trial (268). A major limitation was that the study was simulated and the findings may not reflect real-life decision.

In summary, tailoring information has been shown to be a useful approach in terms of understanding, and also in changing behaviour. However, the usefulness of framing in multimedia information is unclear from the literature and further research is warranted.

4.5: Use of multimedia consent tool in clinical trials

4.5.1: Clinical trials in health care

Beneficial use of multimedia tool has been more extensively documented in clinical care than in clinical trials. A translation of similar benefits has been recommended in clinical trials. Informational videos have the potential to enhance the informed consent process for clinical research, and improve understanding of difficult concepts such as randomisation and placebo (269, 270). Following focus groups and key informant interviews, a prototype multimedia tool was developed for three groups of patients with depression, breast cancer and schizophrenia (269). The multimedia approach was well accepted by the patients, but the impact on their understanding of research concepts was not evaluated.

A Cochrane protocol was planned to conduct a review on the impact of providing an information video, alone or in conjunction with standard forms of information provision

to potential clinical research participants, compared with the provision of standard forms of information alone. The outcomes of interest included understanding, satisfaction, recall of study information, level of anxiety and participant decision (270). The findings of this review are yet to be published.

Ryan et al (26) in a similar Cochrane review examined the effects of audio-visual presentation of study information through internet, DVD or video cassette alone or in addition with standard information. Three randomised controlled trials (RCT) and one quasi-RCT involving 511 people from USA and Canada were included in the review. The results showed that audio-visual interventions did not consistently increase the participants' levels of knowledge/understanding (assessed in four studies), although one study showed better retention of knowledge amongst intervention recipients. Also, it was reported that an audio-visual intervention may transiently increase people's willingness to participate in trials (one study), but this was not sustained at two to four weeks post-intervention. Due to the uncertainty about the effects of audio-visual interventions, further research in term of high-quality randomised controlled trials are recommended (26). The findings of Ryan et al (26) are entirely similar with a recently published Cochrane review involving 1884 participants from 16 studies. Nine of the studies included participants considering real clinical trials, and eight included participants considering simulated clinical trials, with one including both. All studies were conducted in high-income countries (271).

The work of Flory and Emmanuel (25) has earlier been cited in many parts of this thesis. The systematic review examined interventions to improve research participant understanding in informed consent in clinical research from 1966 to 2004. 12 of the

trials included in the review reported multimedia interventions. Five of these trials showed benefits in understanding, including two studies which showed delayed improvement in retention of knowledge several weeks after the consent procedure, but not immediately after disclosure (29, 272).

The reviewers highlighted that multimedia tool is useful outside the clinical trial settings probably because the informed consent process is already formalised through regulatory requirements. They also felt multimedia interventions might not positively influence the disclosure process (25). As previously highlighted, the review was flawed by the terms used in their search strategy, as many important relevant papers were missed. The review also focussed on simulated trials which shared little or no semblance with realities of clinical trial situations.

Ten years after this review was published, the benefits of multimedia tool in the clinical trial settings have been reported. These will be discussed next.

Wirshing et al (182) developed a highly structured video to enhance the informed consent process in schizophrenic trials. The video was compared with a control video, which contained general research information but nothing about the consent process.
The study sample included three groups: (a) patients with schizophrenia (n=83) who were recruited from ongoing clinical trials; (b) medical patients without self-reported psychiatric illness; and (c) university undergraduates. The primary outcome, knowledge, was measured before and after participant viewing of the video through an 80-item quiz. The results showed an increased knowledge by participants in the highly structured video group. The authors concluded that video was an effective consenting tool across the

study population (182).

A two-step education video approach was evaluated among 250 potential participants in an HIV trial in Haiti (273). First, the patients were shown a video based on the consent form of the trial. The second session involved a one-to-one discussion with a social worker. Comprehension was assessed with 16 true/false and 4 open-ended questions. Participants who failed the tests had a repeat one-to-one education session. Ninety percent of the sample (225/250) passed either the first or second evaluation, and were then considered eligible to enrol in the study. This study generated a set of certain standards for enrolment of vulnerable participants into clinical trials.

Participant understanding was assessed by using a 10-item multiple-choice quiz in a clinical trial after assigning participants into video and standard informed consent groups. The video group had significantly better understanding than the control group. The authors concluded by recommending video as part of the informed consent process in clinical trials (274).

A recently published systematic review (275) focussing on modifications designed to improve comprehension of the informed consent in low literacy populations identified six eligible studies. The studies predominantly included populations that were older (median age 61, range 48-64), ethnic minority, and with literacy level of 8th grade or below. Only one study had a randomised design. The specific intervention differed in each study. Two of the studies included the teach-back method or teach-to-goal method and achieved the highest level of comprehension. Two studies changed the readability levels of the

informed consent document and resulted in the lowest comprehension among study participants (275).

The evidence supporting interventions to improve informed consent in low literacy population is extremely limited. Among the interventions evaluated, having a study team member spend more time talking one-on-one to study participants was the most effective strategy for improving informed consent understanding; however, this finding is based on the results of a single study (275).

In a phase I trial, an educational DVD was compared with a placebo DVD (276). The educational DVD increased the participants' knowledge and satisfaction regarding participation. Fifty-five percent of patients felt that the DVD helped them to decide about participation. This was a small scale study (n=49) and limited to cancer patients, for whom the main aim of the trial was to determine the toxicity rather than the efficacy of the drug/treatment.

Hitchcock-Bryan et al (277) developed and evaluated a video about clinical trials among 77 cancer patients. No difference was observed in the objective and subjective understanding scores between participants in the intervention and control groups. A limitation of the study was that pre- and post- testing was not done, and it is not known if the groups were comparable in terms of understanding at baseline prior to the intervention. The small sample size (n=77) also limited the findings. Despite these, the participants reported the video was useful for enriching their information and decision-making. The video was subsequently adopted as part of the informed consent process in the trial centre.

Daugherty et al (278) investigated the effects of a CD-ROM educational intervention for advanced cancer patients enrolling in phase I–II trials. An interactive CD-ROM with touch screen monitor, which contained phase I-II trial information and videos of patients and oncologists talking about early phase trial, was developed. Potentially eligible patients (n=199) were randomised to either view the CD-ROM or receive a written information leaflet. After consulting with their clinicians, patients were interviewed about their understanding. CD-ROM users reported that it changed the way they made a decision to enter a trial (28% compared with 12% of patients receiving the written information), and in some cases changed the decision itself (20% versus 5%). A sub-set analysis reported that 71% of those who completed the CD-ROM subsequently enrolled in the trial compared with 58% of those who received the written information. Although this study involved a specific patient population with advanced cancer, and a unique trial setting (phase I-II), the specific issues of vulnerable populations and complex trial information exist as for African participants in randomised clinical trials.

4.6: Why multimedia might be of value in improving comprehension of informed consent in low literacy research settings in Africa

As discussed above, the potential value of multimedia tool in improving comprehension of informed consent process is not entirely new in clinical care and clinical trial settings outside Africa. However, extensive electronic and manual search revealed that no study is yet to report the actual value of this important intervention tool in clinical research settings in sub-Saharan Africa.

What appears close to the use of multimedia consent tool was reported in a Ugandan study (279) which evaluated the effect of 'Speaking Book' among 201 research participants who were literate in English. Briefly, 'Speaking Book' is a battery-operated audio-visual tool targeted at low literacy research participants. The book explains in simple language what clinical trial participation entails. It is made of hard covers and large pages. Each page of the book is colourfully illustrated, with simple text relating to the illustration. The book has a plastic panel running down the right-hand side enclosed within is a battery. The panel contains a series of 'push buttons', each of which corresponds to a specific page in the speaking book. When activated, the 'push buttons' produce a soundtrack of the text on the relevant page. The soundtrack which is narrated by a person with the appropriate voice and tonal quality is thus 'read' to the study participant using the book (154).

In the Ugandan study (279), participants were randomised either to receive written clinical trials information (control arm), or written clinical trials information followed by instruction on the use of the 'Speaking Book' with a take-home copy (intervention arm). After the sessions, both groups completed a 22-item multiple-choice test on the rights and responsibilities of participants. They returned after one week to complete the same test to assess knowledge retention. Volunteers in the intervention arm had a larger increase in knowledge than those who had no access to the audio-visual tool (t-score=-5.3, p-value<0.0001). Major drawback of the study was the exclusion of participants who could neither read nor speak English, given that this group of participants constitute a substantial proportion in most clinical research settings in Africa. The study also adopted a simulated approach which may not reflect real life situations.

Similar findings were earlier reported by Dhai et al (154) when they evaluated the same audio-visual tool among potential participants in South Africa. The findings of the two studies further underscore the need for a carefully designed study that will establish actual value of multimedia as an alternative consent tool in low literacy research settings in Africa.

In clinical trial settings outside Africa, multimedia has been shown to improve informed consent by increasing participant knowledge and understanding. Furthermore, multimedia has been established as a way of delivering research information in clinical care, with clear benefits in relation to knowledge and understanding, improving compliance, uptake of screening, and also in assisting patients with decision-making. Given these proven benefits in other settings, it is imperative to develop and evaluate a locally appropriate, yet ethically sound multimedia tool for African research settings. It is known that misconceptions and poor understanding about clinical trials are common in most African settings where research participation is influenced largely by perceived medical benefits. This has contributed to low refusal to clinical trials, and hence high clinical trial recruitment rates in most low-income countries, but this achievement has often been on the basis of inadequate comprehension and understanding. It has been suggested that participants who have a better understanding of clinical trial information would have more favourable attitudes towards randomised trials, and would be more willing (i.e. with genuine informed consent) to consider participation in a clinical trial (280). It is possible that improving comprehension using multimedia tool would facilitate participants consenting to enrol in a clinical trial based on correct understanding of the research information.

4.7: Limitations identified from literature review on multimedia tool

Two major limitations could be identified from the literature on use of multimedia as a consent tool. Video was used in most of the studies as a multimedia tool in combination with other methods, such as written information, one-to-one discussion, counselling, flip-charts and checklists. Consequently, it is challenging to determine the precise effect of video in relation with other component of interventions. In most of the studies, 'knowledge' or 'understanding' was the primary outcome measure for evaluating effectiveness of multimedia. However, the outcome was measured with different types of tools, most of which were not validated. Furthermore, the assessment of the outcome measure was conducted at variable times after disclosure of study information.

Having highlighted the strengths and weaknesses of the various studies evaluating effectiveness of multimedia tool, it will be relevant to understand the mechanism of how multimedia technology aids transfer of knowledge to the users. This will help to identify the components of multimedia that needs to be maximised to achieve optimal comprehension of informed consent. This will form the focus of next section.

4.8: Technology mediated learning

Owing to the fast growing scale of technology and its extensive range of applications, the adoption of multimedia technology in informed consent procedure has become a viable and affordable option. Even most African countries that are characterised by low development indices, are rapidly embracing the ever-expanding multimedia devices such as mobile phones, iPad and Kindle. These devices are capable of providing social interactive interface which could be utilised to appropriately deliver crucial research

information to research participants who cannot read or understand information written in international languages (13, 198).

Multimedia could be described in various ways depending on the components included in the final outputs. According to Shavinina and Loarer (281), multimedia application consists of at least three of these seven components:

i. Text (including notes, captions, subtitles, and other resources such as tables of contents, indices, dictionaries, and help facilities)
ii. Data (such as tables, charts, graphs, spreadsheets, statistics, and raw data of various kinds)
iii. Audio (including speech, music, atmospheric background noise, and sound effects)
iv. Graphics (often ranging from traditional media such as drawings, prints, maps, and posters to images processed or created entirely within a computer)
v. Photographic images, from negatives, slides, prints, or even digital cameras (which record photographic images directly as computer graphics)
vi. Animation (whether recorded on film or video, or created with a computer)
vii. Moving pictures (specifically, digital video, either converted from analogue film and video, or created entirely within a computer) (281).

For the purpose of this study, multimedia is taken as the combination of visual and auditory delivery of information, including the use of pictures, animations, recorded words, live words, sounds, or video (282).

Learning may be aided by presenting multimedia in various ways. In a study conducted to investigate the impacts of multimedia signalling in three different kinds of instructional messages: when scientific explanation is presented in oral form as a text passage, when scientific explanation is presented in oral form as speech, and when scientific explanation is presented in verbal and visual forms as a narrated animation. Study participants who received signalled text responded with significantly more acceptable answers than their counterparts who received non-signalled text. This showed that multimedia technology could facilitate successful learning (283).

Nevertheless, it is crucial to recognise that inability to present multimedia technology in an appropriate format can lead to negative results. This is because perception of display on a multimedia application is of considerable importance in terms of transfer learning. A study revealed that excessive multimedia stimulation can hinder cognitive processing of information that is essential for learning (284). Having highlighted how multimedia technology can be used a medium of learning transfer; it is relevant to examine the theory underpinning learning. I will start by giving a brief overview of learning.

4.8.1: Overview of Learning

Learning is defined as a change in knowledge attributable to experience. Major characteristics of learning include: (1) learning involves a change in the learner; (2) what is changed is the learner's knowledge; (3) the cause of the change is the learner's experience. Learning is not measured through one operational definition. Rather, learning is a mixture of comprehension, transfer of new material, and the retention of material. In fact, most transfer studies focus solely on the similarities and differences between the contexts of initial learning and subsequent transfer (285).

4.8.2: Cognitive Theory of Multimedia Learning

This thesis focuses on a multimedia learning device; therefore, it is important to understand the cognitive functioning of people learning from multimedia. Cognitive Theory Mediated Learning (CTML) is based on three cognitive principles of learning: i) the human information processing system which includes dual channels for visual/pictorial and auditory/verbal processing (i.e. dual-channels assumption); ii) each channel has limited ability for processing (i.e. limited capacity assumption); and iii) active learning entails carrying out a harmonised set of cognitive processes during learning (i.e. active processing assumption) (233).

Furthermore, CTML stipulates five cognitive processes in multimedia learning: i) selecting relevant words from the presented text or narration, ii) selecting relevant images from the presented illustrations, iii) organising the selected words into a logical verbal representation, iv) organising selected images into a coherent pictorial representation, and v) integrating the pictorial and verbal representations and prior knowledge (233).

According to the CTML, the visual information processing channel may become overloaded when an individual processes on-screen graphics and on-screen text at the same time (286). However, when words are presented as narration, words can be processed in the verbal channel, thereby reducing the cognitive load in the visual channel. In several studies testing this theory, both non-interactive multimedia environments and interactive media environments were used. The findings showed that interactive (graphics and narration) learning confers deeper and better performance on problem-solving tests than non-

interactive graphics and on-screen text (287, 288).

Based on the three cognitive principles of learning highlighted above, CTML outlines seven factors of multimedia design: i) multimedia principle (people learn better from words and pictures than from words alone); ii) spatial contiguity principle (people learn better when related words and pictures are in close proximity); iii) temporal contiguity principle (people learn better when related words and pictures are close together in time); iv) coherence principle (people learn better when irrelevant words, pictures, and sounds are eliminated from the presentation); v) modality principle (people learn better from narration and animation than from text and animation); vi) redundancy principle (people learn better from narration and animation compared to animation, narration, and text); and vii) individual differences principle (individuals with low prior content knowledge and individuals with high spatial skills benefit most from animation and narration) (286).

The modality principle (people learn better from narration and animation than from text and animation) and the redundancy principle (people learn better from narration and animation compared to animation, narration, and text) serve as theoretical foundations for other principles because they describe how information is processed (233). Researchers reported that the modality principle's combination of pictorial and auditory materials give better test outcomes on transfer performance compared to a combination of written and pictorial materials (233, 289, 290). The modality principle clarifies the process of developing multimedia tools for learning. A combination of visual and hearing aids does not bore study participants and enables better

performance on learning. The principle of redundancy was documented to occur only when materials are presented simultaneously (287). The effects of redundancy were demonstrated with participants exposed only to narration. The participants had higher text scoring on transfer and retention tests. The redundancy principle shows the importance of developing proper multimedia learning tools for learning (233).

From the above description, it can be inferred that multimedia tool integrating video, audio, and animation could provide users with rich information that will enhance learning. The tool can also be adapted to different learning styles to suit varying context. Furthermore, different communication channels can be provided to achieve maximum learning effectiveness (158).

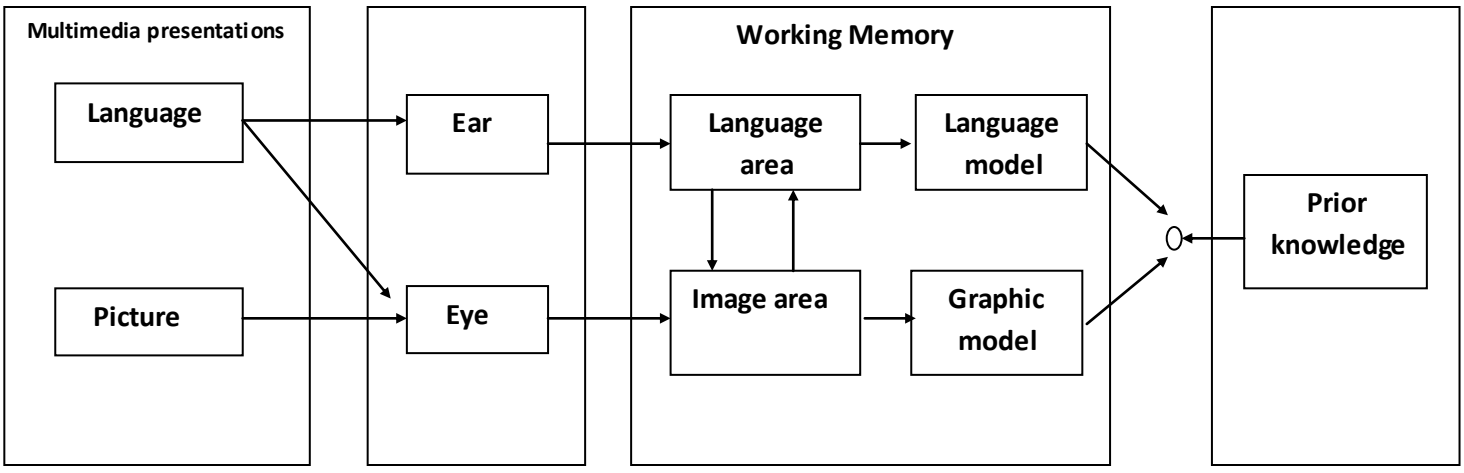
According to Mayer et al (286), the cognitive process differs depending on the types of message being conveyed (Figure 5). They described graphic processing as the process by which visual information is received by the eye. The information is subsequently selected and enters the image area of working memory where it is organised into a graphic model which is then integrated with prior knowledge (286).

Mayer et al (286) further said that audio processing is the process by which audio information is received by the ear, and is selected for entry into the aural area of working memory; the information is organised into the appropriate language model and integrated with prior knowledge. Word processing is the process by which textual information is received by the eye; this is selected and entered into the image area of

working memory and organised into the appropriate language model, and finally integrated with prior knowledge (286).

The theory of multimedia learning supports Mayer et al's description (286) that working memory contains two information-processing units and that, different multimedia information presentations can improve learning effectiveness (158). However, because of limited capacity of working memory, it is suggested that improved learning could be achieved if the design of multimedia learning systems assist learners to utilise working memory more effectively in selecting, organising, and integrating information (286).

Figure 5: The cognitive theory of multimedia learning [adapted from Mayer et al (286)]



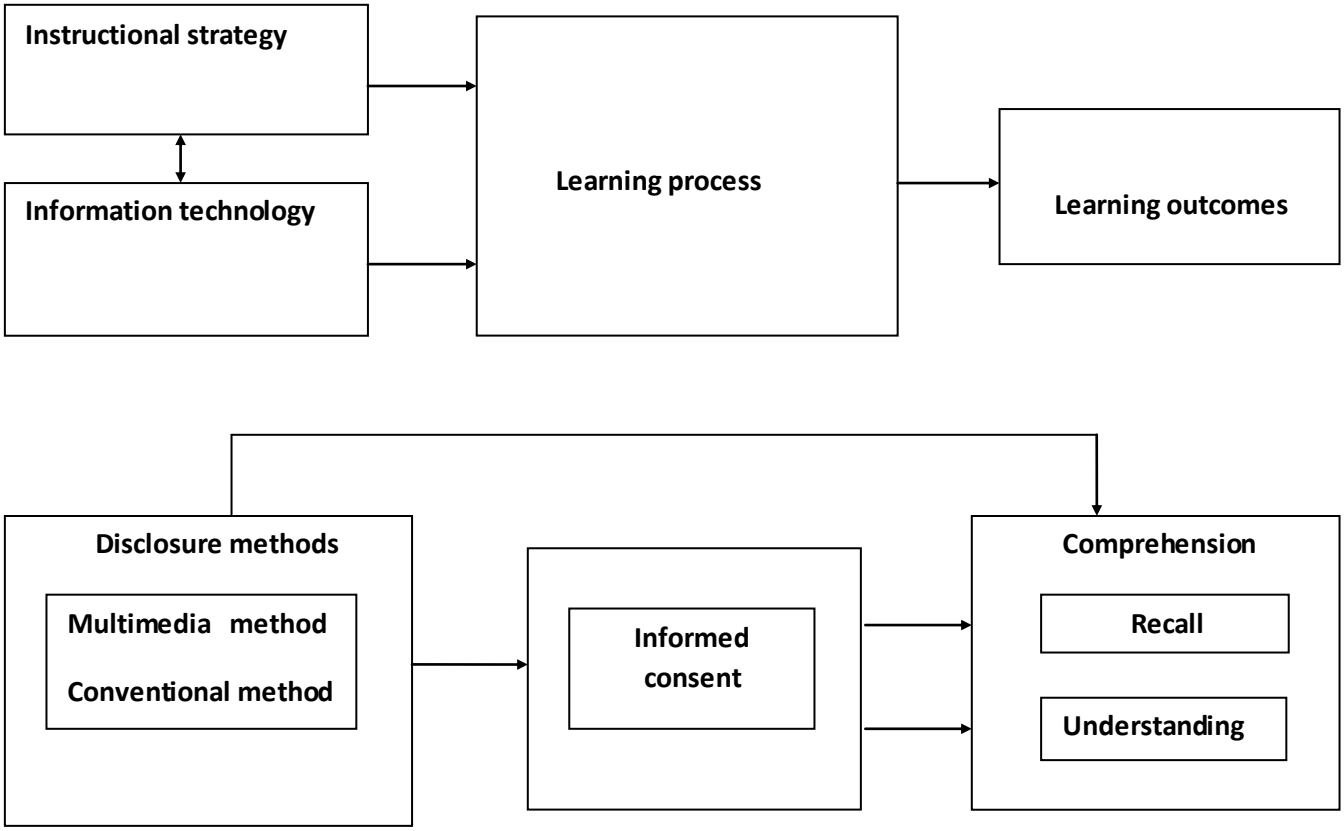
4.9: Conceptual framework of Technology Mediated Learning

The mechanism of learning that underpinned the study reported in this thesis is based on the conceptual framework of Technology Mediated Learning (TML). TML was proposed by Alavi and Leidner (23) who stated that instructional strategy and information

technology affect the cognitive processes of learners and thus influence the learning outcomes (Figure 6). They described learning as a state of mind where the learning processes should be considered when evaluating learning outcomes (23). To maximise the limited capacity of working memory described above, an instructional strategy is employed for presenting, organising, and synthesising instructional materials (23).

TML assumes that learning outcomes are influenced by interactions among information technology, instructional strategy, and the learning processes in specific contexts. Consequently, evaluation of learning outcomes needs to consider the effects of various combinations of instructional strategy and information technology on learning processes, including the learners' ability to process information cognitively, their motivation, and their interest (23). Situating technology mediated learning with the objectives of the study reported in this thesis; I developed a multimedia tool integrating video information of a clinical trial, animations of difficult research concepts with audio narration of the clinical trial information in local languages understandable to potential study participants in The Gambia. The design of the tool made a good blend of information technology (video and animation) as an instructional strategy to deliver clinical trial information during informed consent process which is considered a learning process. The multimedia tool may facilitate learning and increase learning effectiveness by making information transfer during informed consent process interesting and understandable to the study participants.

Figure 6: Conceptual framework of TML (adapted from Alavi and Leidner (23)



4.10: Summary of Part III of the literature review- Interventions developed to improve informed consent comprehension

4.10.1: Summary: Of various interventions, multimedia has been shown to be an effective means for increasing knowledge and understanding in clinical care, health promotion, screening, management of side-effects and medication adherence. Multimedia tools have also been used, to a large extent as an education tool in cancer clinical trials in developed countries where participant literacy is high. Despite the potential benefits of multimedia, there is paucity of evidence on the effectiveness of multimedia tool in facilitating informed consent comprehension among study participants in low literacy settings of Africa.

4.10.2: Conclusion 1

There is a need to develop effective interventions to make clinical trial information comprehensible to participants in low literacy research settings. Multimedia has been shown to be an effective and useful tool for patient education in a variety of health care settings including health promotion, screening, surgery, rehabilitation and cancer care. It has been shown to increase knowledge and understanding, improve compliance, increase uptake of screening and to assist patients with decision making

4.10.2.1: Study implication

- Multimedia was chosen as the intervention for this study due to its potential effectiveness in increasing knowledge and understanding

4.10.3: Conclusion 2

Multimedia tool that is tailored to the context and information needs of participants appears to be more effective than generic tool. The context is important for participant comprehension of informed consent, with respect to researcher-participant interaction.

4.10.3.1: Study implication

- This study developed a locally customised multimedia tool integrating video, animation and audio narrations in local languages as an intervention that might facilitate and encourage discussion with the research team about informed consent issues that are important to participant decision. The study employed an experimental design to evaluate effectiveness of the multimedia intervention compared to standard informed consent process in The Gambia.

4.11: Study Objectives:

The objectives of this study are**:**

1. To develop and validate an informed consent comprehension questionnaire for a Gambian research population.

2. To develop a multimedia consent tool for use among research study participants from The Gambia.

3. To evaluate the acceptability and ease of use of the multimedia informed consent tool among potential research participants in The Gambia.

4. To assess the effectiveness of the multimedia informed consent tool compared with 'standard' informed consent among participants in a clinical trial in The Gambia.

4.11.1: Research questions: i. Does consenting using a multimedia delivery tool makes the information more understandable to low literacy clinical trial participants than 'standard' consent method?

ii. Does a validated digitised audio questionnaire facilitate measuring participant comprehension of informed consent information?

iii. How acceptable and easy to use are multimedia consent tool and digitised audio comprehension questionnaire among low literacy Gambian research population?

4.11.2: Hypotheses: i. A locally appropriate multimedia consent method will make the study information more understandable to low literacy clinical trial participants than 'standard' consent method.

ii. Participants engaged through a multimedia consent approach will perform significantly better across all test performance scores of a validated informed consent comprehension questionnaire than those exposed to 'standard' consent method.

4.11.2.1: Null hypothesis:

i. There will be no difference in the comprehension scores between participants receiving multimedia consent information and those who receive the same information through 'standard' consent procedure only.

I will describe in the next three chapters the methodology employed to meet these objectives, taking into consideration the low literacy context in the study areas and evidence from the literature.

COVER SHEET FOR THE PUBLISHED ARTICLE INCLUDED IN THIS THESIS

1. For a 'research paper' already published

1.1. Where was the work published? **BMJ Open**

1.2. When was the work published? **24 June 2014**

1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion: **Not applicable**

1.3. Was the work subject to academic peer review? **Yes**

1.4. Have you retained the copyright for the work? **Yes**

If yes, please attach evidence of retention. **Evidence included in the attached article on Appendix VI**

If no, or if the work is being included in its published format, please attach evidence of permission from copyright holder (publisher or other author) to include work: **Not applicable**

2. For a 'research paper' prepared for publication but not yet published

2.1. Where is the work intended to be published? : **Not applicable**

2.2. Please list the paper's authors in the intended authorship order: **Not applicable**

2.3. Stage of publication – Not yet submitted / Submitted / Undergoing revision from peer reviewers' comments / In press; **Not applicable**

3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

On completion of the data collection of psychometric evaluation of a digitised questionnaire designed to assess comprehension of informed consent during later stages of my PhD study. My Supervisors encouraged me to publish the findings. I wrote the first draft of the article. All co-authors provided comments on the draft article, many of which I incorporated during revisions of the article. I further revised the article substantially in line with the reviewers' comments

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CANDIDATE'S SIGNATURE ……Date : 15 August 2014

SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above) ……

Chapter five: Development and psychometric evaluation of the study questionnaire (digitised audio informed consent comprehension questionnaire)

5.1: Introduction to the chapter

As described in chapter two of this thesis, international guidelines (41, 42) emphasise that informed consent is provided in a comprehensible manner that allows potential participants to freely decide whether or not they are willing to enrol in the study. To ensure comprehension, the study information may need to be provided in the participant's native language. If the informed consent documents have been originally written in one of the major international languages, they must be translated to the local languages of potential study participants (20, 230). The translated documents are subsequently back-translated by another independent group to the initial language to confirm that the original meaning of the contents of the document is retained.

In sub-Saharan Africa, this process may become extremely challenging because many research concepts like randomisation and placebo, do not have direct interpretations in the local languages (61). Furthermore, in some African countries such as The Gambia, local languages exist only in oral forms and they do not have standardised writing formats making written translation and back-translations of informed consent documents not only impractical, but also less precise (207). Further adding to these difficulties are the high rates of illiteracy and functional illiteracy in such contexts, which contribute to socio-economical vulnerability of these research populations (18).

In contexts characterised by high linguistic variability and illiteracy rates, the use of tools to ascertain comprehension of study information provided during the informed

consent process may be recommended (291). However, assessment of participant comprehension of the consent information could be challenging, owing to lack of agreed definitions of 'comprehension' (24) and inconsistent approaches to measuring it (7, 16). As a result of the absence of uniform guidelines, researchers have documented disparities between what participants think they understand and what they actually understand (113, 292). For example, 91% of participants in a randomised trial reported finding the study information quite easy to understand. However, only 23% knew that they had been randomised, while 51% believed that the doctor had selected the treatment for them (113). This finding underscores the need for an objective approach to assess participant comprehension of consent information.

5.2: Assessment of participant comprehension

Assessment of participant comprehension has been largely carried out through the use of purpose-designed questionnaires. Mason *et al* (100) in a female sterilisation study, assessed participant knowledge using true/false question items. Similarly, a 14-item multiple choice test was employed by Diabetes Control and Complications Trial Research Group (293), in assessing a multi-component process for informed consent. Other tools that have been extensively reported in literature to assess informed consent comprehension include Brief Informed Consent Evaluation Protocol (BICEP) (175), Deaconess Informed Consent Comprehension test (DICCT) (292) and the Quality of Informed Consent test (QuIC) (227).

The DICCT consists of 14 open-ended questions with three scoring options: 2 points for correct answer, 1 point for partially correct and 0 points for incorrect or no answer. As part of the evaluation of the tool, 275 adults completed the test, in addition to the

revised Weschler Adult Intelligence Scale (WAIS) and the reading sub-test of the revised Wide Range Achievement Test (WRAT-R). There was a moderate correlation between the DICCT and the WAIS-R, and the DICCT and the WRAT-R. Inter-rater reliability for the DICCT was determined for the first 50 patients, and was good at 0.84 (292).

More general approaches which aimed to assess the quality of the informed consent process (of which understanding was part) include studies conducted by Joffe et al (173) in cancer, and in non-cancer trials (227), Sugarman et al (175) and Guarino et al (294). Quality of Informed Consent Questionnaire (QuIC) was designed to assess actual understanding (20 questions) and perceived understanding (14 questions). It incorporated the USA requirements for informed consent, assessed therapeutic misconception, and used the language and structure of the National Cancer Institute (NCI) template for informed consent documents. The QuIC was validated among 207 adult cancer patients enrolled in phase I, II or III clinical trials. 32 patients were randomly selected to assess test-retest reliability of the questionnaire; the result of which showed good intra-class correlation coefficients of 0.66 for objective understanding and 0.77 for subjective understanding. Content validity was assessed by two independent expert panels (173, 227). Because of the specific nature of the questions, the QuIC may be more sensitive to the therapeutic misconception, than to other areas of participant misunderstanding. In addition, the QuIC is focused on US federal requirements for informed consent, which may not be directly transferable to Africa research settings.

Sugarman et al (175) developed the Brief Informed Consent Evaluation Protocol (BICEP), and was administered to 632 Americans via telephone. The questionnaire contained only open-ended items focussing on therapeutic misconception and participant satisfaction. Verbatim responses from 191 participants were analysed using a coding system. The results indicated BICEP to be acceptable and efficient in evaluating informed consent but the narrow scope of the questionnaire made it inappropriate for African research settings.

Guarino et al (294) developed an Informed Consent Questionnaire (ICQ) for assessing participant perception of understanding of informed consent. This was evaluated in a Department of Veterans Affairs randomised clinical trial of cognitive behavioural therapy and aerobic exercise for Gulf War veterans, involving 1092 participants. ICQ consists of two sub-scales: 'understanding' sub-scale which has four question items and 'satisfaction' sub-scale which has three question items on satisfaction with study participation. The questionnaire was validated among participants in a randomised clinical trial of Gulf War veterans' illnesses. ICQ exhibited good psychometric properties following standard item-reduction techniques.

Similar reports of inconsistent approaches in measurement of comprehension among African participants have been discussed in chapter two of this thesis and reported in a systematic review (7). Owing to the lack of validated measures to assess comprehension of consent information for African trial participants and the limitations of the instruments discussed, it became imperative to develop and evaluate a locally

appropriate comprehension assessment tool for Gambian trial participants, for whom English is not the native language. This is the first step towards contextualising strategies of delivering study information to research participants; objectively measuring their comprehension of the information using a validated tool and based on this, improving the way information is delivered during informed consent process. I will describe the process of the questionnaire development in the next section.

5.3: Questionnaire development

The items on the questionnaire were generated from the basic elements of informed consent obtained from literature on guidelines for contextual development of informed consent tools (1, 2, 10, 13, 15, 16, 217, 291, 295, 296), international ethical guidelines (38, 42) and operational guidelines from Gambia Government/Medical Research Council Joint Ethics Committee (44).

From the guidelines listed above, I identified 15 independent domains of informed consent that were not appropriately understood among study participants in low literacy settings. These domains include voluntary participation, rights of withdrawal, study knowledge, study procedures, study purpose, blinding, confidentiality, compensation, randomisation, autonomy, meaning of giving consent, benefits, risks/adverse effects, therapeutic misconception and placebo.

Because evidence has shown the deficiencies of using one question format in assessing comprehension of informed consent information (13), I generated a total of 34 question items from the 15 domains using three different response formats. These response options consisted of a categorical 'Yes' or 'No' or 'I don't know', multiple choice response items and open-ended free text responses. The questionnaire was

made up of five sections: the first section contained ten closed-ended and seven follow-up open-ended question items focusing on voluntary participation, right of withdrawal, source of funding for the study, number of participants needed, blinding, insurance/indemnity, contact person for the study, study duration, compensation and confidentiality; the second section had six single choice response items focussing on randomisation, right of withdrawal, meaning of signing/thumb-printing consent form, autonomy, compensation. The third section had four multiple choice response items which focussed on study purpose, study procedures, study benefits while the fourth section had seven free-text open-ended question items which focussed on study activities, randomisation, therapeutic misconception, adverse events, placebo. The last section had nine questions on socio-demographic information of participants and these were not included in the psychometric analysis of the questionnaire.

Follow-up question items were included in the first section to ensure the responses given by participants truly reflected their understanding as asked in the close-ended questions, e.g '*Have you been told how long the study will last*' was followed by '*If yes, how many months will you be in this study*'. No response options were given and the participants were expected to give the study duration based on their understanding of information given during informed consent process. The order of responses to the questions was reversed for some items to avoid participants defaulting to the same answer for each question.

The use of multiple choice and open-ended response items was meant to explore participant 'actual' understanding of study information, because this could not be adequately measured using the closed-ended response options.

To enable non-literate participants understand how to answer questions under multiple and open-ended response options, locally appropriate sample question items were included before the main questions. For example, *'Domoda' soup is made from: a. Bread, b. Groundnut, c. Yam, d. Orang*e. Groundnut is the correct response and participants were directed to choose only one correct response in the question items that followed the sample question. For items with multiple response options, a sample question was included*: 'Which of these are Gambian names for a male child? : a. Fatou, b. Lamin, c. Ebrima, d. Isatou'*. The correct responses are Lamin and Ebrima; and participants were directed to choose more than one correct responses that apply to the question items.

As the questionnaire was intended to be used across different clinical trials, I developed question items that were generally applicable to clinical trials but required a trial-specific answer to an open-ended question. An example of this was: *'What are the possible unwanted effects of taking part in this study'* which allowed participants to explain in his/her words the adverse events peculiar to the clinical trials he/she is participating.

5.3.1: Face and content validity: Face validity was performed to assess the appearance of the questionnaire regarding its readability, clarity of words used, consistency of style and likelihood of target participants being able to answer the questions. Content validity was done to establish whether the content of the questionnaire was appropriate and relevant to the context for which it was developed (297). After generating the question items, I requested five researchers, two from LSHTM and three from MRC, who are experienced in clinical trials methodology, bioethics in African context and social science methods to review the English version of the questionnaire for face and content validity to ascertain its relevance and

appropriateness to the African context. All of them agreed that essential elements of informed consent information were addressed in the questionnaire. And, that the items adequately covered the essential domains of informed consent, with special attention for those whose understanding may be especially challenging in African research settings. They also supported the use of multiple response options as capable of eliciting appropriate responses that might reflect true 'understanding' of participants. One of the reviewers recommended presenting the item in form of question instead of statement. Consequently, question formats were adopted in the items. For example '*I have been told that I can freely decide to take part in this study*' was changed to '*Have you been told you can freely decide to take part in this study*? In line with these changes, the response option was also changed from' True' or 'False' to 'Yes', 'No' or 'I don't know'.

Furthermore, I gave the revised English version of questionnaire to three experienced field assistants at MRC, The Gambia and three randomly chosen lay persons to assess clarity and appropriateness of the revised question items and their response options. The lay persons were selected randomly from a list of impartial witnesses by choosing one person each from three ethno-linguistic groups in The Gambia. They independently agreed that the questions were clear, except three items addressing confidentiality, compensation and right to withdraw. On the basis of these feedbacks, I re-worded the question items to improve clarity. Question on confidentiality was reframed from '*Will non-MRC workers have access to your health information'* to '*Will anyone not working with MRC know about your research information'?* Similarly, '*Will you be rewarded for taking part in this study*' was changed to '*Will you receive money for taking part in this study'*?

5.3.2: Audio-recording in three local languages and development into digitised format: Owing to the lack of acceptable systems of writing Gambian local languages, the question items were audio-recorded in three major Gambian languages: Mandinka, Wolof and Fula by experienced linguistic professionals who are native speakers of the local languages and are also familiar with clinical research concepts. Audio back-translations were done for each language by three independent native speakers and corrections were made in areas where translated versions were not consistent with the English version. A final proof of the audio-recordings was conducted by three clinical researchers (native speakers) who independently confirmed the translated versions retained the original meaning of the English version.

The revised questionnaire was developed into an audio computer assisted interview format at the School of Medicine, Tufts University, Boston, USA. In conjunction with the MRC community relations officer, I identified and selected locally acceptable symbols and signs e.g. star, moon, house, fish, bicycle to represent the response options. The question items were serially developed into the digitised format and draft copies were sent to me for review at each stage. After ensuring the wording of the paper questionnaire were consistent with the digitised version, translated audios in Mandinka, Wolof and Fula were recorded as voice-overs on the digitised questionnaire, which will be subsequently referred to as Digitised Informed Consent Comprehension Questionnaire (DICCQ) in this thesis.

5.3.3: Piloting: On completion of the initial development, the DICCQ was piloted among 18 mothers of infants participating in an ongoing malaria vectored vaccine trial at MRC Sukuta field site (ClinicalTrials.gov NCT01373879). The field site is located

about 5 kilometres from the MRC field site targeted for field testing of the questionnaire. I administered the DICCQ on a computer laptop in a private consultation room within the Sukuta field site. After putting participant's assigned identification number and interviewer's initials into the DICCQ; participant's local language of choice was selected on the computer screen. The question items were serially read aloud to the participants in the local language with the click of a button on the lower toolbar of the computer screen and a 'forward arrow' button to move to the next question item. Participants answered either by vocalising her responses or pointing to the symbols on the computer screen that corresponded to her choice of responses. The participants generally reported the questionnaire to be clear and easy to follow. The audio-translations were also accepted as conforming with the dialects spoken by the majority of Gambians. The average administration time was 29.4 minutes. Suggestions were made to include 'backward', 'repeat' and 'skip' function buttons in the computer toolbar. These amendments were incorporated into the final version of the digitised questionnaire.

5.3.4: Field testing: The final version of DICCQ was tested sequentially among participants in two ongoing clinical trials. The two sites were selected for field testing of the questionnaire based on some similarities of the clinical trials taking place simultaneously at the two diversely distinct research communities within The Gambia.

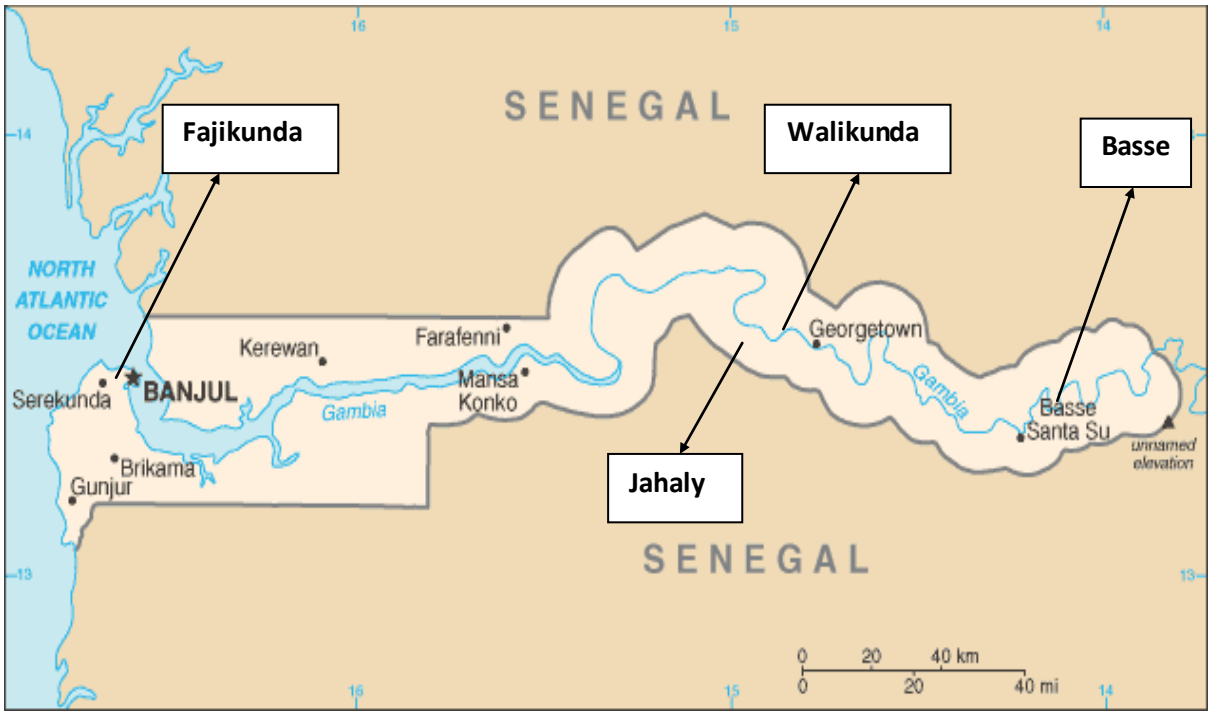
The first field test took place from 4 to 20 February 2013 among mothers of children enrolled in an ongoing randomised controlled, observer blind trial that aimed to evaluate the impact of two different formulations of a combined protein-polysaccharide vaccine on nasopharyngeal carriage of *Streptococcus pneumoniae* in Gambian infants at

the Fajikunda field site of MRC (ClinicalTrials.gov NCT01262872). The site is located within an urban health centre, about 25km south of the capital, Banjul. 1200 infants were enrolled in the trial and mothers brought their children for a total of six study visits over a period of one year.

The second field test took place from 22 February to 15 March 2013 in villages around Walikunda, about 280 km east of Banjul, among participants in an ongoing randomised controlled, observer blind trial (http://www.who.int/whopes/en/). The study was designed to compare the efficacy of two different doses of a newly developed insecticide with the conventional one, used for indoor residual spraying for malaria vector control in The Gambia. Over 900 households in 18 villages around Walikunda field station of MRC were randomly selected to receive any of the three doses of insecticides (Figure 7). Household participants gave informed consent before indoor spraying of the insecticides. Entomologists visited the households every month for six months to collect mosquitoes and interviewed the participants for perception of efficacy and adverse effects of the insecticides.

In the two studies, written informed consent was obtained based on the English version of respective study information sheets. These were explained in the local languages by trained field staff, in the presence of an impartial witness in case of illiteracy. Similarly, prior to administering DICCQ at each trial site, written informed consent was obtained from participants or their parents. One week after first administration, DICCQ was re-administered to randomly selected groups among the participants.

Figure 7: Map of The Gambia showing the study sites



In addition, at the end of first questionnaire administration, each participant in the two sites was administered a modified version of informed consent questionnaire (ICQ) (294), which has been validated in English among participants in a randomised clinical trial of Gulf War veterans' illnesses. Similar to DICCQ, the 'understanding' sub-scale of ICQ covers the domain on meaning of consenting, benefits and risks of trial participation. However unlike ICQ, 'participant satisfaction' domain was not covered by DICCQ. Modified ICQ was orally translated to Mandinka, Fula and Wolof by three independent native speakers who confirmed consistency with original English version. To establish construct validity, the participants' scores on 'understanding' sub-scale of ICQ were compared with their 'understanding' scores on DICCQ.

5.4: Sample size estimation: Sample size for validation studies is usually determined with the aim of minimising standard error of the correlation coefficient for

reliability test. Also, four to ten subjects per question items are recommended to obtain a sufficient sample size in order to ensure stability of variance-covariance matrix in factor analysis (298, 299). Based on these recommendations, I chose seven participants per question items. As stated above, DICCQ has 34 question items (excluding the nine questions on socio-demographic data and information on previous clinical trial participation), to give 34 x 7= 238 participants. Allowing for 5% non-response rate, the sample size was approximated to 250. Half of these participants (n=125) were randomly selected for a re-test one week after first administration of the questionnaire.

5.5: Scoring system for the questionnaire: The scoring algorithm consistent with the level of increasing difficulty of the question items is summarised in Table 5. In designing the scoring algorithm, I considered the possibility that certain question items should attract greater weight than others in determining the summated scores. For example, closed-ended question items were scored 0–3, question items with multiple response options were scored 0–4 and open-ended question items with no response option were scored 0–5. I scored all participants to avoid inter-rater variations. Participant scores on closed-ended and multiple choice question items were summed up as the 'recall' scores while participant scores on open-ended question items were summed as the 'understanding' scores. The total sum of 'recall' and 'understanding' scores for each participant constitutes the 'comprehension' scores (170).

Table 5: Scoring algorithm of question items

Closed ended question items in the first section	Each correct answer was scored 3; wrong answer was scored 0 and responses with 'I don't know' were scored 1
Open-ended question items which are follow-up questions to the closed ended question items in the first section	Each correct answer was scored 5, partially correct answer was scored 3, incorrect answer was scored 0, while 'I don't know' responses were scored 1
In the second section , participants chose ONE correct answer out of FOUR option responses	Each correct answer was scored 3, incorrect answer was scored 0 or 'I don't know' responses were scored 1
In the third section, participants chose more than one correct answers from FOUR option responses	Full correct answers were scored 4, partially correct answers were scored 2, wrong answers were scored 0 and 'I don't know' answers were scored 1
In the fourth section, participants responded using their own words to open-ended question items	Full correct answer was scored 5, partially correct answers were scored 3, wrong answers were scored 0 and 'I don't know' responses were scored 1

For modified ICQ (294), responses were scored as follows: 3 for "Yes completely", 2 for "Yes partially", ''1 for I don't know", and 0 for "No". I assigned the scores based on the responses given by the participants and ticked by the trained assistants who administered the questionnaire to the participants.

5.5.1: Data analysis: Data were retrieved from the in-built database of DICCQ and converted to Microsoft Excel format while data for ICQ were entered directly into Microsoft Excel. Analysis was done with Stata version 12.1 (College Station, USA) and Statistical Package for Social Sciences software version 20.0 (Chicago IL, USA). The significance of group differences was tested by Mann-Whitney U tests for demographic

variables with $p<0.05$ (two-tailed) considered significant. Psychometric properties of the DICCQ were evaluated in terms of reliability and validity using the following steps:

5.6: Steps in validation analysis

5.6.1: Construct validity: Construct validity refers to the degree to which items on the questionnaire relate to the relevant theoretical construct. It represents the extent to which the desired independent variable (construct) relates to the proxy independent variable (indicator)(300, 301). For example, in the DICCQ, 'recall' and 'understanding' were used as indicators of comprehension. This is based on an earlier study (170) which defined 'recall' as success in selecting the correct answers in the question items and 'understanding' as correctness of interpretation of statements presented in the question items. When an indicator consists of multiple question items like in DICCQ, factor analysis is used to determine construct validity (300, 302).

Factor analysis is a statistical method commonly used during instrument development to cluster items into common factors, interpret each factor according to the items having a high loading on it, and summarise the items into a small number of factors. Loading refers to the measure of association between an item and a factor (302, 303). A factor is a list of items that belong together. Related items define the part of the construct that can be grouped together. Unrelated items, that do not belong together, do not define the construct and are recommended for deletion (304).

Exploratory Factor Analysis (EFA) is a type of factor analysis method used to examine the relationships among variables without determining a particular hypothetical model (305). EFA describes the construct based on the theoretical framework, which indicates

the direction of the measure (297) and identifies the greatest variance in the respondents' scores with the smallest number of factors (305).

Kaiser-Meyer-Olkin (KMO) sampling adequacy was adopted to confirm that appropriate sample size was used to perform factor analysis in this validation study. Several types of extraction methods are used to undertake factor analysis. The two most common forms are Principal Component Analysis (PCA) and Principal Axis Factoring (PAF) (305). In PCA, all the variance of a variable (total variance) is analysed, while PAF only analyses common variance (305). Total variance consists of both specific and common variances. Common variance refers to the variance shared by participant scores with the other variables, and specific variance describes the specific variation of a variable (305). Therefore, PCA is assumed to be more reliable (305) and it was used in this study.

Two main criteria were used to determine how many factors should be retained: Kaiser criterion to select factors that have an eigenvalue greater than 1; and Catell's scree plot which is a graphical representation of descending variances that account for the extracted factors. The factors that lie before the point at which eigenvalues begin to drop can be retained. Varimax, the most commonly used orthogonal rotation was undertaken to rotate the factors to maximise the loading on each variable and minimise the loading on other factors (297, 303, 305).

To verify construct validity, the design of the DICCQ was analysed in a stepwise procedure. First, I tested whether the sample size of 250 was sufficient to perform factor analysis of the 34 item-DICCQ according to the Kaiser-Meyer-Olkin (KMO)

coefficient (acceptable value should be >0.50). In the second step, I conducted a principal component analysis (PCA) to derive an initial solution. Third, I determined the number of factors to be extracted according to three different criteria: (i) eigenvalue >1.0 (ii) Cattell's scree plot (iii) the number of factors identical with the proposed number of subscales (i.e 'recall' and 'understanding' subscales) (297, 305). In the last step, I compared the unrotated and rotated factor solution. The rationale of rotating factors is to obtain a simple factor structure that is more easily interpreted and compared. (297, 303, 305).

Furthermore, due to a lack of a specific 'gold standard' tool to measure informed consent comprehension, I could not examine concurrent (criterion) validity in which participants' scores on the DICCQ could be compared with the participants' scores on the 'gold standard' obtained at approximately the same point in time (concurrently). Nevertheless, construct validity provided evidence of the degree to which the participants' scores on the questionnaire were consistent with hypotheses formulated about the relationship of DICCQ with the participants' scores on other instrument measuring similar or dissimilar constructs, or differences in the instrument scores between sub-group of study participants (301). Three forms of construct validity based on hypothesis testing were examined:

5.6.2: Convergent validity seeks to show that the dimensions of an instrument correlate with other dimensions of that instrument or another instrument which theory suggests should be related to it. A good example of an instrument measuring the same construct as DICCQ is the Informed Consent Comprehension (ICQ) questionnaire which

contains four question items on 'understanding' sub-scale and three items on 'satisfaction' sub-scale.

The following *a priori* hypothesis was made: Convergent validity**:** Participant understanding scores on DICCQ will correlate positively with their scores on 'understanding' sub-scale of ICQ because both constructs relate to informed consent comprehension in clinical trial contexts. However, the correlation is not expected to be strong, because 'understanding' sub-scale of DICCQ covers more domains of informed consent comprehension than the 'understanding' sub-scale of ICQ.

5.6.3: Discriminant validity examines the extent to which a questionnaire correlates with other questionnaires of construct that are different from the construct the questionnaire is intended to assess. To determine this, it was hypothesised that participant scores on DICCQ will correlate negatively with the 'satisfaction' sub-scale of ICQ because DICCQ does not include 'satisfaction' domain about study participation. Spearman's correlation coefficients were used because the data of the questionnaires (DICCQ and ICQ) were not normally distributed.

5.6.4: Discriminative validity: To establish further evidence of construct validity, I examined the *discriminative validity* in which participant scores on DICCQ were compared between sub-groups of participants who *a priori* differed on the construct being measured. Using Mann-Whitney U test, the median differences of participant scores on DICCQ were compared based on their demographic variables (i.e. gender, place of domicile: urban versus rural and education status).

5.6.5: Reliability: After completing item-reduction in the validity analysis, the item-reduced DICCQ was investigated for reliability. Reliability describes the ability of a questionnaire to consistently measure an attribute and how well the question items conceptually agree together (297, 306). Two commonly used indicators of reliability: internal consistency and test-retest reliability were employed to examine the reliability of the DICCQ. Cronbach's alpha was computed to examine the internal consistency of the questionnaire. Because the questionnaire contains 'recall and understanding' sub-scales, Cronbach's alpha was computed for each sub-scale as well as the entire scale. Acceptable value for Cronbach's alpha was ≥ 0.7 (299, 300).

Test-retest reliability was examined by administering the same questionnaire to half of the study participants who were randomly selected on two different occasions, one week apart. This was based on the assumption that there would be no substantial change in the comprehension scores of participants between the two time points (297, 304). A high correlation of ≥0.7 between the scores at the two time points indicates that the instrument is stable over time (297, 304). Analysis of the participant scores between the test and re-test was conducted by estimating the intra-class correlation coefficients and 95% confidence interval.

5.7: Results

5.7.1: Participants information

Two hundred and fifty participants consisting of 130 participants from the clinical trial in the urban setting and another 120 clinical trial participants in the rural setting were interviewed. To address the missing data, participants (n=3) who did not respond to three or more items (5%) in DICCQ were excluded from further analysis (303). Those with one or two missing items (n=6), were replaced with the mean value of the participant scores for the question item (303). Thus, data from 247 participants were included in the final analysis. The mean age (SD) was 37.06 ± 15.0 years; there were 129 participants (52.2%) in the urban group and 118 participants (47.8%) in the rural group. Overall mean time of administration of the questionnaire was 22.4 ±7.4 minutes while the overall mean time for re-test of the questionnaire was 18.5 ± 5.4 minutes. Socio-demographic characteristics of the participants are summarised in Table 6.

Table 6: Socio-demographic characteristics of study participants

Characteristics	Frequency % (N=247)
Age group (years)	
18-25	67(26.8)
26-33	65(26.0)
34-41	40(16.0)
42-49	23(9.2)
>49	55(22.0)
Gender	
Female	156 (63.2)
Male	91 (36.8)
Domicile	
Urban	129 (52.2)
Rural	118 (47.8)
Occupation	
Farming	80(32.3)
Trading	39(15.8)
Artisan	7 (2.8)
Civil servant	18(7.3)
Housewife	94 (38.2)
Schooling	4(1.6)
Unemployed	5(2.0)
Education group	
Had Western education	62(25.1)
Had no Western education	185(74.9)
Religious affiliation	
Islam	239 (96.8)
Christianity	8(3.2)
Previous clinical trial participation	
None	200 (81.0)
One or more	47 (19.0)

Table 6 shows that majority of the participants (about 52%) were 33 year old or less; about 63% were female, about 75% had no formal education. About 80% of the participants had no previous trial exposure.

5.7.2: Factor analysis

The KMO coefficient for the DICCQ was 0.62 (acceptable value was >0.5) confirming a sufficient degree of common variance and the factorability of the inter-correlation matrix of the 34 items (305). The first PCA yielded a total variance of 69.02%, which implied that at least 50% of the variance could be explained by common factors and this is considered acceptable. This initial solution after PCA revealed 13 components with eigenvalues >1.0. However, the Catell's scree plot began to level off after two components, consistent with the number of sub-scales. As the scree plot is considered more accurate in determining the numbers of factors to retain especially when sample size is greater than 250, or the questionnaire has more than 30 items (302), a two factor solution after varimax rotation was considered conceptually relevant and statistically appropriate for DICCQ. For psychometric studies involving 200-300 participants, acceptable value of factor loadings range from 0.29-0.38 according to Steven's guideline (302). Because the sample size used in this study was 250, the Steven's guideline was applied and eight items: two items on study duration, four items on funder/sponsor of study, and two items on number of study participants with factor loadings of <0.3 were serially deleted. Five items: voluntary participation, right of withdrawal, placebo, blinding and study purpose were retained despite low factor loadings because they were theoretically important components of informed consent. The final PCA of the two-factor solution with 26 items (corresponding to 'recall and understanding' themes) accounted for 60.25% of the total variance. The factor loadings of the final PCA and their factorial weights are shown in Table 7.

Table 7: Final two-component solutions of DICCQ and their Cronbach's α coefficients

	PCA factor loadings	
Recall items (n=17): closed-ended and multiple choice response formats. Cronbach's α =0.79		
Told I can freely take part	0.719	
Told I can withdraw anytime	0.314	
Will know the study drug/vaccine	0.552	
Unauthorised person will not know about my participation	0.372	
Told the contact person	0.540	
My participation can be stopped without my consent	0.420	
Will I be paid for taking part	0 395	
How were participants divided into groups	0.403	
At what point can I leave study	0.371	
Meaning of signing/thumb-printing consent form	0.390	
How I decided to take part	0.429	
What will you I receive as compensation	0.520	
What will happen if I decide to withdraw	0.464	
Reason for doing the parent study	0.393	
Which are the study procedures	0.489	
Which are the study activities	0.617	
Which are the main benefits of taking part	0.390	
Understanding items: open-ended response format (n=9) Cronbach's α=0.73		
Describe the function of the study drug/vaccine		0.647
Mention the name of contact person		0.451
Tell what researchers want to find in this study		0.312
Number of study visits		0.492
Tell what were done during study visits		0.498
Describe how participants were divided		0.689
Tell difference between taking part in study and going to hospital		0.464
What are the possible unwanted effects of study drug/vaccine		0.388
Why were participants given different drugs/vaccines		0.437

Table 7 shows the factorial weights of each item of the 2 components are greater than 0.30 and the Cronbach's alpha coefficient of each component is greater than 0.70 suggesting high internal consistency.

5.7.3: Internal Consistency Reliability

Cronbach's alpha computed for the item-reduced DICCQ was 0.79 and 0.73 respectively for 'recall and understanding' domains. The overall Cronbach's alpha coefficient for DICCQ was 0.71. These values indicate a high correlation between the items and that the questionnaire is reliable (Table 7).

5.7.4: Test-retest reliability

One hundred and twenty six (51.0%) of 247 participants completed the second questionnaire at a mean of 7.5 days after the first administration. The mean age (SD) of respondents who had re-test was 36.9±15.1 years; 77 (60.6%) were females and 50 (39.4%) were males; 60 (47.2%) were from rural setting while 67(52.8%) lived in the city. The average time of administration was 18.5 ± 5.4 minutes (range, 9-39minutes). Intra-class correlation coefficient of 0.94 (95% CI: 0.923-0.954) was obtained showing that the questionnaire was consistently reliable over the two periods of administration.

5.7.5: Convergent validity

To test the expected relationships between DICCQ and ICQ, the correlation of the participant scores on the 'understanding' sub-scales of DICCQ with ICQ was estimated (n=247). As expected, DICCQ was significantly positively correlated with 'understanding' sub-scale of ICQ ($r = 0.306$, $p<0.001$). However because r is less than 0.4, the correlation between the two questionnaires could be described as weak. These findings provide some evidence of convergent validity.

5.7.6: Discriminant validity

Also as predicted, DICCQ was significantly negatively correlated with 'satisfaction' sub-scale of ICQ (r = -0.105, p=0.049), providing evidence of discriminant validity.

5.7.7: Discriminative validity

The median comprehension scores of women in the urban area who had formal education were significantly higher than uneducated men living in the rural area (p<0.0001). This showed that DICCQ could discriminate participants based on gender, place of domicile and education status. This provides further evidence of construct validity (Table 8).

Table 8: Discriminative validity showing differences of baseline comprehension scores by participants' demographic variables

		Median scores (IQR)	P value*
Gender	**Male (n=91)** **Female (n=156)**	68 (61-72) 84 (78-89)	<0.001
Domicile	**Urban (n=129)** **Rural (n=118)**	86 (81-90) 68 (61-72)	<0.001
Education status	**Educated (n=62)** **No education (n=185)**	93 (81-102) 78 (68-86)	<0.0001

*Significance testing was done by Mann-Whitney U test

5.8: Discussion

This evaluation of a digitised audio informed consent comprehension questionnaire among a sample of clinical trial participants in rural and urban Gambia settings suggests that it has good psychometric properties. This study demonstrates that the digitised

questionnaire can be developed and psychometrically evaluated in three different oral languages.

Expectedly, DICCQ scores were significantly positively correlated with 'understanding' sub-scale of ICQ, and significantly negatively correlated with 'satisfaction' sub-scale of the questionnaire. These significant correlations are evidence of convergent and discriminant validity of the DICCQ respectively, because DICCQ scores correlated with scores on ICQ in the theoretically expected directions. Furthermore, there were significant statistical differences in the participants' scores on DICCQ based on their gender, domicile and education status ($p<0.0001$), providing evidence of discriminative validity of the questionnaire. Together these findings establish construct validity of DICCQ.

This innovative approach of developing and delivering questions has enabled rapid measurement of informed consent comprehension in rural, remote and urban research settings in The Gambia. It overcomes the obstacles of multiple translations of written documents, which are quite challenging in some African countries due to lack of standardised written languages and low literacy. The use of orally recorded translations of the questionnaire and delivery through digitalised format ensured the questions were consistently administered to all participants. This is an advantage given that the communication skills of the interviewer is known to influence comprehension of the information, hence, it was important we used experienced native speakers to translate the English version of the questionnaire to Gambian local languages that are understandable to participants in the rural and urban settings. The questionnaire software also has an in-built database which minimises errors in data entry and reduces

data entry time. This improves the accuracy and quality of the data and ultimately the psychometric properties of the questionnaire.

Another important strength of this study is the reasonable sample sizes used, both in the rural and urban populations. Almost 99% of the participants for the first and re-test assessments completed the study. The representative sample and high response rates could be due to the fact that the participants were recruited from ongoing clinical trials with regimented study visits. Also, the strategy used in administering the questionnaire in the local languages of choice of the participants encouraged greater participation and high retention rates.

A limitation could be that this experience is very specific to The Gambia, a relatively small country with three major local languages. It may be challenging to translate this experience to other contexts. Nevertheless, this effort represents an important development towards improving informed consent comprehension. To date, a lot of literature has explained the challenges of informed consent comprehension in resource-poor contexts, but few concrete recommendations have improved it. If DICCQ can help to identify elements of informed consent which are less understood in a specific context, then further work could be done within a multidisciplinary team and the community for developing better approaches, better wordings, better examples for describing those aspects which are more difficult to understand in that very context.

5.9: Conclusions

The DICCQ was developed using a combination of international and local guidelines. The psychometric evaluation suggests that the questionnaire has two factors, consistent

with definition proposed by Minnies et al (170) suggesting 'comprehension' as comprising 'recall' and 'understanding' components.

It can be concluded that DICCQ has good psychometric properties, and has potential as a useful measure of comprehension of informed consent among clinical trial participants in low literacy communities. It will therefore be used for evaluation of informed consent comprehension in the next stages of the study reported in this thesis.

COVER SHEET FOR THE PUBLISHED ARTICLE INCLUDED IN THIS THESIS

1. For a 'research paper' already published

1.1. Where was the work published? **Journal of Clinical Research and Bioethics**

1.2. When was the work published? **August 2014**

1.2.1. If the work was published prior to registration for your research degree, give a brief rationale for its inclusion: **Not applicable**

1.3. Was the work subject to academic peer review? **Yes**

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2. For a 'research paper' prepared for publication but not yet published

2.1. Where is the work intended to be published? : **Not applicable**

2.2. Please list the paper's authors in the intended authorship order: **Not applicable**

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3. For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)

The successful publication of two previous articles on my PhD findings and the positive interest they generated locally and internationally encouraged me to publish findings of the second stage of the study. I wrote the first draft of the article. All co-authors provided comments on the draft article, many of which I incorporated during revisions to the article. I further revised the article substantially in line with the reviewers' comments.

NAME IN FULL (Block Capitals) AFOLABI, MUHAMMED OLANREWAJU

STUDENT ID NO: LSH298326

CANDIDATE'S SIGNATURE ……Date : 15 August 2014

SUPERVISOR/SENIOR AUTHOR'S SIGNATURE (3 above) ……

Chapter Six: Development and pilot-testing of the study intervention (multimedia consent tool)

6.1: Introduction

Having described the development and psychometric validation of the study questionnaire, I move to the next stage on the development and pilot-testing of the study intervention. As the main goal of this project is to develop a suitable consent tool for Gambian research context, it is appropriate to build the development of the tool on the informed consent document of a clinical trial. This is because evidence has shown that developing informed consent interventions on simulated studies generated conclusions that could not be extrapolated to 'real life' clinical trial settings (129). Consequently, I will start by describing the clinical trial on which the study intervention was developed.

6.2: The PRINOGAM trial

The development of the multimedia tool was done using the informed consent document of PRINOGAM trial (ClinicalTrials.gov NCT01838902). Briefly, PRINOGAM is an open-label, four-arm treatment trial, aimed at determining the lowest possible primaquine dose to obtain a substantial gametocytocidal effect in asymptomatic malaria infected individuals, as this may reduce the risk of harmful effects in Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency.

The trial was planned to take place concurrently at Basse and Jahaly areas of The Gambia where level of literacy of the inhabitants is low (see study sites on Figure 5). As stated in chapter one, The Gambia is one of the smallest West African countries with a population of 1.79 million people and adult literacy rate of less than 30% (33). Mandinka, Fula and Wolof are three major ethno-linguistically distinct groups

populating the study area. In addition to low literacy, no written translation of consent documents to local languages is possible as no standardised written format for the local languages exist (76, 207).

6.2.1: Development of multimedia tool from informed consent document of PRINOGAM.

I worked with a multimedia expert who had extensive training and experience in motion graphics and interactive media design to develop the participant information document of PRINOGAM trial into a multimedia tool. The participant information document was earlier developed by the Principal Investigator of the trial with technical support from the Medical Research Council (MRC) Clinical Trials Support Manager who ensured that all relevant information was adequately and comprehensibly presented in the document. The document was submitted along with the study protocol to an independent body of scientists who reviewed and confirmed that information contained in the document was satisfactory to engender informed decision-making by potential study participants. After scaling the first stage, the information document was forwarded to the local ethical committee who also reviewed and approved the document as conforming to internationally agreed ethical requirements for conduct of clinical trials.

The information in the approved document was presented in 11 sections namely: *introduction, reason for the study, what is G6PD, how to take part, what would happen if one took part in the study, what blood tests would be done, what are the side effects and possible risks of taking part, potential benefits, would taking part in this study be kept confidential, who has reviewed this study, who can be contacted if one has questions*?

With the support of the multimedia expert, the messages in each section were graphically translated into a context-specific visual story. I serially reviewed these storyboards to confirm appropriateness to the Gambia research setting. The stories were acted in role-plays by members of MRC clinical trial team after undergoing several training and rehearsal sessions. The final role-play on each section of the information sheet was serially video-recorded by the multimedia expert.

Three experienced linguistic professionals who are native speakers of the three major Gambian languages and are also familiar with clinical research concepts were contracted to audio-translate each section of the participant information document. The audio- translations were confirmed to be consistent with the English version by another three native speakers of the languages. The audio-translations were recorded as voice-overs on the video-recorded role-plays by the multimedia expert. Sections which could not be visually conveyed in the role-plays e.g symptoms of adverse events of study drugs like headache, diarrhoea, passage of dark-coloured urine were graphically represented with animations.

The video recording of the role-plays was done at one of the MRC field sites and that of narrations of the contents of the participant information documents in Mandinka, Wolof and Fula took place at a multimedia studio in The Gambia. The video was filmed with Canon EOS 7D in full high definition (1920 x 1080) on a white wall using two-point lighting (key and fill lights). The sound was captured using the on-board camera microphone. Still images were developed using Adobe Photoshop CS6 and motion graphics (animations) were done using Adobe After Effects CS6. Editing and composition of all still pictures and animations were done in Adobe Premiere Pro CS6. Final outputs were exported from Premiere to a QuickTime (.mov) file in high definition (1080 x 720).

6.2.2: Review of multimedia tool. The first draft of the multimedia tool was produced in a digital video disc (DVD). It was given to two randomly selected lay persons and two experienced researchers to confirm whether the contents of the tool were consistent with the contents of the participant information document of PRINOGAM trial. The researchers agreed that the tool explained clearly all essential information on the study as requested by ethical and Good Clinical Practice (GCP) guidelines. The lay persons also confirmed the contents were consistent with the information sheet and easily understandable local dialects were used by the narrators. The lay persons however pointed out that one of the narrators wrongly used *'biir bumuti'* which means 'lower abdominal pain' to describe 'abdominal pain' as one of the adverse effects of the investigational products. This was corrected with appropriate word '*nahl bumuti'.* Also, omission of '*hel butey*' meaning 'nausea' was reported and this was included in the revised version. Non-inclusion of dark coloured urine as a major complication of G6PD deficiency was also highlighted by one of the reviewers and this was included in the revised version.

6.2.3: Pilot-testing: A purposive sample of 42 healthy male and female volunteers aged 18-49 years was recruited to pilot-test the multimedia informed consent tool. The upper limit of the age range (49 years) was based on data from previous studies in The Gambia (224, 307). The lower age limit (18 years) was chosen to avoid the logistical challenges associated with obtaining informed consent from under-aged participants. Participants were recruited from the north and south parts of Basse to ensure adequate representation. Despite being representative of the PRINOGAM trial population and participants could in the future become eligible, they were not screened for PRINOGAM trial when the pilot-testing was carried out. After obtaining written informed consent,

the multimedia tool was played on a computer laptop for each participant in his/her preferred local language in noise-free consulting rooms at MRC facilities located within Basse Major Health Centre. The participants were requested to ask questions if they were not clear about the contents of the multimedia tool.

To assess acceptability and ease of use of the multimedia tool, an 8-item questionnaire was adapted from a similar study conducted in South Africa (154). The original questionnaire contained 15 questions on acceptability and ease of use of an alternative informed consent tool. The relevant questions were retained e.g *''do you like the pictures in the tool* while non-relevant questions were removed*: e.g do you know how to replace the battery of the tool'.* After watching the multimedia video and participants confirmed they had no questions, the 8-item questionnaire was administered to each participant to assess acceptability and ease of use of multimedia tool. Participants responded by indicating either 'yes or no' to each question item.

Following the questionnaire administration, the participants' comprehension was assessed using the digitised audio questionnaire (DICCQ) that was previously validated (308) and described in section 5.3 of this thesis.

To assess how much of the study information was retained, the participants were invited one week after first administration and the DICCQ was re-administered to the participants.

6.2.4: Focus group discussions. During the second visit, randomly selected participants from the enrolment register were invited for focus group discussions (FGD) to further explore acceptability and ease of use of multimedia consent tool and digitised informed consent comprehension questionnaire. Two FGD sessions involving separate

groups of six men and women were held. Participants were segregated by gender to ensure open discussions in each group. A purpose-designed FGD guide was used and I served as the facilitator of the discussions. The proceedings were audio-taped after verbal consent was obtained from the participants. These were translated and transcribed into English by two independent native speakers. I identified the main themes of the transcribed texts and performed content analysis of these themes.

6.2.5: Scoring system: The scoring system described in Table 5 was used.

6.2.6: Data analysis: Data on acceptability and ease of use of multimedia tool and digitised questionnaire were entered on Microsoft Excel while data on participant comprehension were retrieved from the in-built database within DICCQ and exported into Microsoft Excel. Acceptability and ease of use were assessed by calculating the percentages of 'yes' responses indicated by participants on the questionnaire. I adopted the definition of comprehension used by Minnies et al (170) consisting of two components: recall and understanding. 'Recall' was defined as correct answers to the close-ended and multiple choice questions while 'understanding' was correct responses given to the open-ended questions (170).

A repeated measures analysis of variance model was used to determine the effect of the multimedia and the effect of time on the participants' recall and understanding scores at the two study visits. Pair-wise comparison of the mean difference of the participants' scores between first and second visits was performed and appropriate Bonferroni corrections were made to allow for multiple comparisons. Analysis was done with Stata version 12.1 (College Station, USA) with $p<0.05$ (two-tailed) considered significant.

6.3: Results of pilot-testing of multimedia consent tool

6.3.1: Participant information*:* Forty-two participants consisting of 20 females and 22 males were recruited. Table 9 shows socio-demographic characteristics of the study participants. The mean age (SD) was 34.5 ± 11; (range, 18-48 years), 90% were Mandinka and less than 10% had Western education. Each playing session of the multimedia tool lasted an average of 20 minutes, while questionnaire administration through DICCQ took an average of 32 minutes.

Table 9: Socio-demographic characteristics of the study participants

Characteristics	Frequency (%) N=42
Age group	
18-25 years	4(9.5)
26-33 years	16(38.1)
34-41 years	13(31.0)
42-49 years	9(21.4)
Sex	
Female	20(47.6)
Male	22(52.4)
Ethnicity	
Mandinka	38(90.5)
Fula	4(9.5)
Highest level of education attained	
Primary	2(4.8)
Secondary	2(4.8)
Arabic	29(69.0)
Vocational education	1(2.4)
No formal education	8(19.0)
Occupation	
Artisan	7(16.7)
Farming	10 (23.8)
Housewife	17(40.5)
Schooling	1 (2.4)
Trading	7(16.7)
Area of domicile	
Basse North	20(47.6)
Basse South	22(52.4)

Table 9 shows that 38% of participants were in 26-33 year age group, about 10% had either primary or secondary education and majority belonged to Mandinka ethnic group.

All participants liked the features of the multimedia tool, would like to use it again, and wanted future study information delivered using the tool (Table 10). About 70% reported that they were comfortable with the tool and that it was easy to follow. The remaining 30% said they felt very comfortable using the tool and it was very easy to follow. However, about 10% of participants suggested changes to the Fula translation of the tool. The dialect (Fula Puta) used in the tool was not generally acceptable to the participants. Fula Torah was suggested as the appropriate dialect.

The colour, pictures and voices used in the DICCQ were acceptable to the participants (Table 11). About 60% reported it was easy to follow; 40% said it was very easy to follow. 70% were comfortable and 30% were very comfortable with it. About 17% suggested changes to the tool mainly on reducing administration time of the tool (8%) and overall waiting time (9%).

Table 12 shows that the mean participant scores were high on the question items on adverse event/risk, voluntary participation, meaning of giving consent, study procedures while lowest mean scores were recorded on the two question items about randomisation, indicating that the participants needed further explanation to comprehend this concept.

The differences in the mean scores for participants' recall between first and second visits showed an increase statistical significance [$F(1, 41) = 25.38$, $p<0.00001$] (Table 13). Similar trend was observed in the mean scores for participants' understanding between first and second visits [$F(1, 41) = 31.61$, $p<0.00001$]. Pair-wise comparison of the significance levels for the time difference of the participants' recall scores at the two study visits showed a mean time difference of 2.33 ($p<0.0001$, 95% CI: 1.398-3.269).

Similarly, the participant understanding scores showed a mean time difference of 3.60 ($p<0.0001$, 95% CI: 2.304-4.887).

Table 10: Participants' responses to questions on acceptability and ease of use of multimedia informed consent tool

1. Overall, how much do you like the following features of the multimedia tool?	**Like (N=42)**	**Dislike (N=42)**	**I don't know (N=42)**
Colour	42(100.0)	0(0.0)	0(0.0)
Pictures	42(100.0)	0(0.0)	0(0.0)
Voices	42(100.0)	0(0.0)	0(0.0)
Duration	42(100.0)	0(0.0)	0(0.0)
2. Do you think the tool provide enough information about the study?	**Yes**	**No**	**I don't know**
	42(100.0)	0(0.0)	0(0.0)
3. Overall, how comfortable are you with the information in the tool?	**Comfortable**	**Very comfortable**	**Not comfortable**
	30(71.4)	12(28.6)	0(0.0)
4. Overall, how easy or difficult did you find the information provided in the tool	**Easy**	**Very easy**	**Difficult**
	30(71.4)	12(28.6)	0(0.0)
5. Will you like to use it again?	**Yes**	**No**	**I don't know**
	42(100.0)	0(0.0)	0(0.0)
6. Would you want future study information delivered through this tool?	**Yes**	**No**	**I don't know**
	42(100.0)	0(0.0)	0(0.0)
7. Do you want any changes to the tool?	**Yes**	**No**	**I don't know**
	4(9.5)	38(90.5)	0(0.0)

Table 11: Participants' responses to questions on acceptability and ease of use of digitised comprehension questionnaire (DICCQ)

1. Overall, how much do you like the following features of DICCQ?	**Like (N=42)**	**Dislike (N=42)**	**I don't know (N=42)**
Colour	42(100.0)	0(0.0)	0(0.0)
Pictures	42(100.0)	0(0.0)	0(0.0)
Voices	42(100.0)	0(0.0)	0(0.0)
Duration	39(92.9)	3(7.1)	0(0.0)
2. Overall, how easy or difficult did you find the questions provided in the tool	**Easy**	**Very easy**	**Difficult**
	24(57.1)	18(42.9)	0(0.0)
3. Overall, how comfortable are you with the information in the tool?	**Comfortable**	**Very comfortable**	**Not comfortable**
	30(71.4)	11(26.2)	1(2.4)
4. Will you like to use it again?	**Yes**	**No**	**I don't know**
	42(100.0)	0(0.0)	0(0.0)
5. Would you want future study questionnaires delivered through this tool?	**Yes**	**No**	**I don't know**
	42(100.0)	0(0.0)	0(0.0)
6. Do you want any changes to the tool?	**Yes**	**No**	**I don't know**
	7(16.7)	35(83.3)	0(0.0)

Table 12: Summary statistics of participants' scores on the audio digitised comprehension questionnaire (DICCQ) at week 0

	Section A: Choose only one right answer	Mean	SD*	Minimum	Maximum
1.	Have you been told that you can freely decide to take part in this study?	2.86	0.65	0	3
2	Have you been told you can withdraw from this study anytime?	2.74	0.83	0	3
3.	During the study, will you know the drug you or your child is receiving?	2.86	0.52	1	3
4.	If yes, describe or mention what the drug is doing? How did this get scored?	2.95	1.10	1	5
5.	During the study, will anyone not working with MRC know about your health information?	2.29	1.23	0	3
6.	Have you been given the name and phone number of the person to contact if you have any questions about the study?	2.50	0.99	0	3
7.	If yes, mention the name of the person?	2.07	1.30	0	3
8.	Can your participation in the study be stopped without your consent?	1.49	1.49	0	3
9.	Will you receive money for taking part in the study?	2.52	0.94	0	3

Section B: Answer the following questions by circling the right answer

10.	How were participants divided into different groups in this study?	0.02	0.15	0	1
11.	At what point can you leave the study?	2.02	1.41	0	3
12.	What does it mean when you sign or thumbprint the study consent form?	2.93	0.46	0	3
13.	How did you decide to participate in this study?	1.79	1.49	0	3
14.	What will you receive as a reward for taking part in the study?	2.79	0.78	0	3
15.	What will happen if you decide to stop taking part in this study?	2.71	0.89	0	3
SECTION C: You will need to circle more than one correct answers in this part					
16.	Which of the following describes why the primaquine study is being done?	2.95	1.01	2	4
17.	Which procedures were you asked to take part in?	3.33	0.95	2	4
18.	Which activities were you asked to complete?	2.76	0.98	2	4

19.	Which describes the main benefits of taking part in the study?	3.04	1.01	2	4
	SECTION D: In this section, you are requested to provide answers that are specific to the study you are currently participating.				
20.	Please tell me what the researchers want to find out in the study?	2.92	0.78	0	5
21.	How many times do you have to come to the clinic for a visit during the study?	3.17	2.17	0	5
22.	Tell me what will be done during the study visits?	2.92	1.26	0	5
23.	How are participant assigned into different groups this study?	0.88	1.13	0	3
24.	What is the difference between taking part in this study and going to see a doctor for treatment?	2.97	2.48	0	5
25.	What are the possible unwanted effects of taking part in this study?	4.36	1.21	0	5
26.	Why do you think some of the study participants were given different medicine?	2.98	2.48	0	3

***SD= Standard deviation**

Table 13: Repeated measures analysis of variance of participants' recall and understanding scores at week 0 and week 1

	'Recall' scores (N=42)	'Understanding' scores (N=42)
Week 0	25.62±4.4	55.00±5.58
Week 1	27.95±4.8	58.5952±7.06
Within-participant effects	F-test=25.38 P<0.001	F-test=31.61 P<0.001
Between-participant effects	F-test=1588.91 P<0.0001	F-test=3743.267 P<0.0001
Pair-wise comparison of significance levels for the time difference	Mean time difference =2.33 S.E=0.463, P<0.0001 95% CI (1.398-3.269)	Mean time difference= 3.60 S.E=0.639, P<0.0001 95% CI (2.304-4.887)

Table 15 shows that mean participant's 'recall and understanding' scores differed significantly between 2 time points (F (1,41)= 25.384, p<0.00001 and (F(1,41)= 31.611, p<0.00001 respectively. Pair-wise comparison of the significance levels using the Bonferroni correction revealed a significant increase in 'recall and understanding' scores over one week period, ($p < 0.0001$).

6.3.2: Findings of FGDs

In the two FGD sessions held with 24 participants from the cohort, the main areas of discussion fell into three categories: acceptability, ease of use and suggestions to improve the tools.

6.3.2.1: Acceptability: Overall, there was a consensus that the multimedia tool was clear, helpful, informative, easy to follow and understand. Most of the participants were excited about watching the video and hearing their local languages being used to explain the study information. One 32 year old male participant expressed that the tool was capable of improving understanding of study information as follows: *'I have been coming to this hospital for over 10 years; I have never seen a thing like this. The sound is very good and clear to me, I am sure this thing will help to improve understanding. I am happy (and) like to join (PRINOGAM) study '*.

A 29 year old female participant also commented: *'Though I have taken part in MRC studies before, but this one will be different. The picture and the information are clear, I am very impressed. My concern is if I get pregnant before the time this study starts, how will I take part?'*

6.3.2.2: Ease of use: The majority of the participants admitted that they could not used a computer, but could use mobile phones for daily activities, which they claimed made the multimedia and DICCQ tools easy to follow and use. A 38 year old male regular attendee at the health centre noted: *'I must thank you people for thinking of this very nice thing. Although, I am not used to a computer, I can use mobile phones very well. (So), I can follow and even use this computer easily'.*

6.3.2.3: Suggested changes to multimedia and DICCQ: One participant said: '*The video is fine but it will be better if background music is reduced'.* (27 year old housewife)

A male participant suggested reducing the time to administer the DICCQ and reduction in overall waiting time. *'I am happy with this tool,' he said, 'but you have to do something about the time (administration and waiting time), so that we can return quickly to our places of work'.* (35 year old trader)

6.4: Revision of multimedia tool and digitised questionnaire

Based on the feedback from the participants, the multimedia tool was returned to the multimedia expert who reviewed the tool and edited the areas that generated concerns from the participants. I searched on the internet for a more appropriate animated picture of 'randomisation process' which was further refined and used to replace the former illustrations. The volume of background music was also reduced and the voices of the narrators became more distinct. Another experienced narrator who speaks fluently the preferred Fula dialect was contracted to make another translation to replace the old one. After editing the multimedia tool, the playing time reduced by about 1.5 minutes.

Similarly, with the help of Drs Sugrue Scott and Alice Tang at the School of Medicine, Tuft University, USA, all deleted question items as a result of weak factor loadings in the psychometric analysis were finally removed from the questionnaire, reducing the time of administration to an average of 25 minutes.

6.5: Discussion

This second stage of the study evaluated a customised multimedia tool that was developed to deliver consent information to low literacy participants who were potentially eligible to enrol in a clinical trial. Despite the fact that only 10% of the study population had formal western education, the computerised tool was well received and easy to administer. Similarly, a digitised audio questionnaire developed in the earlier stage of the study was employed for assessment of the participant comprehension and was also acceptable to these participants. The participants expressed satisfaction with the tools and wanted future studies to adopt them. However, they suggested reducing the administration time for the digitised questionnaire, overall waiting time and background music in the multimedia tool.

The findings of high performance scores of the participants in the domains of informed consent such as adverse events/risk, voluntary participation, meaning of giving consent and study procedures suggest that the participants understood these concepts better. Conversely, low scores recorded on 'randomisation' might show that the participants had difficulty understanding it. This aspect was carefully revised to make the concept clearer in the final version of the tool. Overall, illustrations of the study information using a combination of video, animations and oral explanation in local languages could have contributed to the high comprehension scores. These findings represent a new insight into the use of multimedia tool to deliver consent information to low literacy participants in sub-Saharan Africa.

Furthermore, the multimedia tool increased significantly both recall and understanding scores of the participants and this is consistent with the results from some previous studies (156, 157, 272, 273, 309). The increase in participant recall and understanding scores observed after one week period could be explained by the quiz/feedback strategy adopted in the digitised questionnaire. This introduced the possibility of enhancement or practice effect due to memorisation which might occur when participants gave correct answers or when the researchers clarified area of concerns. To minimise the memorisation or practice effect, the digitised questionnaire used closed ended, multiple-choice and open-ended items which were likely to elicit responses that truly reflect the participants' comprehension of the information.

A major benefit of the multimedia tool is that it consistently provides the same research information to all participants in the same manner. This strategy removes inter-person variations in translations of informed consent information to the low literacy research participants. This becomes crucial as participant comprehension is influenced by the communication skills of the person administering the consent. This is particularly true in contexts like the Gambia, where there is no standard writing format for the local languages and the person administering the consent plays a key role in translating it orally. It was therefore critical that I employed the services of experienced linguistic professionals who were native speakers to translate the written English version of the informed consent document to the audio forms of three major Gambian languages.

Furthermore, the development of the multimedia tool involved many technical processes including graphical translation of elements of the informed consent document to appropriate visual stories. These were further acted in role-plays by trained individuals

before video, animations and audio-translations in local languages are systematically added. Some researchers have argued that the time and cost involved in the production of a multimedia tool might further add to logistic challenges of the conduct of clinical trials (6, 152). However, the ultimate benefits of ensuring well-informed research participants through the use of multimedia intervention could, in addition to improving participant comprehension, protect their freedom to decide, and also potentially improve the quality of data and outcome of the research.

The use of a multimedia tool to deliver study information during informed consent process may weaken compassionate human interactions that form the basis of research ethics (310). Therefore, it could be counter-productive to depend solely on the technology to meet the information needs of participants during the informed consent process. The research team needs to keep enough time in discussing the participants' concerns about the research, in addition to the multimedia. The multimedia could in fact replace the first part of 'traditional' consent interview. It could be followed by an interview where the participants would still be free to ask clarification questions. Thus, the overall acceptance and success of the tool will ultimately depend on a well-balanced combination of the technology and human elements.

Although both quantitative and qualitative assessments adopted in this study consistently revealed improvements in the participants' comprehension scores, caution is required in interpreting these observations because this stage of the study targeted healthy volunteers who were not enrolled in any study. The simulated trial situation might have over-estimated the advantages of the multimedia tool and under-estimated other factors which would be present in real life. Nevertheless, increase in participant comprehension

scores over a one-week period was consistent with the design of this study. The use of repeated measures design allowed the study participants to serve as their own control. This improves the precision of the study by reducing the size of the error variance.

Another limitation of this study may be due to the fact that it reflects the situation in The Gambia, where local languages do not have written standardised forms. Consequently, it is suggested that the tool should be tested and adapted in different sub-Saharan African contexts.

This stage of study provides important information on the development and evaluation of a multimedia strategy for improving comprehension of informed consent among low literacy individuals. It gives an initial assessment of the strength of the tool and identified areas for further improvement. Based on the findings of this study, the weak areas of the tool were comprehensively improved to make it more appropriate for the next evaluation study where I compared the multimedia consent tool with the 'conventional' consent procedure among participants enrolled in the PRINOGAM trial. The methods, results and discussion of the findings of evaluation of the revised multimedia tool will be discussed in the next three chapters of this thesis.

Chapter Seven: Methods

7.1: Introduction

This chapter describes the methods employed to achieve the third objective of the study reported in this thesis i.e. randomised controlled trial evaluating the effects of multimedia consent tool on participant comprehension. I will start by giving further background information on the parent trial, and this will be followed by the study design, sampling, recruitment and data collection processes.

7.1.1: Context of the study

This stage of the study was nested within PRINOGAM clinical trial. To avoid being confused with the PRINOGAM trial by the participants and trial staff, this study was referred to as the 'multimedia study'. This name will be used subsequently in this thesis. As described above in section 6.2, PRINOGAM is an abbreviated title of 'Primaquine's gametocytocidal efficacy trial in malaria asymptomatic carriers treated with dihydroartemisinin-piperaquine (DHAPQ)'. The trial is based on new WHO guidelines for treatment of uncomplicated *Plasmodium falciparum* malaria which recommend addition of a single dose of primaquine (PQ) (because of its gametocytocidal properties) to an artemisinin-based combination treatment (ACT). However, primaquine use has been limited by its haematological toxicity (haemolytic anaemia), particularly in individuals with glucose-6-phosphate dehydrogenase deficiency (G6PDd). The trial aimed to determine optimal dosage of PQ required for a gametocytocidal and transmission blocking effect; as this may reduce the risk of harmful effect in G6PDd individuals.

The parent study is an open-label, four-arm treatment trial, with a follow up of participants until 42 days after treatment. Potentially eligible participants aged 1 year and above were identified in a mass screening for malaria infection in villages around Basse and Jahaly sites, using a rapid diagnostic test (RDT) and microscopy. Individuals with confirmed malaria infection were further screened for G6PDd and were excluded if positive. Participants attended the trials sites at Day 0, 3, 7, 14, 21, 28, 35 and 42. At each visit, safety assessments were performed by the trial staff and blood samples were collected to determine haemoglobin and gametocytaemia. For participants' convenience and to avoid deviation from the trial protocol, participant visits in the multimedia study were made to coincide with the scheduled visits of the PRINOGAM trial.

7.1.2: Study design

The study design for this stage was experimental in the form of a randomised controlled trial (RCT). This design was aimed at comparing the comprehension scores of the study participants who received the multimedia consent information (intervention) with the participants who received the 'standard' consent information (control).

Randomisation is designed to maximise equal distribution of known or unknown variables that may likely influence the primary outcome of interest i.e. comprehension scores of participants in the intervention or control groups and this minimises the chance of confounding (311). According to Shadish et al (311), randomisation of participants may not be practicable or desirable in certain conditions. These include emergency situations where study information needs to be delivered urgently to participants; availability of high quality prior information about clinical trial participation; situations which do not give rooms for adjustment of independent variables (e.g. age, gender); and

for ethical reasons where participant cannot be randomised to an intervention which could cause harm. It was established that none of these conditions were present in the present study.

The justification for this study design was further supported by an international guidance which states that before RCT could be conducted, it is important to justify that "... the present conditions need improvement, that the proposed improvement is of unclear value, that only an experiment could provide the necessary data to clarify the question, that the results of the experiment would be used to change the practice or policy, and that the rights of individuals would be protected in the experiment (311)".

The conditions highlighted above perfectly fit this study because an important need exists to improve the comprehension of low literacy Gambian participants about informed consent. Also, owing to scarcity of empirical evidence in African research settings, the benefits of multimedia intervention have not been established despite various studies suggesting its potential usefulness.

The process of randomisation for the participants enrolled in the multimedia study will now be discussed in greater detail. Stratification was adopted in the randomisation to increase the statistical power of the study and to enhance validity of statistical conclusions(311),(p45-46). An independent statistician used RANDI3, (http://dschrimpf.github.io/randi3/), a web-based open source application to generate the randomisation list for each of the sites. During trial configuration process, the software allowed specification of participants' demographic characteristics that were required for

stratification. For this study, participants were stratified by age groups namely 18-29years, 30-49 years and ≥50 years and gender: male or female. Randomisation was done at a 1:1 ratio across intervention and control arms using a fixed block size of four allowing participant allocation in any of the orders: IICC, ICIC, CICI, ICCI, CIIC, or CCII where 'I' represents intervention and 'C' represents control arm.

7.1.2.1: Risk of bias

It is generally accepted that validity is critical to the design adopted in a study (311),(p38-39). Given its significance and relevance to the experimental study design used in this stage of the study, factors which might jeopardise validity of the study findings were carefully considered and addressed. Two types of validity are widely documented: internal validity which refers specifically to whether the experimental intervention makes a difference or not, or whether there is sufficient evidence to support this claim. External validity, on the other hand, refers to generalisability of the intervention outcomes (311).

A major threat to external validity was selection bias and this was minimised by random assignment of the participants to the study arms (311),(p56). To avoid participant sensitivity or responsiveness to the experimental variables, the participants recruited for the pilot-testing of the study interventions (second stage of the study) were not included in the randomised controlled trial (third stage of the study). All participants were informed that the study was designed to identify ways of improving understanding of study information. They were told that the study was aimed to determine whether multimedia delivery of consent information would improve participant comprehension when compared with the written information delivered verbally by trained field

assistants. Because the intervention constitutes a compulsory ethical requirement that must be achieved before trial-related procedures are performed, it was not possible to blind participants and/or investigators in this study.

Furthermore, allocation of participants using the randomisation list generated by the statistician was done by administrative members of the trial team. The field staff involved in recruiting participants to the study were therefore not involved in the randomisation process and did not have a pre-knowledge of the study arms which participants were allocated.

7.1.3: Intervention

For clarity, I will describe first the control arm as it involves the 'standard' practice in informed consent procedure in The Gambia.

7.1.3.1: Control arm

The control arm of the multimedia study involved the current 'standard' practice approved by the local ethics committee in The Gambia for presenting clinical trial information to potential participants (36). The position was taken because there is no standardised writing format for local languages in The Gambia, making it impractical to translate participant information sheet from English to the local languages. Experienced field staffs who are native speakers of the major local languages are trained on the correct interpretation of the contents of English version of the participant information sheet by the study's Principal Investigator. To ensure that the field staffs understand the study information correctly, they perform the informed consent session in role-plays and these are supervised by the study's Principal

Investigator. The trained field assistants deliver the study information verbally to the prospective participants during sensitisation exercise. The participants are given appointment to return to the trial site after discussing the study information with their husbands (in case of mothers of child participants) or parents (in case of minors). In subsequent visits, the participants are seen by a trained field assistant who performs a formal informed consent by giving oral presentation of the contents of participant information sheet in the local languages. Literate participants give consent by signing the consent form while non-literate participants thumb-print the consent form in the presence of an impartial witness (76, 207).

7.1.3.2: Intervention arm

Following randomisation to the intervention arm of this study, a trained field assistant selected a local language preferred by a prospective participant from the multimedia DVD menu and this was played individually to the participant on a computer laptop in a quiet room at the trial sites. The process of developing the multimedia tool has been described in detail in section 6.2.1.

7.1.4: Primary endpoint

Adopting the operational definition of 'comprehension' given by Minnies et al (170), the primary study endpoint is the 'comprehension' of consent information as measured by the total test scores of participants who succeed in selecting correct answers to the closed ended and multiple choice question items and give correct interpretations or responses to the open-ended question items on DICCQ at Day 0 visit.

7.1.4.1: Secondary endpoints: 'Comprehension' of consent information as measured by total test scores of participants who succeed in selecting correct answers to the closed

ended and multiple choice question items and give correct interpretations or responses to the open-ended question items on DICCQ at Days 7,14,21 and 28 after Day 0 visit.

The participant scores at each of these time points are considered independent irrespective of the baseline (Day 0) scores.

7.1.5: Sample size determination

Findings of a systematic review, (discussed in Chapter 3 of this thesis), showed that the comprehension scores of African participants on basic research concept such as randomisation was 47% when conventional written informed consent procedure was used (7). Given this assumption, the power calculation indicated that, in order to achieve 90% chance of detecting a 20% difference at the 5% significance level (two-sided) when a multimedia consent tool (intervention) is compared with conventional consent procedure (control); a total of 137 participants would be required in each study arm. Adding a 10% attrition rate, an approximated sample size of 150 participants was required per study arm.

7.1.6: Coordination of the study

All stages of the study reported in this thesis were conceived, planned and executed by me, with the support of four research assistants for data collection during participant recruitment, enrolment and follow-up. Oversight functions were performed by my Supervisor, Associate Supervisors and members of PhD Advisory Committee to whom I gave regular reports on the study activities. The PRINOGAM and multimedia study staff held weekly meetings to monitor recruitment rates and addressed operational challenges which affected participant recruitment and follow-up.

7.1.7: Sampling

For this stage of the study, sampling was carried out at the PRINOGAM trial sites in Basse and Jahaly areas (see map on Figure 7), located respectively in the Upper and Central River Region of The Gambia from 15 August 2013 to 12 March 2014. Participants were eligible for the multimedia study if they:

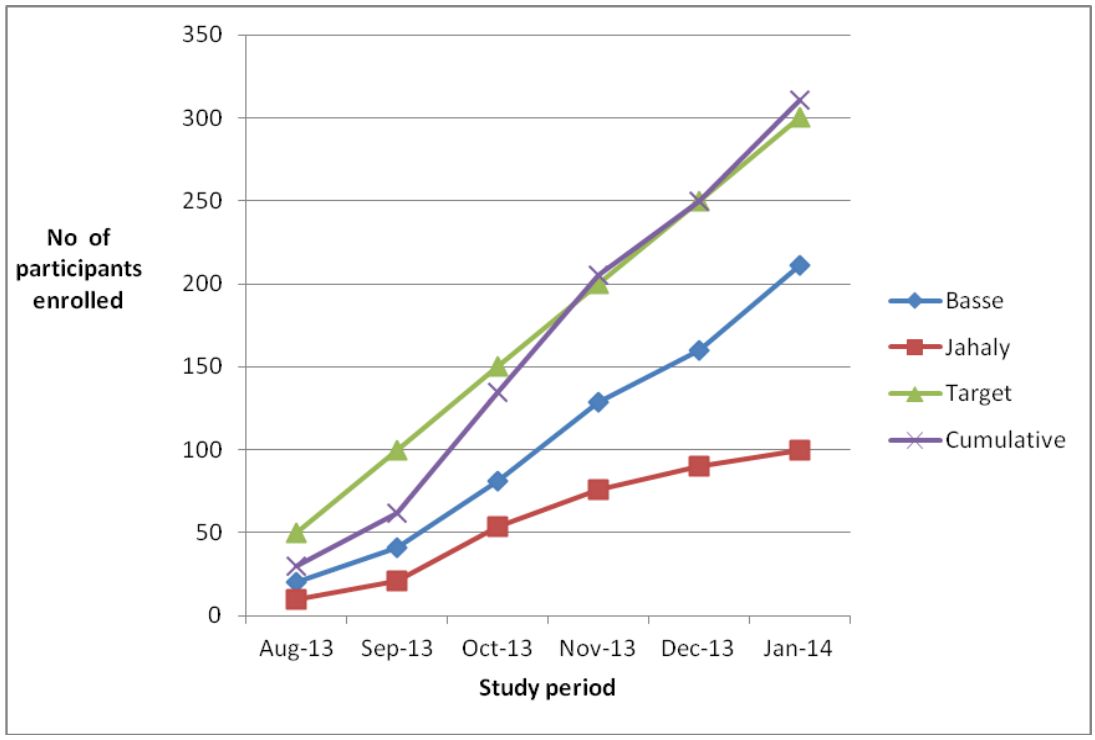
i. were eligible for the PRINOGAM trial at either of the two sites;
ii. were able to speak and understand any of the three major Gambian languages: Mandinka or Fula or Wolof;
iii. did not have obvious communication or visual problems (e.g. language problems, deafness, blindness);
iv. did not have obvious cognitive impairment or intellectual disability.

7.1.8: Participant recruitment

7.1.8.1: Timeframe and targets

Based on the recruitment plan for the parent trial which was built around the malaria transmission season from August to January, the timescale for recruitment and follow-up for the multimedia study was estimated at 6-8 months. I anticipated that recruitment of participants to the multimedia study would be influenced by the number of eligible participants for the parent trial at the two sites. A graph of recruitment targets based on a six month timeframe was projected, with a target of 50 participants per month to meet the overall target of 300 participants by January 2014. Every month, recruitment rates were mapped against the target. Cumulative monthly recruitment targets for the duration of the study are shown in Figure 8 along with the actual numbers of participants recruited.

Figure 8: Recruitment targets for multimedia study at Basse and Jahaly, 2013/14



As illustrated on the graph, the overall target of 300 participants was achieved at the two sites by January 2014. Follow-up of participants continued till middle of March 2014.

A number of participants enrolled in PRINOGAM trial were not recruited into the multimedia study, mainly because the participants refused to give consent for the multimedia study. In few other instances, some participants preferred to be allocated to multimedia group without going through formal randomisation process. These participants were excluded from the multimedia study. Also, parents or guardians who had more than one child enrolled in the parent trial were considered as a single participant in the multimedia study. Similarly, irrespective of whether allocated into the control or intervention arm, these parents or guardians were assessed for comprehension of study information at all study visits as a single participant. Overall,

89.6% (311/347) of potential participants found eligible for PRINOGAM trial were enrolled into the multimedia study.

7.1.8.2: Recruitment process

As highlighted above, potential participants for the multimedia study were identified by the multimedia research team who worked in close conjunction with the PRINOGAM trial staff. After participants had met eligibility criteria, the PRINOGAM trial staff consisting of two clinicians, four nurses and four field assistants informed the potential participants about the PRINOGAM trial and multimedia study. Participants were free to decide on participating only on PRINOGAM trial. When participants agreed to participate in the two studies, then a member of administrative staff who was not involved in the day-to-day running of the trial was called to select a randomisation envelope that had previously been computer-generated by an independent statistician.

7.1.8.3: Consent

Written and verbal information about the parent and multimedia studies were given to consenting participants by trained field staff as described in section 7.1.3.1. Before formal consenting procedure at the trial sites, community sensitisation meetings were held to raise awareness about the PRINOGAM trial and multimedia study. Because of the leadership structure in Gambian communities, the studies were first introduced to the village heads called "Alkalo". During the visits, the study rationale and justifications were explained to the "Alkalo" and his chiefs. Concerns like the issues of blood collections and required laboratory tests were explained to the community leaders in lay language. I also used the opportunity to explain the need to identify appropriate method for delivering consent information to trial participants. This was followed by presentation of

traditional 'kola nuts', which signified the symbolic introduction of the studies to the host communities. Subsequently, the "Alkalo" passed the information about the studies to potential participants through household heads and religious leaders (76).

Separate meetings were held to step down the sensitisation to potential participants at various communities. The English version of the participant information sheet for both studies was given to the participants and they were encouraged to discuss the contents with literate members of their families. A period of one to two weeks was given for the participants to decide, following which they were invited by the field staff to the trial sites.

The participants were not pressurised to give consent at the initial clinic visit, as it was made clear that participation was voluntary. Nevertheless, most participants gave consent at first visit. As described in section 7.1.3.1, for participants randomised to the 'standard' consent group, trained field staff provided the trial information orally in the local language understood by the potential participant. If participants agreed to join the PRINOGAM trial, he/she signed or thumb-printed the consent form. The same procedure was repeated by giving the information about multimedia study to the participants and he/she also signed or thumb-printed the consent form to enrol in the multimedia study.

The participants randomised to the multimedia arm were seen in separate rooms from the 'standard' consent arm. The multimedia DVD developed on PRINOGAM trial was played either by me or the trained research assistants to the participants in his/her preferred local languages on computer laptops designated for this study. Consent form

was signed or thumb-printed if participant agreed to join the parent trial. After this procedure, oral information about multimedia study was provided by the multimedia staff and participants signed or thumb-printed the consent form to confirm agreement to participate in the multimedia study.

Participants were allowed to ask questions about any area of concerns on the two studies. These questions were satisfactorily addressed either by me or the research assistants before enrolling the participants into the studies. The estimated target of 300 participants was achieved within the anticipated timeframe; another 11 participants were recruited to further improve the power of the sample size.

7.1.9: Data collection

Participants were seen for a total of seven times during the scheduled visits for PRINOGAM trial. These visits included Day 0 which was the first visit where randomisation took place and intervention was applied to participants randomised to the multimedia arm. Baseline comprehension assessments were done at this stage for participants in the control and intervention arms. Further comprehension assessments were performed at subsequent visits i.e. Days 7, 14, 21 and 28. Data were collected at these time points through the digitised audio comprehension questionnaire (DICCQ). At Day 35 visit, focus group discussions were held among randomly selected participants and at Day 42 visit, exit interviews were conducted by administration of modified version of Informed Consent Questionnaire (ICQ) (294).

7.1.9.1: Measures/instruments

7.1.9.1.1: Digitised Informed Consent Comprehension Questionnaire (DICCQ)

The development and psychometric evaluation of DICCQ has been described in detail in section 5.3. Because there was no appropriate tool that could measure comprehension of consent information among low literacy participants in The Gambia, DICCQ was developed in the first stage of this study. It underwent rigorous evaluation and was found to be a reliable and valid measure of comprehension questionnaire in Gambia research population (308). The questionnaire was also reported to be well acceptable and easy to administer among a group of prospective participants living in the study areas (312). The paper and electronic copies of the questionnaire are included in the appendix.

7.1.9.1.2: Modified version of Informed Consent Questionnaire (ICQ)

The original version of ICQ contains four question items in the understanding sub-scale and three question items in the satisfaction sub-scale (294). The modification of ICQ was described in section 5.3.4 and this format was administered to all participants in multimedia study at their exit from PRINOGAM trial i.e. Day 42 visit.

7.1.9.1.3: Focus group discussion*:* Eight sessions of focus group discussions were held among selected participants in Basse while six sessions were held among Jahaly participants due to the relative small number of participants at Jahaly site. The sessions were arranged to coincide with Day 35 visit of the PRINOGAM trial. After participants had completed the parent trial activities, they were randomly selected from the enrolment register of multimedia study. Verbal consent was obtained from each selected participant for participation and for audio-recording of the sessions. A separate group of seven to eight men and women were invited for each FGD session.

Because of cultural norms which promote male dominance in Gambian communities, the participants were segregated by gender to allow free expression of views in each homogenous group. To further ensure free interaction and easy identification of areas of agreement/disagreement on understanding of various concepts of informed consent presented during the study, the participants were not segregated by randomisation groups. A purpose-designed FGD guide was used to facilitate the session (Appendix IV). A trained research assistant and I served as the facilitators of the discussions at Basse and Jahlay sites. The sessions explored the participants' 'actual' understanding of research concepts like randomisation, placebo, blinding, therapeutic misconception in the context of PRINOGAM trial. Also, acceptability of the multimedia tool and DICCQ were explored among the participants. They were requested to identify areas (e.g. languages, pictures and administration time) where the instruments could be improved for future trial activities. Each item was extensively discussed until no new information could be obtained from the participants. Each session lasted between 45 minutes to one hour.

7.1.10: Recruitment challenges

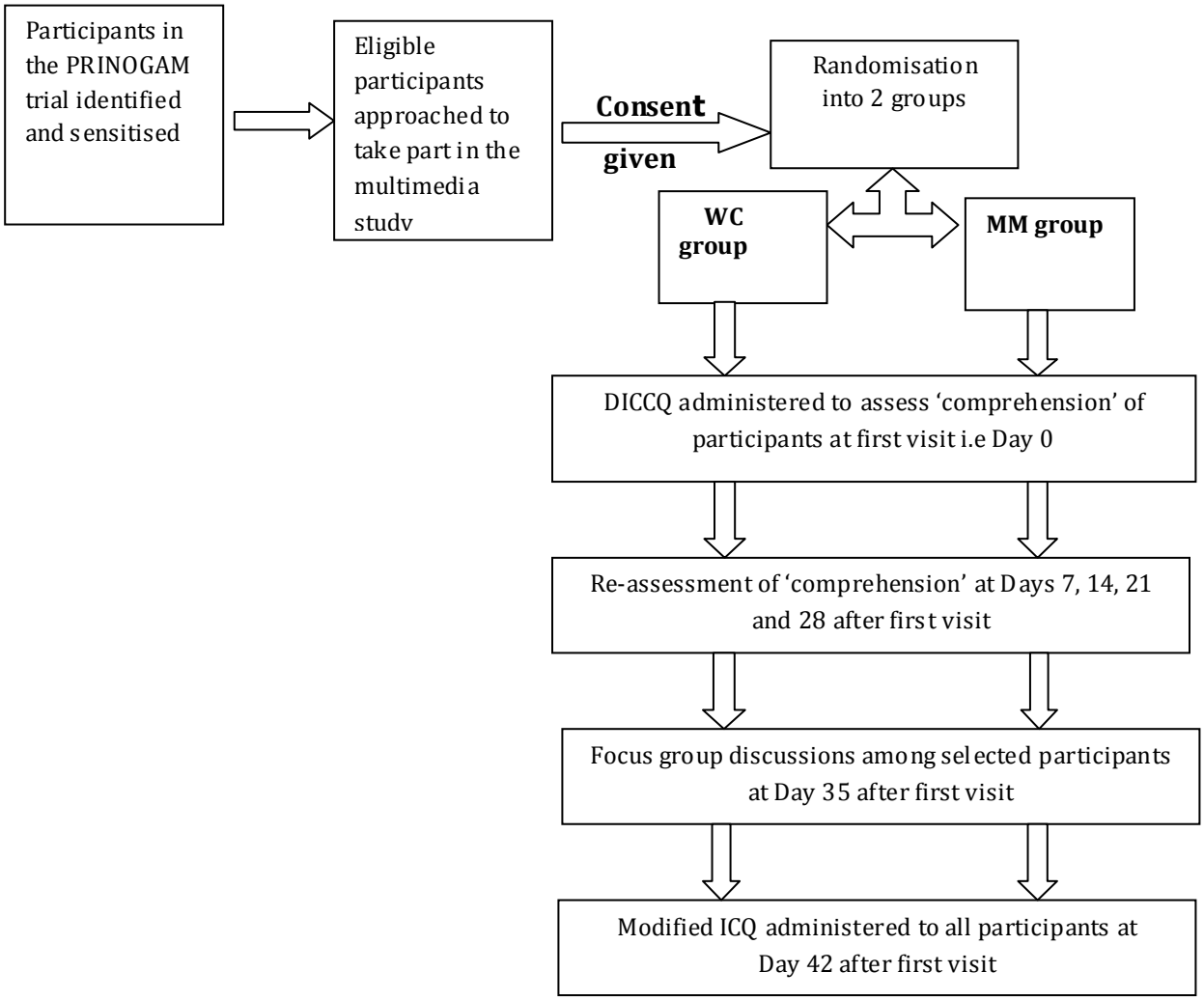
I encountered a number of challenges during the recruitment to this study. Because the multimedia study was embedded within a parent trial which was tied to malaria parasite positivity among residents of a low malaria transmission area in The Gambia, it was not possible to meet the projected recruitment target at Jahaly site. The eligibility criteria for the parent trial were also strict and restrictive, thereby contributing to the slow recruitment rates at the site. For example, apart from having a positive malaria test by rapid diagnostic kit, a potential participant must also have a malaria parasiteamia of ≥20 parasites/microlitre by microscopy; negative result for G6PD deficiency test and

haemoglobin of greater than 12g/dl. Also, because the multimedia study was not a 'stand alone', higher consideration was given to the trial procedures of the parent trial before activities in the multimedia study could be done. This increased participants' waiting time and sometimes, participants expressed anxiety about further participation. There were also substantial logistic challenges recruiting participants simultaneously from two trial sites which were about 100 kilometres apart. Addressing diverse logistic issues at the two sites involved additional financial expenses.

7.1.11: Schedule of events

Figure 9 illustrates the sequence of events which participants passed through for data collection in this stage of the study.

Figure 9: Schedule of multimedia study activities



Key:

MM-multimedia
WC-written consent
DICCQ- Digitised Informed Consent Comprehension Questionnaire
ICQ- Informed Consent Questionnaire

7.1.12 : Data entry

As described in section 6.2.6, DICCQ had an in-built database in which data collected from participants were stored electronically. Security checks were built into the system, such that participant data could only be entered with the same unique identifier number at all study visits. In addition to data checking that I regularly conducted, drop-down menu which gave options rather free text were included in the system to enhance accuracy. The data were retrieved from the database of DICCQ and converted to Microsoft Excel format. Similarly, the data from ICQ were double-entered into the Microsoft Excel by two experienced data entry clerks.

7.1.13: Data Analysis

Analysis of the quantitative data was performed with Stata version 12.1 (College Station, USA). For clarity, I describe the data analyses based on the study endpoints.

7.1.13.1: Primary endpoint: Comprehension scores (i.e. total recall and understanding scores) at Day 0 visit. Comprehension scores of participants in the multimedia and 'standard' consent arms who gave correct answers to the question items addressing the domain of 'recall' and 'understanding' at Day 0 were compared using Mann-Whitney U tests.

7.1.13.2: Secondary endpoint: Comprehension (i.e. total recall and understanding scores) at follow-up visits. Similarly, comprehension scores of participants in both study arms who gave correct answers to the question items addressing domain of 'recall' and 'understanding' at Days 7, 14, 21 and 28 after Day 0 visit were compared using Mann-Whitney U tests.

Because the data were not normally distributed, the median participant comprehension scores and inter-quartile ranges were calculated at each visit and were compared across the study arms. The association between the participant baseline characteristics and baseline comprehension scores was assessed using the Mann-Whitney U test (2 categories), or Kruskal-Wallis test (>2 categories). A multivariate logistic regression (using comprehension scores dichotomised at the median values with variables selected by a forward-stepwise method) was undertaken to examine which participant characteristics were independently associated with baseline comprehension.

Although not a study endpoint, the proportions of participants in the multimedia and 'standard' consent arms who gave correct answers to each of the question items addressing the domain of 'recall' and 'understanding' at Day 0 and follow-up study visits were compared with the proportions of the participants who gave wrong answers. Chi-squared statistics was used to assess significance between the two study arms.

Because participants were recruited from two different sites (Basse and Jahaly), the effect of clustering on the participant comprehension scores was investigated using mixed-effects regression model. Also, the extrapolated drop in participant comprehension scores beyond the study follow-up was used to capture the long-term benefits of multimedia consent tool. The survival time within the trial follow-up period was estimated from the parent trial (mean follow-up of 42.7 days). I assumed that participants retaining comprehension of consent information throughout the multimedia study had an expected additional time that could be determined by fitting a survival probability to the parent trial data. Statistical significance was defined as $p<0.05$.

7.1.13.3: Understanding and Satisfaction scores on modified ICQ

A parallel analysis similar to that described for the comprehension scores on DICCQ was done for the 'understanding' and 'satisfaction' scores on ICQ. Participant responses were scored as follow: 3 for "Yes completely", 2 for "Yes partially", 1 for ''I don't know", and 0 for "No". Descriptive analysis of participants' responses to ICQ across study arms was performed using Chi-squared statistics.

7.1.13.4: Participant withdrawal

Descriptive analysis was performed to assess the distribution of withdrawal among participants randomised to either study arm. Reasons for dropping out of the study before completion were also documented.

7.1.13.5: Focus group discussions

The audio recordings of the FGD sessions were transcribed into English by three native speakers who also understood English language. The consistency of the English transcription with the local languages was confirmed by another three independent native speakers. The transcribed texts were entered into NVivo software version 10.0 and I conducted the analysis by initially coding the main themes that emerged from the transcribed texts. This involved line-by-line analysis of the transcribed texts to elucidate the meanings and processes. The themes were subsequently sorted and collated into categories and sub-categories. Hypotheses and concepts were developed inductively from the themes. The relationships among data codes from Basse and Jahaly sessions were compared, integrated and refined. Final comparisons of themes on understanding of consent information expressed by the participants in multimedia and 'standard' consent arms were illustrated using selected verbatim quotations from the participants.

The findings of the FGD and quantitative data addressing similar concepts were triangulated.

7.1.13.6: Cost analysis

Although not an endpoint, the economic and financial costs of developing and administering multimedia consent tool and DICCQ were itemised prospectively. This is done to address the concern associated with cost implications of introducing a new method like multimedia consent tool in low-resource settings. The information may also be useful to determine sustainability and reproducibility of multimedia consent procedure in future clinical trials in The Gambia.

7.1.14: Ethical considerations

7.1.14.1: Protocol approval

Before the commencement of the first stage of the study reported in this thesis, the study protocol was first submitted to the Scientific Coordinating Committee (SCC) of the Medical Research Council Unit, The Gambia (MRC). After clarifications on administrative management of the study and minor amendment to the introductory statement of the study questionnaire, the protocol was forwarded to the Gambia Government/MRC Joint Ethics Committee who gave approval. Following recommendation of the Ethics Committee, the statement: 'participation in the trial is voluntary and that the participant may refuse to participate or withdraw from the trial at any time, without penalty or loss of benefits to which the subject is otherwise entitled' was clearly indicated on the participant information sheet.

The protocol was also submitted to the Research Ethics Committee of London School of Hygiene & Tropical Medicine, UK. The Committee gave approval following clarifications on the study design, sample size and wordings of the study questionnaire.

7.1.14.2: Confidentiality

In adherence to ICH-GCP guidelines, participant confidentiality was ensured at all times throughout the study. The only study information which contained participant names was the enrolment log sheet. This was considered necessary to ensure that participants were correctly followed up at all study visits. This log sheet was safely kept in a locked cabinet. The computer laptops used for data collection were also kept in separate locked cabinets and only the multimedia study team had access to them. Electronic information was password-protected.

Each participant was assigned a unique study identification number. This was used on the digitised and paper questionnaires to make it possible to link them. Following completion of the study, the data was stored and archived in accordance with Standard Operating Procedures of Medical Research Council Unit, The Gambia.

7.1.15: Trial Registration: This trial was registered with the Pan African Clinical Trial Registry (www.pactr.org) with the unique identification number PACTR201402000775274.

7.1.16: Research costs and funding

7.1.16.1: Costs

Financial costs were calculated for implementation of various activities in this project and these are shown in Table 14. The majority of costs were associated with development, filming, production of the tools and personnel cost.

Table 14: Cost of expenses incurred in the multimedia study

Item	Cost in GMD	Equivalent in GBP*
Development of digitised questionnaire at Tuft University, USA	69,183.97	USD 1,840= £1,109.87
Audio-translation of study questionnaire to 3 Gambian languages	9,000.00	144.38
Multimedia development:		
i. Filming and production cost	47,000.00	753.99
ii. Narrative translations in 3 Gambian languages	11,500.00	184.49
i. Purchase of 2 computer laptops	64,823.62	1,039.92
ii. Loan of 1 MRC laptop @£1/day for 4 months	7,480.22	120.00
Personnel cost: 4 research assistants for 8 months	130,600	2,095.13
Field trips	49,868.17	800.00
Consumables e.g. stationeries, internet , telephone recharge cards, reimbursement of transport fares to participants	28,425.00	456.00
Total	**GMD 417,880.97**	**£ 6,703.78**
Unit cost per participant		**£6,703.78/311= £ 21.6**

* 1GMD = 0.0160423 GBP http://www.xe.com/currencyconverter 5 August 2014

7.1.16.2: Funding

The study was funded as part of a capacity building grant by the European and Developing Countries Clinical Trials Partnership (IP.2008.31100.001). The grant covered my PhD registration and tuition fees, research costs, and monthly stipends for the research assistants.

7.1.17: Copyrights/Intellectual property rights

According to LSHTM Intellectual Property policy, research degree students are not considered employees of the School and thus they take sole ownership of any inventions generated by them, unless it is done in collaboration with the School or using School facilities or funding, in which case joint ownership may arise. In such circumstances the School shall seek an assignment from the student or third party in order to secure sole ownership, in return for a specified share in any future revenues (313). This provision of the policy applies because my PhD studentship is a collaborative site scheme arrangement between LSHTM and MRC, The Gambia. Although, the audio digitised questionnaire and multimedia informed consent tool were initially copyrighted to me, there are plans for documentation of shared ownership between LSHTM and MRC, in anticipation of the final results of the study and future plans for the tools.

Chapter Eight: Results

8.1: Participant information

Of 347 participants enrolled in the PRINOGAM trial, 26 refused to take part (7.5 %) in the multimedia study; a large proportion of whom cited not having time to wait as they had pressing domestic or family issues to attend. An additional 10 participants (2.9%) insisted on having the study information through the multimedia tool without going through the formal randomisation process. These participants most likely knew about the multimedia tool through their friends or family members who were already enrolled in the study. As this would amount to selection bias, these 10 participants were not enrolled in the multimedia study. A total of 311 participants (311/347, 89.6%) were enrolled in the study and included in final analysis.

Of the 311 participants recruited from the parent trial, 155/311(49.8%) were randomised into multimedia arm and 156/311 (50.2%) randomised to 'standard' consent arm (Figure 10). The median age of participants in the multimedia arm was 34 years, (IQR= 28, 42) and 33 years (IQR=26.5, 42) for those in the 'standard' consent arm. About 60% of the study participants were female (61.9% for multimedia and 64.1% for standard arm) and about 70% were resident in Basse (65.8% for multimedia and 69.9% for standard group). The predominant local language spoken by almost half of the participants was Mandinka (48.4% for multimedia and 51.9% for standard group). Almost three-quarter of participants in the multimedia arm had no Western education (73.5%), while 81.5% of those in standard consent arm had no western education. About one-tenth of the participants in multimedia arm had been previously involved in clinical trials while about one-fifth had previous clinical trial experience among participants in the 'standard' consent arm. However none of these differences in the characteristics

between the two arms were statistically significant at the 5% level (Table 15).

Figure 10: Participants flow chart

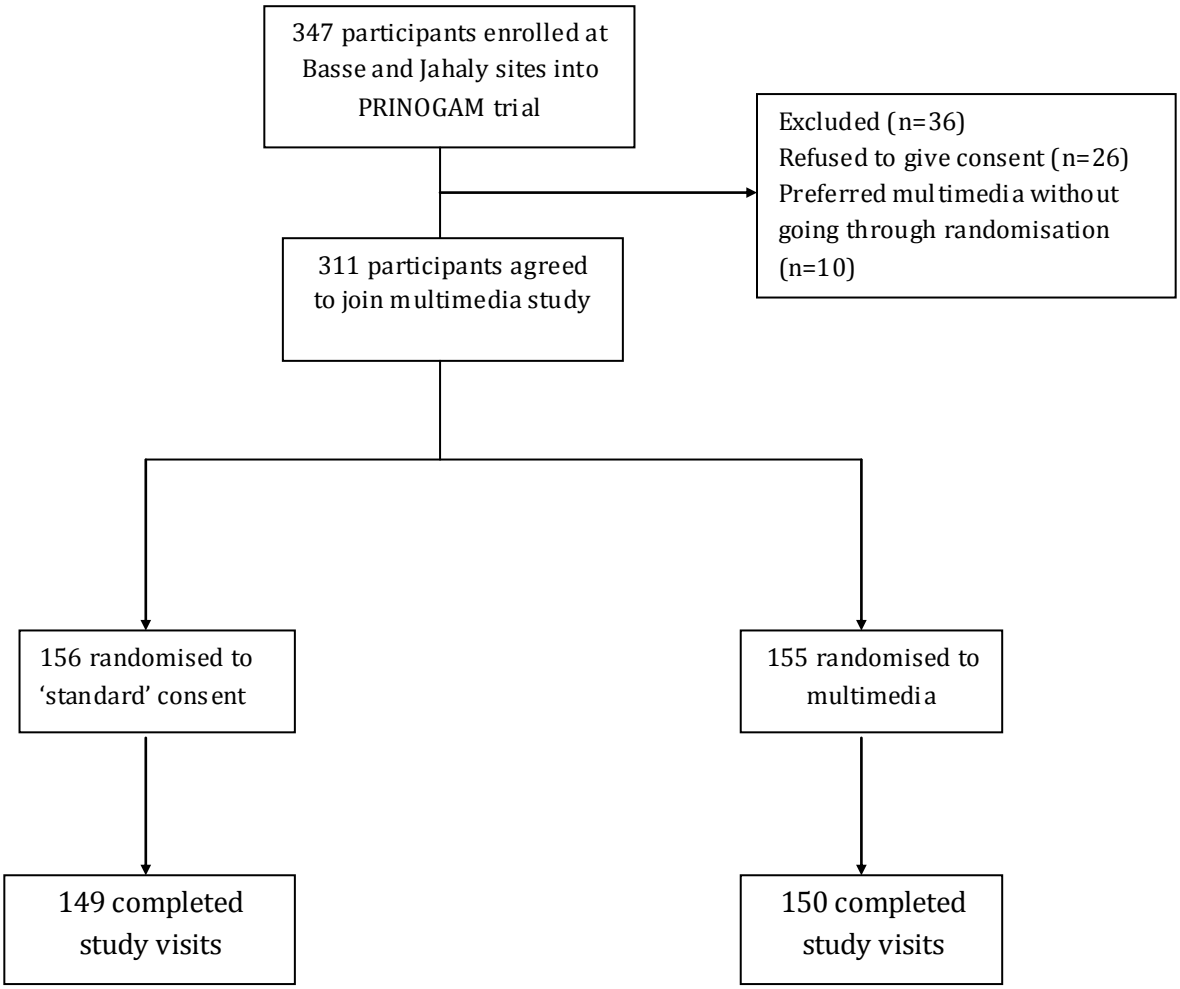


Table 15: Socio-demographic characteristics of study participants, Gambia, 2014

Characteristics	Study arms		
	Multimedia (n=155)	Standard consent (n=156)	P value
Age group (years)			0.247
18-25	23(14.8)	35(22.4)	
26-33	50(32.3)	44(28.2)	
34-41	40(25.8)	35(22.4)	
42-49	28(18.1)	34(21.8)	
>49	14(9.0)	8(5.1)	
Gender			0.692
Female	96 (61.9)	100 (64.1)	
Male	59 (38.1)	56(35.9)	
Domicile			0.443
Basse	102 (65.8)	109(69.9)	
Jahaly	53(34.2)	47(30.1)	
Ethnicity			0.666
Mandinka	75(48.4)	81(51.9)	
Fula	66(42.6)	62 (39.7)	
Wolof	8(5.2)	5 (3.2)	
Sarahule	5(3.2)	7(4.5)	
Manjago	1(0.7)	0(0.0)	
Education group*			0.097
Had Western education	41(26.5)	29(18.6)	
Had no Western education	114(73.5)	127(81.4)	
Religious affiliation			0.995
Islam	153(98.7)	154(98.7)	
Christianity	2(1.3)	2(1.3)	
Previous clinical trial participation			0.071
Yes	14 (9.0)	28(18.0)	
No	140(90.3)	127(81.4)	
I don't know	1(0.7)	1(0.6)	

**For the purpose of this study, western education is defined as having basic formal education based on English curriculum i.e. completion of primary school education with or without three years of junior secondary school education*

8.2: Participant scores on DICCQ

8.2.1: 'Understanding' and' recall' scores

At Day 0 visit, the median (IQR) recall score of participants in the multimedia arm doubled the median score of participants in the 'standard' consent arm: 48(43,51) versus 24(19,31.5), while the median understanding score was slightly higher among multimedia participants compared with the 'standard' consent arm: 20(17,24) versus 17(13,19). Similarly, at follow-up study visits on Days 7, 14, 21 and 28, participants in the multimedia arm had higher median 'recall' and 'understanding' scores than their counterparts in the 'standard' consent arm. While significant statistical differences were observed in the median 'recall' scores between the study arms at Day 0, 7, 14, 21 and 28 ($p<0.05$); the differences in the median 'understanding' scores at these study visits did not reach statistical significance. Also, the minimum scores between the multimedia and standard consent arm were significantly different, whereas the maximum scores when compared between the multimedia and standard consent participants wer similar (Table 16).

8.2.2: Comprehension scores

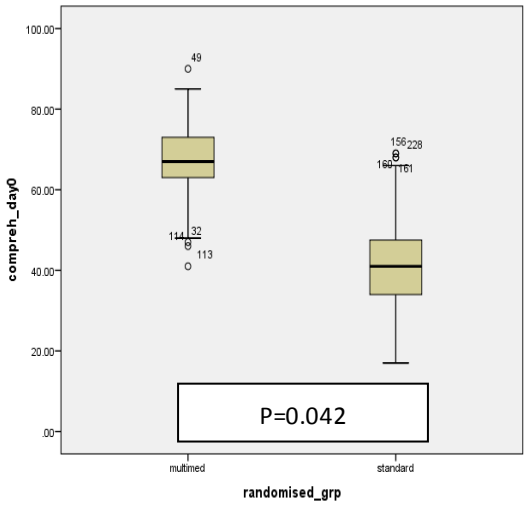
The median (IQR) comprehension scores of participants was 67(63, 73) while participants in the standard arm had a median score of 41 (34, 47.5) at Day 0 visit. This trend continued throughout the follow-up study visits showing significant statistical differences between the study arms at all time-points ($p<0.05$) (Figure 11).

Table 16: Descriptive scores of participants on DICCQ at Days 0, 7, 14, 21 and 28

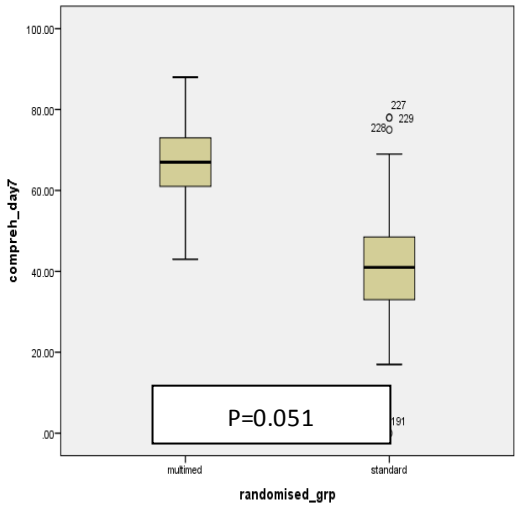
Participant scores	Median (IQR)	Minimum score	Maximum score	P value*
Total recall score (Day 0)				**0.03**
Multimedia	48(43,51)	30	59	
Standard consent	24(19,31.5)	10	55	
Total understanding score (Day 0)				0.30
Multimedia	20(17,24)	11	39	
Standard consent	17(13,19)	5	31	
Total recall score (Day 7)				**0.03**
Multimedia	47 (44,52)	32	57	
Standard consent	25(19,29)	2	54	
Total understanding score (Day 7)				0.36
Multimedia	19(16,22)	10	31	
Standard consent	17(17,30)	1	31	
Total recall score (Day 14)				**0.04**
Multimedia	48(44,52)	28	59	
Standard consent	24(17,29)	4	54	
Total understanding score (Day 14)				0.27
Multimedia	20(17,23)	10	35	
Standard consent	15(12.19)	3	35	
Total recall score (Day 21)				**0.04**
Multimedia	47(43,50)	21	57	
Standard consent	23(17,29)	5	55	
Total understanding score (Day 21)				0.30
Multimedia	19(16,23)	10	33	
Standard consent	15(13-19)	0	33	
Total recall score (Day 28)				**0.04**
Multimedia	47(43,51)	22	60	
Standard consent	22(16,27.5)	0	55	
Total understanding score (Day 28)				0.33
Multimedia	18(16,22)	10	35	
Standard consent	16(12.5,19)	0	35	

*Mann-Whitney U test

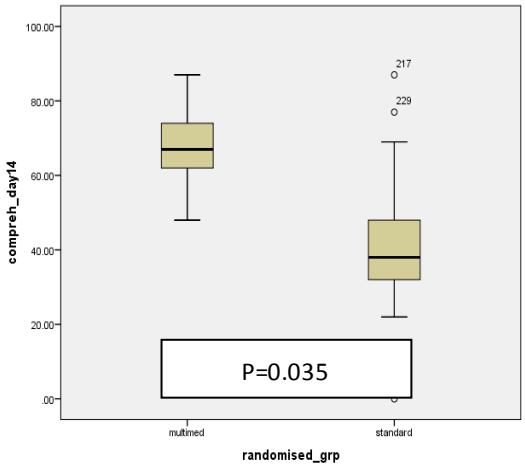
Figure 11: Box-plots showing comparison of participant comprehension scores on DICCQ across study arms at Days 0, 7, 14, 21 and 28



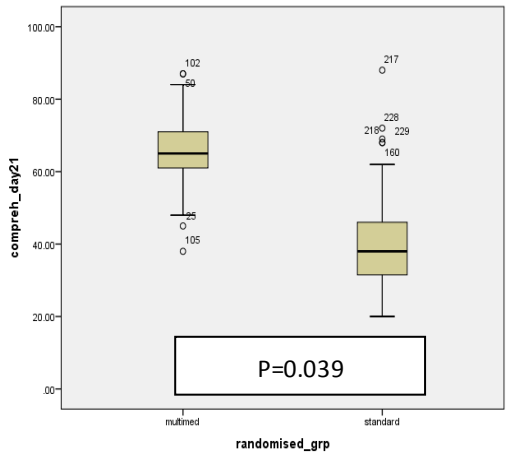
Day 0



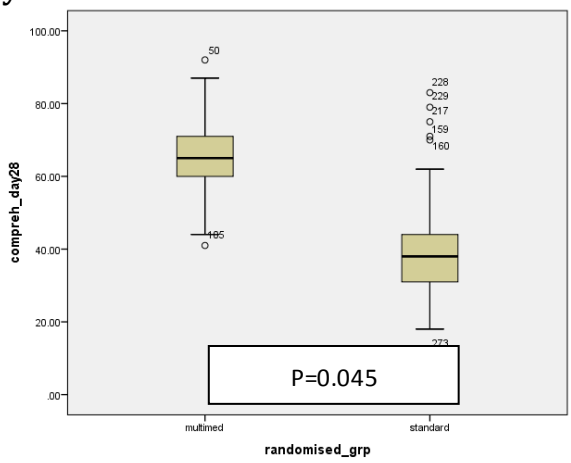
Day 7



Day 14



Day 21



Day 28

Figure 11 shows the box plots where the bars represent the median, the upper line of the box is the 75^{th} percentile and the lower line of the box is the 25^{th} percentile; 50% of the data is therefore inside the box. The tails represent the minimum and maximum values, excluding outliers. The circles are individual outlying data points, with some circles being slightly outside the tails and others much further away.

In this figure, the median comprehension scores at Days 0, 7, 14, 21 and 28 were high among participants in the multimedia arm at just over 80% with a wide spread. A lower median score was recorded in the no-intervention arm at about 40%. At all time-points, the upper lines (maximum values) of the comprehension scores among participants in 'standard' consent group correspond to the median values of comprehension scores of participants in multimedia arm. There were statistical significant differences between the median comprehensions of participants in both study arms across all study visits ($p<0.005$).

8.3: Proportion of participants with correct and wrong responses on DICCQ

For each of the five time points, the proportions of participants answering the question items correctly and incorrectly are shown in Table 17. There were statistically significant differences between the study arms in the proportions of participants who had correct responses compared with those with incorrect responses at Day 0 on several question items except items 6, 8, 9, 11, 13, 15, 18. Question item 6 assessed whether participants were told the name of study persons to contact, which generated almost similar percentage of correct responses from participants in both study arms. However, when asked to mention the specific name of the contact person in question 7, a higher proportion of participants in the multimedia arm gave correct answers than their counterparts in the 'standard' consent arm. This showed a significant statistical difference at all time-points across the two study arms except Days 21 and 28.

Table 17: Comparison of proportions of participants with correct and incorrect responses across study arms per question item

Question		Day 0		Day 7		Day 14		Day 21		Day 28	
		(n=155) Multimedia	(n=156) Standard	(n=155) Multimedia	(n=156) Standard	(n=155) Multimedia	(n=156) Standard	(n=155) Multimedia	(n=156) Standard	(n=155) Multimedia	(n=156) Standard
Q1	Correct	144 (92.3)	101(64.7)	145(92.9)	103(66.0)	140(90.3)	100(64.1)	150(96.8)	95(60.9)	149(96.1)	90(57.7)
	Wrong	11(7.7)	55(35.3)	10(7.1)	52(34.0)	15(9.7)	56(35.9)	5(3.2)	61(39.1)	6(3.9)	66 (42.3)
		p<0.001		**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**	
Q2	Correct	152 (98.1)	114(73.1)	149(96.1)	120(76.9)	153(98.7)	127(81.4)	154(99.4)	118(75.6)	148(95.5)	110(70.5)
	Wrong	3(1.9)	42(26.9)	6(3.9)	36(23.1)	2(1.3)	29(18.6)	1(0.6)	38(24.4)	7(4.5)	46(29.5)
		p<0.001		**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**	
Q3	Correct	116(74.8)	54(34.6)	94(60.6)	65(41.7)	108(69.7)	60(38.5)	107(69.0)	55(35.3)	109(70.3)	53(43.0)
	Wrong	39(25.2)	102(65.4)	61(39.4)	91(58.3)	47(30.3)	96(61.5)	48(31.0)	101(64.7)	46(29.7)	103(66.0)
		p<0.001		**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**	
Q4	Correct	82 (52.9)	42(27.0)	89(57.4)	43(27.6)	86(55.5)	50(32.1)	65(41.9)	44(28.2)	59(38.1)	43(27.6)
	Wrong	73 (47.1)	114(73.0)	66(42.6)	113(72.4)	69(44.5)	106(67.9)	90(58.1)	112(71.8)	96(61.9)	113(72.4)
		p<0.001		**p<0.001**		**p<0.001**		**p=0.011**		**p=0.045**	
Q5	Correct	126(81.3)	98(62.8)	127 (81.9)	95(60.9)	125(80.6)	90(57.7)	123(79.4)	91(58.3)	133(85.8)	96(61.5)
	Wrong	29(18.7)	58(37.2)	28(22.9)	61(39.1)	30(19.4)	66(42.3)	32(20.6)	65(41.7)	22(14.2)	60(38.5)
		p=0.001		**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**	
Q6	Correct	124(80.0)	114(73.1)	132(85.2)	128(82.0)	114(73.5)	110(70.5)	111(71.6)	118(75.6)	123(79.4)	122(78.2)
	Wrong	31(20.0)	42(26.9)	23(13.8)	28(18.0)	41(26.5)	46(29.5)	44(28.4)	38(24.4)	32(20.6)	34(21.8)
		p=0.150		p=0.459		p=0.55		p=0.42		p=0.804	
Q7	Correct	91(58.7)	65(41.7)	83(53.5)	53(34.0)	71(45.8)	38(24.3)	80(51.6)	74(47.4)	78(50.3)	65(41.7)
	Wrong	64(41.3)	91(58.3)	72(46.5)	103(66.0)	84(54.2)	118(75.7)	75(48.4)	82(52.6)	77(49.7)	91(58.3)
		p=0.003		**p=0.001**		**p<0.001**		p=0.461		p=0.126	
Q8	Correct	107(69.0)	92(59.0)	117(75.5)	94(73.1)	120(77.4)	97(62.2)	121(78.1)	91(58.3)	115(74.2)	95(60.9)
	Wrong	48(31.0)	64(41.0)	38(24.5)	62(21.8)	35(22.6)	59(37.8)	34(21.9)	65(41.7)	40(25.8)	61(39.1)
		p=0.065		**p=0.004**		**p=0.003**		**p<0.001**		**p=0.012**	

Q9	Correct Wrong	139(89.7) 16(10.3)	130(83.3) 26(16.7)	127(81.9) 28(18.1)	126(80.8) 30(19.2)	119(76.8) 36(23.2)	121(77.6) 35(22.4)	115(74.2) 40(25.8)	113(72.4) 43(27.6)	129(83.2) 26(16.8)	112(71.8) 24(28.2)
		p=0.102		p=0.792		p=0.868		p=0.726		p=0.844	
Q10	Correct Wrong	113(72.9) 42(27.1)	56(35.9) 100(64.1)	105(67.7) 50(32.3)	58(37.2) 98(62.8)	101(65.2) 54(34.8)	54(34.6) 102(65.4)	102(65.8) 53(34.2)	56(35.9) 100(64.1)	109(70.3) 46(29.7)	53(72.4) 113(11.5)
		p<0.001		**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**	
Q11	Correct Wrong	65(41.9) 90(58.1)	51(64.1) 105(32.7)	62(39.4) 94(60.6)	49(57.7) 107(39.1)	68(43.9) 87(56.1)	52(33.3) 104(66.7)	69(44.5) 86(55.5)	55(35.3) 101(64.7)	64(41.3) 91(58.7)	54(34.2) 102(65.8)
		p=0.092		p=0.124		p=0.056		p=0.095		p=0.225	
Q12	Correct Wrong	151(97.4) 4(2.6)	141(90.4) 15(9.6)	150(96.8) 5(3.2)	145(92.9) 11(7.1)	149(95.5) 7(4.5)	140(89.7) 16(10.3)	150(96.8) 5(3.2)	141(90.4) 15(9.6)	152(98.1) 3(1.9)	142(91.0) 14(9.0)
		p=0.019		p=0.127		**p=0.051**		**p=0.0022**		**p=0.013**	
Q13	Correct Wrong	107(69.0) 48(31.0)	115(73.7) 41(26.3)	128(82.6) 27(17.4)	121(77.6) 35(22.5)	117(75.5) 38(24.5)	112(71.8) 44(28.2)	107(69.0) 48(31.0)	116(74.4) 40(25.6)	125(80.6) 30(19.3)	127(81.4) 29(18.6)
		p=0.361		p=0.268		p=0.460		p=0.297		p=0.863	
Q14	Correct Wrong	144(92.9) 11(7.1)	134(85.9) 22(14.1)	140(90.3) 15(9.7)	131(84.0) 25(16.0)	142(91.6) 13(8.4)	135(86.5) 21(13.5)	139(98.7) 16(1.3)	130(98.7) 26(1.3)	141(99.4) 14(0.6)	128(99.4) 28(0.6)
		p=0.045		p=0.095		p=0.152		p=0.361		p=0.361	
Q15	Correct Wrong	148(95.5) 7(4.5)	143(91.7) 13(8.3)	145(93.5) 10(6.5)	145(93.5) 11(6.5)	149(96.1) 6(3.9)	149(96.1) 7(3.9)	145(93.5) 10(6.5)	151(96.8) 5(3.2)	144(92.9) 11(7.1)	139(89.1) 17(10.9)
		p=0.170		p=0.833		p=0.786		p=0.182		p=0.242	
Q16	Correct Wrong	146(94.2) 9(5.8)	130(83.3) 26(16.7)	148(96.5) 7(4.5)	131(84.0) 25(16.0)	152(98.1) 3(1.9)	135(86.5) 21(13.5)	151(97.4) 4(2.6)	129(82.7) 27(17.3)	143(92.2) 12(0.6)	136(87.2) 20(12.8)
		p=0.004		**p=0.001**		**p<0.001**		**p<0.001**		p=0.141	
Q17	Correct Wrong	140(89.7) 15(10.3)	115(73.7) 41(26.3)	142(91.6) 13(8.4)	113(72.4) 43(27.6)	144(92.9) 11(7.1)	110(70.5) 46(29.5)	139(89.7) 16(10.3)	114(73.5) 42(26.5)	143(92.3) 12(7.7)	112(72.3) 43(27.7)
		p<0.001		**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**	
Q18	Correct Wrong	147(94.8) 8(5.2)	140(89.7) 16(10.3)	147(94.8) 8(5.2)	143(91.7) 13(8.3)	146(94.2) 9(5.8)	143(91.7) 13(8.3)	141(91.0) 14 (9.0)	139(89.1) 17(10.9)	141(91.0) 14(9.0)	146(83.6) 10(6.4)

		p=0.092		p=0.265		p=0.385		p=0.583		p=0.386	
Q19	Correct Wrong	142(91.6) 13(8.4)	111(71.2) 45(28.8)	144(92.9) 11(7.1)	112(71.8) 44(28.2)	141(91.0) 14(9.0)	117(75.0) 39(25.0)	145(93.5) 10(6.5)	114(73.1) 42(26.9)	140(90.3) 15(9.7)	113(72.4) 43(27.6)
		p<0.001		**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**	
Q20	Correct Wrong	129(83.2) 26(16.8)	106(67.9) 50(32.1)	125(80.6) 30(19.4)	110(71.0) 46(29.0)	121(78.1) 34(21.9)	113(72.9) 43(27.1)	128(82.6) 27(17.4)	102(65.8) 54(34.2)	122(78.7) 33(21.3)	105(67.7) 51(32.3)
		p=0.002		**p=0.038**		p=0.250		**p<0.001**		**p=0.024**	
Q21	Correct Wrong	108(69.6) 47(30.4)	89(57.0) 67(42.9)	105(67.7) 50(32.3)	95(60.9) 61(39.1)	103(66.5) 52(33.5)	93(59.6) 63(40.4)	104(67.1) 51(32.9)	90(57.7) 66(42.3)	102(65.8) 53(34.2)	95(59.6) 61(39.1)
		p=0.021		p=0.208		p=0.212		p=0.087		p=0.369	
Q22	Correct Wrong	150(96.8) 5(3.2)	122(78.2) 34(21.8)	149(96.1) 6 (3.9)	124(79.5) 42(20.5)	145(93.5) 10(6.5)	123(78.8) 33(21.2)	143(92.3) 12(7.7)	111(71.6) 45(28.4)	144(92.9) 11(7.1)	114(73.1) 42(26.9)
		p<0.001		**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**	
Q23	Correct Wrong	118(76.1) 37(23.9)	47(30.21 109(69.9)	105(67.8) 50(32.2)	52(33.3) 104(66.7)	101(76.2) 54(34.8)	63(40.4) 93(59.6)	115(74.2) 40(25.8)	48(30.8) 108(69.2)	112(72.3) 43(27.7)	45(28.8) 111(71.2)
		p<0.001		**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**	
Q24	Correct Wrong	83(53.5) 72(46.5)	52(33.3) 104(66.7)	86(54.8) 70(45.2)	50(32.1) 106(67.9)	88(56.8) 67(43.2)	59(37.8) 97(62.2)	82(52.9) 73(47.1)	54(34.6) 102(65.4)	85(45.2) 70(54.8)	47(30.1) 109(69.9)
		p**<0.001**		**p<0.001**		**p=0.001**		**p=0.001**		**p<0.001**	
Q25	Correct Wrong	132(85.2) 33(14.8)	87(55.8) 69(44.2)	129(83.2) 26(16.8)	84(53.8) 72(46.2)	127(81.9) 28(18.1)	83(53.2) 73(46.8)	120(77.4) 35(22.6)	85(54.8) 71(45.2)	121(78.1) 34(21.9)	86(55.1) 70(44.9)
		p<0.001		**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**	
Q26	Correct Wrong	101(65.2) 54(34.8)	67(42.9) 89(57.1)	105(67.7) 50(32.3)	63(40.4) 93(59.6)	103(66.5) 52(33.5)	64(41.0) 92(59.0)	100(64.5) 55(35.5)	61(39.1) 95(60.9.)	104(67.1) 51(32.9)	60(38.5) 96(61.5)
		p<0.001		**p<0.001**		**p<0.001**		**p<0.001**		**p<0.001**	

* For ease of interpretation, 'I don't know' response was categorised as 'wrong' response

Item 8 which assessed understanding about right of withdrawal elicited higher correct responses from the participants in the multimedia arm than those in the 'standard' consent arm at Day 0; this however did not reach statistical significance. However, statistical significance was observed at subsequent follow-up visits due to higher proportions of multimedia participants giving correct responses on this question item. Although, a higher proportion of participants in the multimedia gave correct responses on question 9 which assessed whether participants would receive money as a form of reward for research participation, this did not reach a statistical difference at all study visits. Similar trend was observed in questions 11 and 13. Question 11 asked the point at which participants could leave the study while question 13 assessed autonomy/decision-making on study participation. Relatively higher proportion of participants in multimedia arm gave correct answers on the two items, but this did not attain statistical difference across the two study arms. Almost equal proportion of participants in both arms gave correct responses to questions 15 and 18 at Day 0 and follow-up visits. Question 15 focussed on understanding of right of withdrawal which must not attract penalty or loss of entitled benefits. Question 18 on the other hand assessed the recall of participants about the study activities. Question 21 which assessed understanding about frequency of study visits showed a different trend as statistical difference was observed only at Day 0 despite a comparatively higher proportion of participants in the multimedia arm giving correct responses at all study visits. This might be due to marginal differences in the proportion of participants in both arms who gave correct answers at all visits.

Table 18: Association between participants' characteristics and baseline (Day 0) comprehension scores, Gambia, 2014

	Study arms		
Characteristics	**Multimedia (n=155) Median score (IQR)**	**'Standard' consent (n=156) Median score (IQR)**	**P value**
Age group (years)			0.54*
18-40	63(68,73)	33.5(40.5,46.5)	
≥ 41	61(65.5,72)	35.5(43,53)	
Gender			**0.03***
Male	65 (68,73)	38(45,51)	
Female	61 (67,72)	33 (39,46)	
Place of domicile			**0.02***
Basse	63(67.5,73)	39 (44,51)	
Jahaly	61(67,74)	30 (33,38)	
Education status			**0.005***
Had no Western education	61 (66.5,72)	33(40,48)	
Had Western education	65 (70,74)	40(45,47)	
Language of assessment			0.92‡
Mandinka	64(67,73)	33(41,47)	
Wolof	62(67.5,73)	35(42,50)	
Fula	61(69,74)	30(38,45)	
Previous clinical trial participation			
Yes	63(67,73)	34(41,48)	0.21‡
No	65(69,72)	33(40,47)	
I don't know	48(48,48)	43(43,43)	

*Mann-Whitney U test, ‡Kruskal-Wallis test

Table 18 shows that there was statistically strong evidence of intervention among male participants (p=0.03), who resided in Basse (p=0.02) and had western education (p=0.005). Participant gender (p=0.006, 95% CI: 0.12-0.70) and domicile (p=0.017, 95% CI: 0.13-0.82)

were independently associated with the baseline comprehension after controlling for the effect of other co-variables. Participants in the multimedia arm were 4.76 times more likely to comprehend the consent information than those in the standard consent arm ($p<0.0001$, 95% CI: 3.85-5.67) (Table 19).

The mixed-effects model showed that place of domicile is 0.85 times likely to account for variation in the comprehension scores between Basse and Jahaly participants and this was not statistically significant ($p=0.61$) (Table 20).

Survival analysis of the extrapolated drop in participant comprehension scores beyond the multimedia study follow-up showed that the median time in drop of comprehension scores to 50% of baseline (Day 0) values by participants in the intervention and control arms were 67 days and 40.6 days respectively. The rate of drop per 100 person-unit was 1.49 (95% CI: 1.46-1.52) in the multimedia arm and 2.37 (95% CI: 2.28-2.37) in the control arm. The hazard ratio showed that participants in the multimedia arm had 0.22 less risk of drop in comprehension scores to 50% of Day 0 values than those in the control arm. The log rank test was statistically significant ($p<0.0001$) thereby supporting this finding (Table 21).

Table 19: Multivariate logistic regression analysis of predictors of comprehension scores at Day 0 post-intervention, Gambia, 2014

	0dds ratio	95% CI	P value
Age group	1.41	0.62-3.21	0.42
Gender	0.29	0.12-0.70	**0.006**
Domicile	0.33	0.13-0.82	**0.017**
Randomised group	4.76	3.85-5.67	**<0.0001**
Education status	0.67	0.23-1.93	0.46
Assessment language	0.56	0.29-1.08	0.084
Previous trial participation	1.07	0.42-2.73	0.89

Table 20: Mixed-effects model estimating domicile effect on participant comprehension scores, Gambia, 2014

Comprehension scores	Odds ratio	S.E	p	95% CI
Domicile	0.85	0.28	0.613	0.45-1.60
***Sigma_u**	1.91	0.99		0.69-5.31
‡rho	0.53	0.26		0.13-0.90

S.E= Standard error, Likelihood ratio test statistic=107.9, p=0.61

*Sigma_u is a measure of how much participant comprehension scores vary between Basse and Jahaly sites

‡rho is a measure of within-site correlation

Table 21: Extrapolated time to drop in participant comprehension scores to 50% of Day 0 values, Gambia, 2014

	Multimedia	'Standard' consent
Median time	67.0 days	41.0 days
Standard error	1.037	1.041
	95% CI: 65.0-69.0	95% CI: 39.0-43.0
Log rank test (with continuity correction	M=16.304	**p<0.0001**
Hazard ratio	0.22 (95% CI: 0.16-0.31)	

8.4: Participant withdrawal

Fourteen participants (14/311, 4.5%) did not complete the study for various reasons. Almost equal proportions of participants were lost to follow-up in both study arms. Most withdrew after days 21 and 28 assessments. The recall, understanding and comprehension scores of participants who withdrew were included in the final analysis. Table 22 shows the summary and the reason given for withdrawal.

Table 22: Descriptive analysis of withdrawal among participants

Study arms	Reasons	Frequency
Multimedia (n=5)	Loss to follow-up	1(20%)
	Gave no reasons	4(80%)
Standard consent (n=9)	Loss to follow-up	2(22.2%)
	No more interested	7(77.8%)

Table 23: Reliability coefficient for the questionnaire on participants' comprehension scores

	Cronbach's alpha coefficient	Inter-item correlation	Corrected total-item correlation
Day 0	0.8211	0.949	0.922
Day 7	0.8126	0.882	0.936
Day 14	0.8315	0.887	0.954
Day 21	0.8274	0.864	0.944
Day 28	0.8154	0.852	0.935

Overall Cronbach's alpha coefficient=0.9644, intra-class correlation coefficient =0.864; 95% CI 0.958-0.97

Cronbach's alpha was used to estimate the internal consistency of the questionnaire at the Day 0 and post-Day 0 time points, which was shown to be high at 0.8211 (Day 0) and ranged between 0.8126 and 0.8315 at follow-up study visits. The overall Cronbach's alpha coefficient was 0.9644 which is an indicator of high reliability (Table 23).

8.5: Responses of participants to ICQ

Exit interviews were conducted by administering a modified version of Informed Consent Questionnaire (ICQ) to assess the participant level of understanding and satisfaction at the last study visit (Day 42). The questionnaire was administered to 150 participants in the multimedia arm and 136 participants in the standard consent arm of the study. A higher proportion of participants in the multimedia arm admitted understanding the study information before enrolment, felt potential benefits and risks were explained, although there were no statistical difference between the two study arms ($p>0.05$). Participants in the multimedia arm showed better understanding than those in the control arm on the question item exploring whether their expectations were met during study participation ($p<0.001$). Similarly, multimedia participants demonstrated better satisfaction than standard consent participants on the question

items exploring repeatability of the index study and future participation in similar studies (p=0.003 and p=0.0017 respectively) (Table 24).

Table 24: Descriptive analysis of participants' responses to ICQ

		Multimedia (n=150) %	Standard (n=136) %	P value
'Understanding' sub-scale				
Did you understand the study when you decided to participate	Yes	102(68.0)	80(58.8)	0.11
	No	48(32.0)	56(41.2)	
Do you feel the potential benefits of the participation were explained?	Yes	114(76.0)	93(68.4)	0.15
	No	36(34.0)	43(31.6)	
Do you feel that the inconveniences and potential risks of participation in this study were explained?	Yes	98(65.3)	77(56.6)	0.13
	No	52(34.7)	59(43.4)	
Did participating in this study meet your expectations?	Yes	108(72.0)	70(51.5)	**<0.001**
	No	42(38.0)	66(48.5)	
'Satisfaction' sub-scale				
Would you participate again if this study is repeated?	Yes	136(90.7)	103(75.7)	**0.003**
	No	6(4.0)	16(11.8)	
	Not sure	8(5.3)	17(12.5)	
Would you participate in any MRC study in future?	Yes	132(88.0)	102(75.0)	**0.017**
	No	8(5.3)	15(11.0)	
	Not sure	10(6.7)	19(14.0)	
Did you feel that study personnel were willing to answer your questions or concerns about the study?	Yes	116(77.3)	100(73.5)	0.18
	No	2(1.3)	7(5.2)	
	Not sure	32(21.4)	29(21.3)	

8.6: Findings from focus group discussions

The profile of 63 randomly selected participants engaged in eight sessions of FGDs at Basse and six sessions held among 56 Jahaly participants showed that the participants' ages ranged from 23-47 years. There were more female participants (40/63, 63.4%) at Basse site, while (39/56, 69.6%) of Jahaly participants were male. The themes which emerged from these discussions were categorised into the four main areas: attitude toward research, actual comprehension of concepts of informed consent, acceptability and ease of administration of multimedia tool (for those randomised into multimedia arm) and acceptability and ease of use of digitised questionnaire (for participants in both study arms).

8.6.1. Participant attitude towards research

The FGD participants generally understood research as a form of investigation to solve a medical problem affecting a group of people. They frequently defined the purpose of research as efforts to identify the cause of a disease affecting people and provide *'better'* drugs to cure the disease. These notions featured prominently among Basse and Jahaly participants as they variously described the reasons for conducting the trial as: '*to see how malaria can be reduced, eradicate malaria in the Gambia, to know how effective the drug is, to prevent people from getting malaria' (33 years, female, Basse and 41 years, male, Jahaly).*

Nevertheless, the parent trial was perceived as a project that was typically designed for the benefits of the participants. This became a persistent theme throughout the discussion on appropriate methods of study information delivery; most participants from Basse expressed expectations for research benefits such as: '*I joined this MRC programme so that my child can be cured with the new anti-malaria drug' (28 years, female, Basse)*

Another participant from Jahaly said: My friend told me that they carried people in MRC cars, gave them food and also treated them without collecting money' (29 years, female, Jahaly)

These statements clearly support previous evidence that motivation for research participation among vulnerable population is driven by benefits that would be derived through their involvement (219, 307).

When asked about how they decided to join the study, the participants emphasised they made the decision (individually or jointly with their spouses) after the research team visited them during the community sensitisations. However, two participants expressed contrary opinions:

'I was not at home when you came to our village, but I got a message from my village head who said all of us should join MRC study, (so) I decided to join'... (34 years, male, Jahaly)

'I know whatever MRC brings to us is good, I do not waste time before joining MRC study' (29 years, female, Basse)

Some participants in both arms expressed culturally unique practice that they perceived was relevant to informed consent. These comments focused on community sensitisation about research. For example, several participants described informed consent as a process of '*raising awareness*' in the community or a process where members of the community '*partner*' with MRC to fight diseases like malaria. They believed that communities should be given a chance to contribute to research planning and design.

8.6.2: Comprehension of informed consent

The primary responses among participants in both sites reflected what informed consent meant to them. There was general consensus that signing or thumb-printing consent forms

implied commitments to participate in the research. A participant from Basse said: *'When you put your hand in that paper, then you have promised to be part of the study' (35 years, female, Basse).*

8.6.2.1: Right of withdrawal: Understanding about right to withdraw after enrolment generated divergent opinions among the participants. While most participants in the 'standard' consent arm strongly felt it was morally wrong for someone to stop participation before the end of the study, a majority of participants in the multimedia consent arm expressed that participants had freedom to leave the study at any time. This reflected the performance scores on the DICCQ where higher proportion of participants in the multimedia arm gave correct answers than their counterparts in the control arm.

A participant in the multimedia arm said: '*What we always think is that our doctors will be angry if we leave before the end of the study, but I now know after watching the 'film' that we have freedom to leave at any time , without telling them the reason for this'..... (34 years, female, Basse)*

8.6.2.2: Risks and benefits*:* Participants were unequivocal about the need to provide incentives to motivate them to join and be retained in the study. While majority of them considered benefits as free medical care for the participating child and rest of the family members, provision of food during study visits and payment of transport fares (in some cases, transport in MRC vehicles); a minority group described expected benefits to include provision of fertilisers during farming seasons and sponsorship of their children education.

One of them said:

'*We appreciate all the good things you have done to care for us and our children, but the real help that we expect from you and which we will never forget is to give us fertilisers for our crops and train our children to be like you'... (47 year, male, Basse)*

When asked about their understanding of the risks involved in the trial participation, most participants in the 'standard' group could not mention any. They either said *'I do not know or I forgot'.* On further probe, one participant from Basse said:

The frequent pricking of fingers (to collect blood) from my child is what I think is bad. At times, I am afraid to bring him to the clinic because of this... (28 years, female, Basse)

The participants in the multimedia arm were able to give illustrative descriptions of the adverse events of the study medications. Four out of the five participants in multimedia arm in one of the sessions in Basse independently described the risks as follows*: 'If one takes the drug, it may cause headache, abdominal pain, vomiting and diarrhoea'...*

When asked about other possible adverse events of the study medication, one participant in the multimedia arm in another FGD session remembered 'passage of dark-coloured urine' which he described as urinating '*wonjo'. 'Wonjo*' is a popular local drink prepared by boiling hibiscus leaves in water. The participant likened the dark-red colour of the drink to passage of dark-coloured urine that is associated with haemolysis caused by intake of primaquine in G6PD deficient individuals. These descriptions were consistent with the findings of higher comprehension scores obtained by participants in the multimedia arm on the question items assessing understanding about study risk and adverse events whereas those in the'standard' consent arm had low scores on this concept persistently at all study visits.

8.6.2.3: Study procedures*:* Consistent with the performance scores on DICCQ, participants in both study arms gave vivid descriptions of what the study procedures entailed. However, better ability to give details and specific names of study procedures and activities were noticed mainly among participants in the multimedia arm. One of the participants in the multimedia arm in Basse said:

'First, a person is tested to confirm if he has malaria (parasite) in his blood, the doctor will then check your body to make sure you do not have this problem of G6PD that can make you become very sick later'. Then, they will give you a drug that will not allow mosquitoes spread malaria to other people'……. (39 years, male, Basse)

8.6.2.4: Randomisation: Similarly, a graphical illustration of how participants was randomised was given by most participants in the multimedia arm; although some participants in the 'standard' group also said randomisation was done to ensure participants had equal chance of participation. A participant in the multimedia arm said:

'MRC wants to know the amount of primaquine that will work. Before giving someone the drug, MRC first checked that that you are okay before you can take part, you'll be divided into groups , like tossing a coin, to make sure you have equal chance to take part'….. (24 years, female, Jahaly)

All participants in both arms except one in the 'standard' consent arm said they could advise their friends or family members to join the study. When asked the reason the participant would not recommend participation to friends, he said:

'I am not sure of what to tell my friends. I can only tell them they will be given a drug and they will be treated free (of charge). I don't know how to explain other things....I think that is the job of MRC doctors'..... (28 years, male, Basse).

8.6.3: Acceptability and ease of use of the multimedia consent tool

A high proportion of participants in the multimedia arm (42/60, 70%) expressed that the pictures, voices, and study information delivered through the computer were clear and easy to understand. However, few of them expressed reservations about the tool. One of the participants in Jahaly said:

'Although I like the (computer) pictures and sounds, I prefer face-to-face talking. I can easily ask (the consenter) questions that are not clear to me and this will make me understand better'. (42 years, male, Jahaly)

Another participant from Basse said: '*The Fula man (interpreter) on the computer (video) repeated the same information over and over, and this made everything boring to me'..... (34 years, female, Basse)*

8.6.4. Acceptability and ease of use of the digitised questionnaire

Most participants (98/119, 82.4%) in the multimedia and 'standard' consent arms said they liked the digitised questionnaire in their local language of choice. They however complained that the questionnaire took long time to complete. One of the participants summarised his feelings thus: *' I like this new way of asking questions. I am happy with it. I have seen what I have not seen before and know what I have not known before. What bothers me a lot is the long time it took before completing it. At times, it is like a waste of time, (because) some of the questions are easy while others are not'..... (25 years, male, Basse)*

Chapter Nine: Discussion and Conclusions

9.1: Introduction

This chapter discusses the interpretations of findings of quantitative and qualitative evaluation of multimedia consent tool as well as the study limitations, implications, recommendations for further research and conclusions. The main findings include:

- Participants in the multimedia consent arm have higher 'recall', 'understanding' and 'comprehension' scores than their counterparts in the 'standard' consent arm.
- Multimedia tool was considered by the participants to be a useful and acceptable comprehension aid during informed consent process.
- The digitised comprehension questionnaire was shown to be a reliable and acceptable tool to assess 'recall' and 'understanding' of participants in a randomised clinical trial.

9.2: Participant demographic characteristics

This is the first report of evaluation of effectiveness of a customised multimedia tool for delivering consent information to low literacy research participants in The Gambia. The peculiarity of high illiteracy levels coupled with a lack of standardised writing formats for Gambian languages make implementation of traditional informed consent procedure to be fraught with a number of ethical challenges. A substantial majority of participants (95%) in this study aged between 18-49 years; females constituted more than 60% of study population, of whom only 20-30% had formal western education. This profile suggests that poor socio-economic factors are prevalent in typical African research settings such as The Gambia and these have been documented to increase the vulnerability of research participants to poor comprehension of consent information (1, 115, 116).

Several factors such as education status, place of domicile, gender and occupation were strongly associated with the participant comprehension scores at Day 0 visit. However, gender and place of domicile were independently associated with the participants' comprehension. This differs from previous studies which reported level of education as a major independent predictor of comprehension (21, 314). This contrast may be explained by the fact that majority of the study participants had no formal education and this further strengthens the case for the use of interventions like the multimedia tool to deliver study information to low literacy and non-literate participants.

The finding of gender influence on participant comprehension in this study may also be explained by the role of gender perception in ethical decision-making in African context. Empirical studies have shown that decision-making by women tend to be influenced by factors ranging from concerns about uncertainty, doubts, and the dynamism that are involved in the decision. Conversely, men assign more importance to the analysis of the information required to carry out the decision and to the definition of the goals or purposes of the decision. They are more motivated during the process and also feel more intense pressure from all work-related aspects of the information involved in decision-making(315, 316).

9.3: Information content of multimedia tool

A combination of generic and trial-specific approaches to randomised clinical trials was adopted in developing the multimedia intervention. The information contained in the multimedia tool focussed on research concepts which are commonly misunderstood by study participants who either have little or no education. In making a good blend of the generic and trial-specific information to be relevant to study participants, the multimedia

tool was customised in three major local languages that are widely spoken by study participants in The Gambia. The development of multimedia tool had the input of local multimedia expert and linguistic professionals, local geographical focus in filming locations, a local approach to the supporting music, all of which contributed to the effectiveness in improving participants comprehension of the research concepts. This is consistent with the findings by Wallace et al (317) which revealed that, in research settings characterised with challenges of communication of crucial information to prospective participants, a multi-professional education session, which included viewing a customised video, did increase participant comprehension. This is however contrary to the findings of Hutchison et al (314) who employed a generic approach in information contents of an audio-visual tool in cancer trials. They reported transient improvement in participant knowledge. Their finding underscores that customisation of both generic and trial-specific information to participant context is central to comprehension (262, 264).

9.4: Assessment of comprehension

The use of a combination of question formats such as closed-ended, open-ended, multiple choice response formats minimises the possibility of guesswork that are common in comprehension assessment study (318). For example, two different question formats were adopted in the digitised questionnaire to assess participants' understanding of randomisation. Question item 10 had a 'choose the best' answer from a multiple response options while item 23 was an open-ended question where participants freely expressed their understanding of the concept. At the baseline and subsequent follow-up visits, significant proportion of participants in the multimedia arm demonstrated better comprehension of the concept of randomisation ($p<0.001$). Consistent with the literature which suggests that many participants believe that researchers decide treatment allocation for them (113,

280), about 30% at baseline (Day 0 visit) in the multimedia arm and 60% in the standard consent arm incorrectly answered the question about how the treatment was allocated, with the majority of participants in the 'standard' consent arm believing that the doctor chose for them. This trend persisted throughout the follow-up visits for this question item.

Similar trends were observed in other concepts like adverse events, right of participation and placebo. However, there were differences in the proportions of participants who demonstrated better comprehension about contact person, benefit, right of withdrawal, autonomy, penalty of withdrawal, study activities and number of study visits. The question item which assessed participant 'recall' of the name of study contact persons generated almost similar proportions of correct responses from participants in both study arms. However, when asked to mention the specific name of the contact person in the follow-up open-ended question which assessed 'understanding' of the preceding question, a higher proportion of participants in the multimedia arm gave correct answers than their counterparts in the 'standard' consent arm. This showed a statistically strong difference at all time-points across the two study arms ($p<0.001$), suggesting better comprehension among participants in the multimedia arm.

Although, a higher proportion of participants in the multimedia arm had better comprehension about whether participants would receive money as a form of reward for research participation, this did not reach a statistical difference. Similar trend was observed regarding participant comprehension of right of withdrawal. Relatively higher proportion of participants in multimedia arm gave correct answers on the question item on how decision to participate was made (autonomy), but this did not attain statistical difference between the two study arms. This pattern of responses may indicate a potential

benefit of reinforcing the consent information through a repeat viewing of the multimedia tool by the participants. It may also suggest a need to further revise and refine the question items on these domains of informed consent in future studies.

The wide differences in the comprehension scores of participants in many domains of informed consent between the two study arms showed that existing process for informing participants in The Gambia is not adequately effective in improving understanding in these areas while the current informed consent procedure may be partially effective in some domains such as study procedures, contact person, frequency of study visits, where the participant scores in both study arms were almost similar.

Participants in the multimedia arm had higher comprehension scores in the domains of voluntariness of the participation decision, freedom to withdraw from the trial and penalty for refusing or withdrawing from participation. Issues around voluntariness were also identified as major factors affecting participant decision to accept or decline the trial. This finding was further supported during focus group discussions by participants in the multimedia arm who admitted that the intervention helped in knowing that they could leave the study at any time. Voluntariness was shown to be an important component within the ethical framework of informed consent, linked to participant understanding (22) and it appears that multimedia tool can increase the understanding about voluntariness.

The concept of 'substantial understanding' was discussed in the literature review as an important endpoint in terms of informed consent (22), despite the challenge of clearly describing it. The principle of 'substantial understanding' was considered as the core generic information, in additional to the trial-specific information required by the study

participants. The multimedia tool incorporated the information required for 'substantial understanding' as well as trial-specific information which was blended in the right mix to engender the participants' comprehension. Faden and Beachamp's definition of understanding - understanding *that* you are being asked to decide about taking part in a trial, and understanding *what* is communicated about the trial - was also integral to the multimedia tool (22).

It must be acknowledged, however, that although the digitised questionnaire was designed to assess important domains of informed consent relevant to low literacy African settings, comprehension was not measured in terms of whether or not it was substantial. No attempt was also made to specify how much understanding is necessary for it to be considered 'substantial' since no absolute level was defined in literature. This is mainly because the study endpoints focussed on the comparisons of comprehension scores across the study visits in the two study arms.

Nevertheless, this study explored the objective assessment of comprehension, through the use of the digitised questionnaire as well as participant interviews during focus group discussions. Participant perceptions were also assessed through exit interviews conducted via an adapted version of informed consent questionnaire (294), where participants were asked questions about their understanding of the information received. Participant interviews at FGD sessions also provided further insights about comprehension of the research concepts. This supports the views that qualitative approach could engender a forum where a deeper assessment of participant comprehension could be ascertained (319).

9.5: Participant comprehension scores

The study hypotheses were confirmed that the multimedia consent method made the study information more understandable to the clinical trial participants than the 'standard' consent method. Also, the participants engaged in multimedia consent tool performed significantly better than the participants in the 'standard' consent tool across all test performance scores: recall, understanding and comprehension. Furthermore, the performance test scores on the digitised questionnaire discriminated between participants engaged with the multimedia consent tool and those exposed to 'standard' consent procedure. This was demonstrated in the higher median scores among participants in the multimedia arm at baseline and subsequent follow-up visits.

This study adds to the emerging body of evidence in African clinical trial settings where audio-visual tool has been shown to improve participant comprehension as part of the informed consent process (154, 279). Because of previous uncertainty about the effectiveness of multimedia tool, this is an encouraging first step which demonstrated that multimedia consent tool improved comprehension of study participants better than the verbal interpretation that is currently adopted as standard practice in The Gambia.

9.6: Relationship between participant withdrawal and comprehension

The relatively low withdrawal of 4.5% of participants in this study can be explained within the context of participant withdrawal for the parent trial, where only about 5% did not complete the study. It could therefore be concluded that the sample was largely representative of the population under study. Of the few who withdrew, whether or not a reason was given was not balanced across the arms. Though the study team asked everyone withdrawing for a possible reason, 80% of participants in the multimedia arm did not give reasons. While this could be considered acceptable as the participants' rights to withdraw, it

may be worthy of further investigating the reasons for this withdrawal. This is to ensure that the participants' reasons for withdrawal are not due to misconceptions commonly held about clinical trial participation. Nonetheless, appreciably low withdrawal rates in clinical trials conducted in vulnerable populations have been reported in several reviews (7, 15, 16) and this was partly attributed to poor comprehension of the right of withdrawal by the participants (114, 210, 215, 216). Furthermore, misconceptions and poor comprehension are common in clinical trials, partly due to participant vulnerability and also due to difficult terminologies used in describing the research concepts. This has led to assumptions that poor understanding of basic research concepts like study purpose, right of refusal and right to withdraw, contribute to high recruitment and high retention rates in African research settings. This is also said to expose the people to research exploitation (5, 6, 61).

That participants in the multimedia arm did not give a reason for withdrawal may suggest an improved understanding of their right to withdraw without giving a reason. This finding may further suggest that a change in comprehension of study information may be associated with a change in behaviour or decision. There is a general consensus that giving appropriate information can influence people's behaviour or decision (64, 314). This also manifested during the focus group discussions where participants in the multimedia arm expressed correct understanding of right to withdraw. This assumption has its basis in rational models of decision making, where decisions are made logically, and the decision-output (or behaviour) is influenced as a consequence of improved comprehension of an individual (185, 201).

9.7: Retention of study information: The extrapolated data beyond the study completion showed that participants in the multimedia arm retained the study information significantly longer than those in the control arm, and even beyond the length of the follow-

up for the parent trial which ended at Day 42. The finding also suggests that participants exposed to 'standard' consent procedures would have forgotten half of the information before the end of the parent trial follow-up. While this is a remarkable finding in support of effectiveness of multimedia consent tool, not only to improve participant comprehension but also retain the information for a reasonable period of time, there may be a need for reinforcement by repeat viewing of the multimedia consent tool by participants in studies with longer follow-up.

9.8: Cost of production: The process of developing the multimedia tool for a specific clinical trial attracts enormous practical and financial challenges, particularly if introduced in the context where increasing number of trials are being conducted in low-resource countries. Cost-analysis showed that the unit cost of producing and administering multimedia consent tool and DICCQ was about £22 per participant. This is likely to be reduced if the production involves only multimedia consent tool. The multimedia tool can be made available to potential participants in video CD or DVD, but effective use may depend on whether the participants have a video CD/DVD player at home or electricity is available to power the player to view the multimedia consent tool.

Therefore, a trade-off is needed in introducing a multimedia tool within a clinical trial set-up in developing countries. The cost involved in the production of a multimedia tool for each clinical trial could be covered within a research grant and it may be worthwhile, particularly for research centres involved in a substantial number of clinical trials, to set up a multimedia production unit within their centres. A generic software may also be developed in conjunction with multimedia consultants, to which trial-specific information of individual trials could be added when needed. This will reduce the cost and time of production of a multimedia consent tool for every trial.

***9.9: Acceptability of the tools*:** The multimedia tool and digitised questionnaire were well received by the participants. This was highlighted during recruitment when some participants insisted they want to be allocated into the multimedia group without undergoing formal randomisation. Also, during focus group discussions, participants expressed preference for the pictures, sounds and information content of multimedia tool while those in the standard consent arm expressed acceptance of the digitised

questionnaire. This finding suggests that the two tools have the potential of gaining acceptance among participants in similar research settings.

9.10: Challenges and opportunities of developing and using the tools

The study interventions were successfully developed, but there were substantial challenges and opportunities during the process which will now be discussed. The major problems encountered were logistical, financial and technical constraints. The initial plan was to use an audio-visual tool called 'Speaking Book' as the study intervention. However, huge financial implications of producing the book, inability to include trial-specific information and lack of flexibility in editing the book following a pilot study posed considerable threats to planning and implementation of the study. These concerns led to the decision to use current technology to provide an innovative and flexible solution to deliver study information in a developing country context.

Considerable challenges were also faced to identify another suitable parent trial to nest the study within, following a protracted delay in the take-off of the previously agreed parent trial. To meet the timelines for the development, production, piloting and field-testing of the intervention, the study had to be conducted in two recruitment sites which further increased financial and logistic challenges.

Another challenge was identifying a local multimedia expert as MRC does not have a Medical Illustration Unit. After several enquiries, I was directed to a multimedia expert in The Gambia who was involved in producing a documentary video on MRC activities. As this project was on a relatively large scale and required a developmental approach to incorporate expertise from a variety of areas (study participants,

nursing, medical and linguistic professionals, scripting and filming), I shared the draft of the script with relevant clinical trial teams who expressed enthusiasm and readiness to undergo necessary training and rehearsals to ensure the success of the project. It was very challenging bringing out the skills and talents of the volunteers involved. This became more challenging with coordinating the production work with the multimedia expert. Some members of the team did not know each other prior to working on the project, and had to quickly adapt and work together as a team, in a fairly intense environment where good leadership was essential. Despite the difficulties of working in non-traditional roles, filming, audio-recording of study information in the three local languages went well with minimal hitches and the quality of final production was of acceptable standard.

9.10.1: Opportunities

A number of unique opportunities were identified despite several challenges faced in developing the multimedia tool. Working effectively across multi-disciplinary teams consisting of clinical and non-clinical staff generated mutual respect and better appreciation of individual roles. The ability to harness the team expertise effectively was central to the success recorded in the local production of the tool. Collaborating with colleagues with diverse expertise was a positive finding of the process that was also reported by Meade (320) and Hutchison et al (314, 321) in their work. There was significant goodwill generated from both study participants and the team, all of whom were enthusiastic and motivated about the work and keen to offer the required support. The process provided important learning opportunities, leading to much discussion about various areas in the conduct of clinical research in developing countries including informed consent and other ethical issues.

One of the most important opportunities was the contribution of the study participants. This experience led the team to a fuller appreciation of their contributions and the need to involve them in similar interventions in future. Following publication of the findings on the development and testing of the tools in scientific journals, I received several requests across African countries and beyond, for collaboration and further development of the tools. One of such was the invitation to participate in discussions on topical ethical issues by *Switching the Poles Clinical Research Network*, a forum which brings together researchers from South-East Asia, sub-Saharan Africa and Latin America. These discussions led to a scientific publication on the need for further research on the issue of participation in medical research as a resource-seeking strategy among vulnerable populations(73). These collaborations will hopefully contribute to the expansion of relatively small body of knowledge on the use of multimedia consent tool in low literacy African research settings.

9.10.2: Implications for informed consent clinical trials

Based on the findings of this study, a multimedia tool that integrates video, animation and audio narration of informed consent information in the participants' local languages can be proposed as an alternative informed consent tool in low literacy research settings like The Gambia.

The tool could be adapted into a generic version to inform participants about clinical trials prior to their decision about participation, in view of its effective role in increasing comprehension. The multimedia tool containing the generic and trial-specific information could also form part of the initial discussion, which could be provided for participants who have VCD/DVD player to view at home. This could influence participant

decision before they return to the trial site for a formal consent process. This is capable of promoting an informed decision.

There is also a need to think carefully on how to address the cost implications involved in production of multimedia tool for every clinical trial. This cost can be defrayed into the research grants for setting up a multimedia production unit within the research centres. The cost may initially be high but may gradually become minimal as the production gains further acceptance within the system.

The digitised questionnaire could be used for assessment of participant comprehension as this may provide opportunity for researchers to identify area of misconceptions and correct these before consenting. This may be supported by a customised checklist and personal discussion with the participants. A model similar to that evaluated by Joseph et al (273) and Woodwong & Karim (204) could be adopted, where the multimedia and questionnaire are used as part of a multi-layer education approach.

9.11: Study limitations

Despite the practical and useful information generated by this study on alternative consent tool in low literacy setting, a number of limitations were identified. This study was conducted in The Gambia where research projects have been continuously carried out in various communities for more than 67 years. This familiarity with research projects may affect the responses of the participants; effectiveness of multimedia tool may be different in other settings with less research activities.

As this study was nested within a parent trial, due to low malaria prevalence in Jahaly

site, the sample consisted of a particularly high number of participants from Basse. Although the two sites share similar socio-epidemiologic features, this may potentially introduce clustering effect which may invariably affect interpretation of the findings. However, mixed-effects model showed that place of domicile accounted for an insignificant difference in participant comprehension scores, suggesting an insignificant clustering effect.

Although, the use of qualitative and quantitative approaches to explore participants comprehension provided an in-depth interpretation and understanding of the data; there is however an important need for further qualitative work to gain a deeper understanding of what is important to participants about comprehension of clinical trial information.

9.12: Recommendations for further research

Further research could be considered in four major areas namely: further validation of digitised questionnaire in other African settings; further customisation of multimedia tool in other African settings; consideration of verbal vocalisation of informed consent as an alternative for thumb-printing for non-literate participants; and using behaviour decision theory to better understand the factors influencing participant comprehension.

First, the digitised questionnaire would benefit from further testing in randomised clinical trials in other African settings to establish its reliability and validity in these settings where local languages are likely to be more diverse. This may determine the generalisability across African research settings. An abridged version of the questionnaire may also be developed from the original version and tested in varying settings for validity

and reliability and this could be used for routine assessment of comprehension. Similarly, the multimedia tool could be further evaluated in other African settings and in different phases of clinical trials to determine if effectiveness of the tool varies with the different phases of the trials.

Second, because the multimedia tool has overcome the challenge of written translation of informed consent documents from English to Gambian languages, this needs to be taken further by addressing the challenge of signing the consent form which is impracticable for non-literate participants. This symbolic aspect of informed consent is replaced with thumb-printing, which has been a subject of debate by many schools of thoughts (2, 131). This important area could be replaced by vocalisation of freely given informed consent (269), and could be audio-recorded and stored in archive for as long as required by regulatory and ethical committees. This model was described by Jimison et al (269) where literate participants gave consent using electronic signature while non-literate participants vocalised the consent.

Third, some factors in the communication process are central to facilitate the participant comprehension in particular the participant-researcher interaction. Although this was not a study objective, this area requires further research where multimedia tool is evaluated in combination with reflective, participant-centered interaction. Albrecht et al (322) developed a model to explain patient decision- making in the context of clinical trials and hypothesised that 1) the characteristics of the researcher; 2) the nature of the trial protocol itself; 3) predisposing factors of the participant; and of the participant's family member or significant others, affect a participant's decision to enrol in a clinical trial. The authors also suggested that the impact of all of these variables on the actual participation decision is mediated by the kind of communication that

occurs between the participants and the researchers. Involvement of the family members in this approach is valuable in view of the substantial influence that families often have in terms of decision-making in the clinical trial context in African settings where participants live within extended family system and communal decision is taken within kinship structure (97). Another dimension that needs to be explored are the specific aspects of the informed consent process including researchers' communication skills, the effect of enhanced communication on comprehension, in addition to assessing improvements in the communication process.

The fourth potential area for further research identified by this study is the exploration of individual clinical trial participation decision in depth, based on behaviour decision theory and a fully elaborated theoretical framework, with the aim of understanding more about the processes and factors that influence the actual decision. Adopting an approach to decision-making which goes beyond rational choice models would take due account of the socio-cultural and affective factors, such as information gained from sources other than health care professionals, cultural norms and emotion (185).

9.13: Conclusions

Despite the limitations, findings from this study supports the use of multimedia tool as a useful addition to the consent process for clinical trials in low literacy settings for improving participant comprehension. The tool addresses the fundamental ethical challenges of informed consent by improving participant comprehension. It has been demonstrated to be an acceptable medium for delivering clinical trial information to low literacy participants.

The main study conclusions can be summarised as follows:

- Multimedia tool has been shown to be a useful and acceptable addition to

the consent process in a clinical trial in a low literacy research setting.

- Multimedia tool can increase participant comprehension of clinical trial information. By improving participant comprehension, the tool supports the fundamental ethical framework necessary for valid informed consent.
- The digitised questionnaire was also shown to be a reliable and effective instrument for measuring participant comprehension in a randomised clinical trial, although further work is necessary.
- Multimedia tool can be used as part of the standard information package for participants considering clinical trials.
- The digitised questionnaire could be abridged, validated and introduced to routine practice as a tool to determine participant comprehension.

Further research focusing on multimedia tool specific to individual trials would be helpful to determine if a more customised approach would affect clinical trial recruitment. Studying other aspects of the consent process, such as the interaction between the researchers and participants, in addition to a more detailed exploration of the factors affecting participant decisions, is needed.

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Appendix I : Informed Consent Document

Evaluation of alternative informed consent procedure in clinical trials conducted in The Gambia (Stage I)

Participant Information Sheet

Version 4.0 - 8 January 2013

Informed consent is a way by which researchers explain to you what a study entails before you decide to join the study or not. We observe that most people do not understand study information before they or their children join the study. We thought this might be due to the way the information is passed to you.

The study information should be given in a way that will make you understand it but we do not know which way this will be. This is the reason we want to see if putting the study information in picture/speaking method will make you understand the information better.

This study has three stages: This is the first stage; we want to know the relevance and usefulness of a questionnaire which tests understanding of study information. This will be done among 250 participants in ongoing clinical trials in Fajikunda and Walikunda. If you agree to participate in this stage, the questionnaire will ask you some information about the study you are currently participating. The questionnaire has been designed on a computer laptop and the investigator or his assistants will explain how you will answer the questions. Some of the participants will be called back after one week for a re-test of the same questionnaire. Answering the questions will not take more than 30 minutes of your time.

Your participation in this study is voluntary and you may refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which you are otherwise entitled.

You will not get paid for taking part in this study. Your information will not be told to anybody not working with us. If something is not clear to you about this information, you can ask Dr Muhammed Afolabi on phone number 4495442-6, extension 5037.

Thank you for taking time to read or listen to this information. To take part in this study, you will need to sign or thumbprint the consent form.

CONSENT FORM

The information sheet has been read to me/I have read it and I understand what participation in the study means for me and/or my child. I have also had the chance to ask questions about the study.

I understand that there are three stages in this study.

I understand this first stage of the study is to know the relevance and usefulness of a questionnaire which tests understanding of study information.

Name of participant _____ Study No: ICS |__|__|__|

Signature or thumb print of participant: _____

Date: |__|__| / |__|__| / |__|__|__|__|

This form has been read / explained to_____

in _____, a language that the participant understands.

I believe that he/she has understood what I explained and that he/she has freely given consent to take part in the study.

Name of Investigator: _____

Signature: _____Date: |__|__| / |__|__| / |__|__|__|__|

Name of Independent Witness: _____

Signature: _____Date: |__|__| / |__|__| / |__|__|__|__|

Evaluation of alternative informed consent procedure in clinical trials conducted in The Gambia (Stage II)

Participant Information Sheet

Version 4.0 - 8 January 2013

Informed consent is a way by which researchers explain to you what a study entails before you decide to join the study or not. We observe that most people do not understand study information before they or their children join the study. We thought this might be due to the way the information is passed to you.

The study information should be given in a way that will make you understand it but we do not know which way this will be. This is the reason we want to see if putting the study information in picture/speaking method will make you understand the information better.

This study has three stages: we have determined the relevance and usefulness of a questionnaire which tests study information in the first stage of the study.

In the second stage, we will pilot the picture/speaking method of delivering study information among 40 male and female participants aged 18-49 years in Basse. This is to know if the method will be acceptable and easy to use. There are two visits for participants at this stage. At first visit, participants will listen to the malaria study information that has been put in picture/speaking method; after which, we will ask them questions about ease of use and acceptability of the method. The participants will come back one week after to listen to a questionnaire in picture/speaking method and they will also be asked to answer questions if it is easy to use and acceptable.

During the second visit, some selected participants will be invited for further discussions about how easy and acceptable are picture/speaking methods of giving information and asking questions in a study.

Your participation in this study is voluntary and you may refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which you are otherwise entitled.

You will not get paid for taking part in this study. Your information will not be told to anybody not working with us. If something is not clear to you about this information, you can ask Dr Muhammed Afolabi on phone number 4495442-6, extension 5037.

Thank you for taking time to read or listen to this information. To take part in this study, you will need to sign or thumbprint the consent form.

CONSENT FORM

The information sheet has been read to me/I have read it and I understand what participation in the study means for me. I have also had the chance to ask questions about the study.

I understand that there are three stages in this study.

I understand this second stage of the study is to assess acceptability and ease of use of multimedia consent tool and a new method of asking study questions

Name of participant _____Study No: ICS |___|___|___|

Signature or thumb print of participant: _____

Date: |___|___| / |___|___| / |___|___|___|___|

This form has been read / explained to_____

in _____, a language that the participant understands.

I believe that he/she has understood what I explained and that he/she has freely given consent to take part in the study.

Name of Investigator: _____

Signature: _____Date: |___|___| / |___|___| / |___|___|___|___|

Name of Independent Witness:_____

Signature: _____Date: |___|___| / |___|___| / |___|___|___|___|

Evaluation of alternative informed consent procedure in clinical trials conducted in The Gambia (Stage III)

Participant Information Sheet

Version 4.0 - 8 January 2013

Informed consent is a way by which researchers explain to you what a study entails before you decide to join the study or not. We observe that most people do not understand study information before they or their children join the study. We thought this might be due to the way the information is passed to you.

The study information should be given in a way that will make you understand it but we do not know which way this will be. This is the reason we want to see if putting the study information in picture/speaking method will make you understand the information better.

This study has three stages: we have done the validation of a questionnaire which tests study information in the first stage of the study. And in the second stage, we have assessed acceptability and ease of use of the two picture/speaking methods for delivering study information and asking study questions. In this third stage, we will need 300 participants in the malaria study taking place in Basse to compare the picture/speaking method with written method to know which one will aid better understanding of study information. The participants will be divided into two groups by chance (liking tossing a coin). The first group will receive information about the malaria study in written form with oral explanation by research assistants. The second group will have the information by picture/speaking method. Thereafter, the two groups will be asked questions about their understanding of the information at the first visit, days 7, 14, 21, and 28 after first visit. Answering these questions will not take more than 30 minutes of your time.

During day 35 and 42 visits, some selected groups among the participants will be invited for discussions on what they understand about the study they participate in. They will also be asked about how easy and acceptable are picture/speaking methods of giving information and asking questions in a study.

Your participation in this study is voluntary and you may refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which you are otherwise entitled. You will not get paid for taking part in this study.

Your information will not be told to anybody not working with us. If something is not clear to you about this information, you can ask Dr Muhammed Afolabi on phone number 4495442-6, extension 5037.

Thank you for taking time to read or listen to this information. To take part in this study, you will need to sign or thumbprint the consent form.

CONSENT FORM

The information sheet has been read to me/I have read it and I understand what participation in the study means for me and/or my child. I have also had the chance to ask questions about the study.

I understand that there are three stages in this study and this is the third stage of the study

I understand that participants in the third stage will be divided into two groups by chance and they will be asked questions to assess their understanding of study information at first visit and days 7, 14 and 28 after first visit.

I also understand that during day 35 and 42, some of the participants will be invited for a group discussion on their understanding, acceptability and ease of use of the 2 new instruments.

Name of participant _____Study No: ICS |___|___|___|

Signature or thumb print of participant: _____

Date: |___|___| / |___|___| / |___|___|___|___|

This form has been read / explained to_____in _____, a language that the participant understands.

I believe that he/she has understood what I explained and that he/she has freely given consent to take part in the study.

Name of Investigator: _____

Signature: _____Date: |___|___| / |___|___| / |___|___|___|___|

Name of Independent Witness:_____

Signature: _____Date: |___|___| / |___|___| / |___|___|___|___|

Appendix II: Paper copy of DICCQ

Participant ID: ICS |__|__|__| Site code |__|__|__|

Time interview starts |__|__|:|__|__| Time interview ends |__|__|:|__|__|

Dear participants, we observe that some people do not understand study information before they or their children join the study. We thought this might be due to the way the information is passed to you. One of the steps taken to know if you understand the study information you are currently participating is to answer the set of questions below. The questions have been translated and audio-recorded in the local language you understand. Please, listen carefully and answer the questions truthfully. Answering the questions will take only 30 minutes of your time. Thank you for helping in this regard.

Section A: SOCIO-DEMOGRAPHIC DATA		
1.	Age last birthday	|__||__| (in years)
. 2.	Gender	|__| Male=1, |__| Female=2
3.	Place of domicile	.....
4.	Highest level of education attained	|__|Primary=1, |__|Secondary=2, |__|Arabic=3, |__|Technical/vocational education= 4, |__|University= 5, |__|No formal education=6
5.	Occupation	|__|Farming=1, |__|Trading=2, |__|Artisan=3, |__|Civil servant= 4, |__|Housewife=5, |__|Schooling= 6, |__|Pensioner=7, |__|Unemployed =8
6.	Ethnicity	|__|Mandinka =1, |__|Wollof=2, |__|Fula=3, |__| Jola=4, |__|Sarahule=5, |__|Other, please specify.....6
7.	Religious affiliation	|__|Islam=1, |__|Christianity =2, |__|Traditional = 3, |__|Other= 4
8.	Have you ever taken part in a clinical study?	|__|Yes=1, |__|No=2, |__|I don't know=3
9.	If yes, in how many clinical studies have you taken part?	|__|None=1, |__|Only one=2, |__|More than one=2

Section B: Choose the correct answer and provide the correct response to the follow-up question, where applicable		
10.	Have you been told that you can freely decide to take part in this study?	|__|Yes=1, |__|No=2, |__|I don't know=3
11.	Have you been told you can withdraw from this study anytime?	|__|Yes=1, |__|No=2, |__|I don't know=3
12.	During the study, will you know the drug you or your child is receiving?	|__|Yes=1, |__|No=2, |__|I don't know=3
13.	If yes, describe or mention what the drug is doing?	.....
14.	During the study, will anyone not working with MRC know about your health information?	|__|Yes=1, |__|No=2, |__|I don't know=3
15.	Have you been given the name and phone number of the person to contact if you have any questions about the study?	|__|Yes=1, |__|No=2, |__|I don't know=3
16.	If yes, mention the name of the person?	.....
17.	Can your participation in the study be stopped without your consent?	|__|Yes=1, |__|No=2, |__|I don't know =3
18.	Will you receive money for taking part in the study?	|__|Yes=1, |__|No=2, |__|I don't know=3

Section C:*Please listen to these two sample questions to see how you are expected to answer the questions that follow:*

i) The Gambian word for the festival marking end of Ramadan fast is called:

a) Tobaski b) Ngeten c) Koriteh d) I don't know

ii) Domoda soup is made from *a) Bread b) Groundnut c) Yam d) Orange*

Now answer the following questions by circling the right answer

19.	How were participants divided into different groups in this study?	a. Participants will be divided in different groups based on their health needs b. Participants will be divided into different groups equally by chance. c. Participants are free to decide which group they would be placed d. I don't know

20.	At what point can you leave the study?	a. I can leave at any time without giving a reason b I can only leave with the permission of village elders c I can only leave when the study is over d I don't know
21.	What does it mean when you sign or thumbprint the study consent form?	a. I would like to take part in similar studies b. I do not want to take part in this study c. I am agreeing to take part in this study d. I don't know
22.	How did you decide to participate in this parent study?	a. Was decided by the village leaders. b Was decided by me and my husband and it was completely optional. c Was decided by the scientists and doctors. d Was decided by my parent
23.	What will you receive as a reward for taking part in the study?	a. A small amount of money in addition to weekly checkups. b. Free medicine, money, and weekly checkups c. A small amount of food (rice, bread or sugar in addition to weekly checkups for your child. d. Health care if you or your child is ill, but nothing more
24.	What will happen if you decide to stop taking part in this study?	a. You will still be given weekly checkups, but no food or money. b. You will be given nothing - including access to healthcare services for your children. c. You will be fined and punished. d. You will be given nothing, but will always have access to healthcare in case of a medical problem or emergency

	SECTION D: You will need to circle more than one correct answers in this part *Please listen to these two sample questions to see how you are expected to answer the questions that follow:* ***i. Which of these are possible methods of transport to the market*** *a) Ride on a donkey-cart b) Ride a bicycle c) Take a taxi or bus* *d) Travel on a ferry* ***ii. Which of these are Gambian names for a male child*** *a) Fatou b) Lamin c) Ebrima d) Isatou*	
25.	Which of the following describes why the primaquine study is being done?	a. To test how well the drug works b. To test how much of the drug can be given without causing harm c. To improve my child's health condition d. I don't know
26.	Which procedures were you asked to take part in?	a. Blood sample collection b Urine sample collection c Body examination by study doctor / nurse d I don't know
27.	Which activities were you asked to complete?	a. Attend scheduled study visits b. Inform study doctor/nurse before taking other medications c. Receive routine vaccine d. I don't know
28.	Which describes the main benefits of taking part in the study?	a. Developing drug for people suffering from disease e.g malaria b. Free medical care c. Improve my health condition d. I don't know
	SECTION E: In this section, you are requested to provide answers that are specific to the study you are currently participating. A test question is given below: *What are the tribes in Gambia: Possible answers are: Mandinka, Wolof, Fula, Jola, Serehule, Manjago, Aku*	
29.	Please tell me what the researchers want to find out in the study?	.....
30.	How many times do you have to come to the	.....

	clinic for a visit during the study?	
31.	Tell me what will be done during the study visits?	.....
32.	How are participant assigned into different groups this study?	.....
33.	What is the difference between taking part in this study and going to see a doctor for treatment?	.....
34.	What are the possible unwanted effects of taking part in this study?	.....
35.	Why do you think some of the study participants were given different medicine?	.....

Appendix III: Modified ICQ

Informed Consent Questionnaire	Yes, completely	Yes, partially	No	I don't know
Understanding sub-scale				
1. Did you understand the study when you decided to participate?				
2. Do you feel the potential benefits of the participation were explained?				
3. Do you feel that the inconveniences and potential risks of participation in this study were explained?				
4. Did participating in this study meet your expectations?				
Satisfaction sub-scale				
1. Would you participate again if this study is repeated?				
2. Would you participate in any MRC study in future?				
3. Did you feel that study personnel were willing to answer your questions or concerns about the study?				

Appendix IV: Focus group discussion guide

Theme	Question guide
Comprehension of study information	i. Why is this study being carried out? ii. What makes you to participate in this study? iii. Would you advise your friend to join this study? iv. How will you explain different aspects of this study to your friend? (Explore participants' understanding about the following concepts in the context of primaquine trial: study purpose, study procedures: (how does primaquine works, G6PD deficiency), risks and benefits, randomisation, placebo, blinding, confidentiality, compensation, rights of withdrawal, therapeutic misconception).
Acceptability and ease of use of multimedia consent tool and DICCQ	i. Describe how much you like or dislike the following features of the tools: colour, pictures, voices, duration? ii. How comfortable are you with the information in the tools? iii. How easy or difficult did you find the information given in the tools iv. Will you like to use the tools again? v. Would you want future study information or questionnaire delivered through these tools? vi. Do you want any changes to the tools? If yes, what are these changes?

Appendix V: DVD containing DICCQ and multimedia consent tool

Instructions on how to access the contents of the DVD:

- The multimedia consent tool runs automatically on insertion of the DVD into a DVD player of a desktop or laptop computer. The language of interest is selected by clicking it on the screen and the content is played.

- The DICCQ is in a separate file on the DVD; right click on the DVD icon on 'Computer' menu. Select 'Open' and double-click on the file **THE-GAMBIA-ACASI-2013-05-06**. Again, double-click on the macromedia autoware (purple) icon with the title **THE-GAMBIA-ACASI-2013-05-06-exe**. When prompted for a password, use 'demo' without the inverted commas. Click the forward arrow buttons and follow the instructions on the menu bar to play the tool.

Appendix VI: Ethical approval letters

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www.lshtm.ac.uk

Observational / Interventions Research Ethics Committee

Muhammed Afolabi
Research Degree student
DDC/ITD
LSHTM

30 January 2013

Dear Mr. Afolabi,

Study Title: **Evaluation of an alternative informed consent procedure for clinical trials conducted in The Gambia**
LSHTM ethics ref: **6337**

Thank you for your letter of 23 January 2013, responding to the Interventions Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

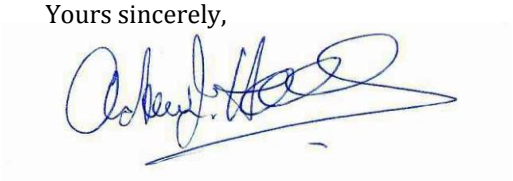
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM ethics application	n/a	13/12/2012
Revised Upgrading document		23/01/2013
Information Sheet & Consent Form	3.0	01/11/ 2012

After ethical review

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form. All studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. An annual report form (form E3) is required on the anniversary of the approval of the study and should be submitted during the lifetime of the study. At the end of the study, please notify the committee via form E5.

Yours sincerely,



Professor Andrew J Hall
Chair
ethics@lshtm.ac.uk
http://intra.lshtm.ac.uk/management/committees/ethics/

The Gambia Government/MRC Joint
ETHICS COMMITTEE

C/o MRC Unit: The Gambia, Fajara
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The Gambia, West Africa
Fax: +220 – 4495919 or 4496 513
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16 January 2013

Dr Muhammed Afolabi
Vaccinology Theme
MRC Unit, The Gambia
Fajara

Dear Dr Afolabi

SCC 1314v2, Evaluation of an alternative informed consent procedure for clinical trials conducted in The Gambia

Thank you for submitting your revised participant information sheet dated 8 January 2013, incorporating the recommendations of The Gambia Government/MRC Joint Ethics Committee at its meeting held on 21 December 2012.

I am happy to give Chair's full approval to your proposal.

With best wishes

Yours sincerely

[redacted]
Mr Malcolm Clarke
Chairman, Gambia Government/MRC Joint Ethics Committee

Additional documents submitted for review:-

- Participant Information Sheets (stages I – III), Version 4.0 – 8 January 2013
- Informed Consent Forms (stages I – III), Version 4.0 – 8 January 2013
- PhD upgrading document
- Questionnaire

The Gambia Government/MRC Joint
ETHICS COMMITTEE

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31 December 2012

Dr Muhammed Afolabi
Vaccinology Theme
MRC Unit, The Gambia
Fajara

Dear Dr Afolabi

SCC 1314v2, Evaluation of an alternative informed consent procedure for clinical trials conducted in The Gambia

Thank you for submitting your revised proposal dated 10 December 2012 for consideration by The Gambia Government/MRC Joint Ethics Committee at its meeting held on 21 December 2012.

The Committee is pleased to approve your proposal. However, the Committee strongly recommends that you clearly indicate on the subject information sheet that the subject's participation in the trial is voluntary, and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

The Chair would be happy to review the revised information sheet incorporating the recommendation of the Committee.

With best wishes

Yours sincerely

[redacted]
Mr Malcolm Clarke
Chairman, Gambia Government/MRC Joint Ethics Committee

Additional documents submitted for review:-

- Participant Information Sheets (stages I – III), Version 3.0 – 1 November 2012
- Informed Consent Forms (stages I – III), Version 3.0 – 1 November 2012
- PhD upgrading document
- Questionnaire

SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

SOUTH AFRICAN COCHRANE CENTRE

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THE SOUTH AFRICAN COCHRANE CENTRE

THE COCHRANE COLLABORATION

26 February 2014

To Whom It May Concern:

RE: Evaluation of an alternative informed consent procedure for clinical trials conducted the The Gambia.

As project manager for the Pan African Clinical Trial Registry (www.pactr.org) database, it is my pleasure to inform you that your application to our registry has been accepted. Your unique identification number for the registry is **PACTR201402000775274**

Please be advised that your trial is registered under an initiative within our system that allow us to capture data of trials that are already in progress or completed. As such, your trial registration may not adhere to the mandates set forth by the International Committee of Medical Journal Editors for registration requirements, and it is your duty to be transparent to any journal that may ask about the retrospective status of your registration.

Please note you are responsible for updating your trial, or for informing us of changes to your trial. Additionally, please provide us with copies of your ethical clearance letters as we must have these on file (via email, post or fax) at your earliest convenience if you have not already done so.

Please do not hesitate to contact us at +27 21 938 0835 or email epienaar@mrc.ac.za should you have any questions.

Yours faithfully,

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Appendix VII: Articles published or submitted for publication from the study

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Systematic Review

Informed consent comprehension in African research settings

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Abstract

OBJECTIVE Previous reviews on participants' comprehension of informed consent information have focused on developed countries. Experience has shown that ethical standards developed on Western values may not be appropriate for African settings where research concepts are unfamiliar. We undertook this review to describe how informed consent comprehension is defined and measured in African research settings.

METHODS We conducted a comprehensive search involving five electronic databases: Medline, Embase, Global Health, EthxWeb and Bioethics Literature Database (BELIT). We also examined African Index Medicus and Google Scholar for relevant publications on informed consent comprehension in clinical studies conducted in sub-Saharan Africa. 29 studies satisfied the inclusion criteria; meta-analysis was possible in 21 studies. We further conducted a direct comparison of participants' comprehension on domains of informed consent in all eligible studies.

RESULTS Comprehension of key concepts of informed consent varies considerably from country to country and depends on the nature and complexity of the study. Meta-analysis showed that 47% of a total of 1633 participants across four studies demonstrated comprehension about randomisation (95% CI 13.9–80.9%). Similarly, 48% of 3946 participants in six studies had understanding about placebo (95% CI 19.0–77.5%), while only 30% of 753 participants in five studies understood the concept of therapeutic misconception (95% CI 4.6–66.7%). Measurement tools for informed consent comprehension were developed with little or no validation. Assessment of comprehension was carried out at variable times after disclosure of study information. No uniform definition of informed consent comprehension exists to form the basis for development of an appropriate tool to measure comprehension in African participants.

CONCLUSIONS Comprehension of key concepts of informed consent is poor among study participants across Africa. There is a vital need to develop a uniform definition for informed consent comprehension in low literacy research settings in Africa. This will be an essential step towards developing appropriate tools that can adequately measure informed consent comprehension. This may consequently suggest adequate measures to improve the informed consent procedure.

keywords informed consent, understanding, Africa, vulnerable population, systematic review

Introduction

Comprehension is one of the essential elements of a truly informed consent. International ethical guidelines stipulate that informed consent must be given in a comprehensible manner to a competent person who freely decides to participate after understanding the information (NBAC 2001; CIOMS 2002; Marshall 2006). However, the amount and quality of study information required to engender comprehension of a potential participant is unclear. There are also divergent opinions among researchers on the level of comprehension a potential participant should reach to be able to freely decide (Ijsselmuiden & Faden 1992; Hyder & Wali 2006). In most African settings, the majority of research participants have low literacy, but informed consent documents are designed and delivered in a complex, lengthy manner that makes comprehension very challenging for the participants (Priestley *et al.* 1992;

Jefford & Moore 2008; Falagas *et al.* 2009). In such settings, what constitutes 'satisfactory or adequate' comprehension of informed consent is vague (Sreenivasan 2003; Woodsong & Karim 2005). This phenomenon has raised concerns about the quality and ethics of data generated from the increasing number of clinical trials being conducted in these low literacy communities (Annas 2009).

A previous review of studies conducted in developed countries reported a lack of consensus definition of comprehension and an absence of a standardised tool to measure objectively the adequacy of participants' comprehension (Sand *et al.* 2010). The authors concluded that a contextual definition of comprehension and systematic design of an instrument could guarantee adequate measurement of participants' comprehension (Sand *et al.* 2010; Mandava *et al.* 2012). This underscores the need to contextualise the definition of comprehension of informed consent information for different research settings as this may inform the development of a locally acceptable, culturally sensitive measure of informed consent comprehension.

We undertook this review to examine how participants' comprehension of informed consent information has been defined and measured in clinical studies conducted in sub-Saharan Africa (SSA). This will be a major step towards reaching a consensus definition of informed consent comprehension in African research settings, which in turn will help to design improved informed consent procedures.

Methods

Literature search strategy

We searched five electronic databases for empirical studies on comprehension levels of different domains of informed consent among participants in SSA. The databases were Embase (1947–2010), Medline (1960–2010), Global Health (1960–2010), EthxWeb and Bioethics Literature Database (BELIT). To complement these databases, we also searched African Index Medicus (AIM) and Google Scholar for relevant bibliographies and grey literature. The last search was conducted on 11 October 2013. Studies were included if they satisfied the following three criteria:

- assessed or evaluated participants' comprehension of informed consent information;
- involved participants who were in clinical studies rather than hypothetical trials;
- were conducted in a SSA country.

The initial search was conducted on Ovid MEDLINE using a combination of medical subject headings (MeSH) and text words and then translated into the terms appropriate to Ovid Embase, Ovid Global Health, EthxWeb and BELIT. The AIM and Google scholar databases were also searched using text words. The search terms included (*informed consent* OR *consent* OR *informed decision*) AND (*understanding* OR *comprehension* OR *retention* OR *knowledge* OR *awareness* OR *recall*) AND (*clinical trials* OR *clinical research OR randomi ed clinical trials*). 'Sub-Saharan Africa' was searched using *Africa south of Sahara* OR *developing countries* OR *low-income countries* OR *vulnerable population* OR *underserved population*. To ensure all relevant countries were included in the review, sub-Saharan African countries listed in World RePORT database of global research (Collins *et al.* 2013) were used as a guide. Furthermore, to ensure the search was not limited to English language studies, specific Francophone and Lusophone country names such as Angola, Burkina Faso, Cape Verde, Cote d'Ivoire, Gabon, Guinea-Bissau, Mali, Mozambique, Sao Tome and Principe and Senegal were also included in the search terms. Specific search algorithms used in each database are presented in Table 1.

Duplicate results from the searches were removed, and thereafter, the abstracts of retrieved articles were reviewed for relevance prior to accessing the full paper. We excluded letters or responses to published articles, commentaries and editorials. Conference abstracts that had not been published as full papers were included where the abstracts could be retrieved, provided that the abstracts had sufficient information for either qualitative or quantitative analysis. In situations where a conference abstract had been published as a full paper, the paper was retrieved and the conference abstract excluded. We contacted authors of conference abstracts whose full-paper publications could not be accessed to ask whether the abstract had been published as a full paper and if not, to seek more information about the study. Of five authors contacted, only one responded by providing the full text paper of the conference abstract. However, the published article provided by the author (Ravinetto *et al.* 2010) did not meet the eligibility criteria and was not included in the final analysis.

Data extraction

We obtained 245 articles from the primary search and 64 articles from AIM and Google scholar. Two of the review authors (MOA and JUO) independently screened the searches and applied the eligibility criteria. Of these 309 articles, 192 were removed because they were duplicates. Another 88 articles were sequentially excluded for the reasons of ineligibility. 29 studies satisfied the three inclusion criteria and were reviewed in detail. Figure 1 illustrates the inclusion process. Twenty-three of the studies were

Table 1 Search strategy for the systematic review

Concept	Search terms	EMBASE via Ovid (1947–2013)	Global Health via Ovid (1910–2013)	Medline via Ovid (1946–2013)	EthxWeb	BELIT via DRZE (1850–2013)
Informed consent	#1: (informed consent OR consent OR informed decision). mp.	319882	10179	164307	22586	59923
Comprehension	#2: (understanding OR comprehension OR retention OR knowledge OR awareness OR recall). mp.	1318519	158692	662692	880	9630
Clinical research	#3: (biomedical research OR clinical research OR clinical trials OR randomi*ed controlled clinical trials OR random allocation trials OR intervention trials). mp.	275353	25182	363991	50885	117927
sub-Saharan Africa	#4: (Africa south of Sahara OR low-income countr* OR developing countr* OR vulnerable populations OR disadvantaged populations OR underserved populations).mp. exp Angola/ OR exp Burkina Faso/ OR exp Cape Verde/ OR exp Cote d'Ivoire/OR exp Gabon/ OR exp Guinea-Bissau/OR exp Mali Mozambique/ OR exp Sao Tome and Principe/ OR exp Senegal. mp.	107234	610100	103689	189847	373209
All	#1 AND #2 AND #3 AND #4	74	27	104	36	4

BELIT – Bioethics Literature Database: extensive bibliographic directory of literature in the area of bioethics, containing monographs, academic dissertations, collective works, reference works, books, journal articles, newspaper articles, legal documents, grey literature and electronic document. EthxWeb – Bioethics Research Library at Georgetown University, USA, Medline mp: [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier], Embase mp: [mp=title, subject headings, heading word, drug name, original title, device manufacturer, drug manufacturer, device trade name, keyword].

conducted in Anglophone countries (Abdool Karim *et al.* 1998; Leach *et al.* 1999; Joubert *et al.* 2003; Molyneux *et al.* 2004; Moodley *et al.* 2005; Pace *et al.* 2005; Marshall *et al.* 2006; Manafa *et al.* 2007; Hill *et al.* 2008; Minnies *et al.* 2008; Oduro *et al.* 2008; Taiwo & Kass 2009; Tekola *et al.* 2009; Vallely *et al.* 2010; Chaisson *et al.* 2011; Friedland *et al.*, 2011a,b; Hussein & Ahmed 2011; Kiguba *et al.* 2012; Ndebele *et al.* 2012; Vreeman *et al.* 2012; Oria *et al.* 2013; Saidu *et al.* 2013); five in Francophone countries (Préziosi *et al.* 1997; Coulibaly-Traore *et al.* 2003; Ekouevi *et al.* 2004; Krosin *et al.* 2006; Ellis *et al.* 2010) and one in a Lusophone country (Ciampa *et al.* 2012). Similarly, 12 of these studies were conducted in West Africa (Préziosi *et al.* 1997; Leach *et al.* 1999; Coulibaly-Traore *et al.* 2003; Ekouevi *et al.* 2004; Krosin *et al.* 2006; Marshall *et al.* 2006; Manafa *et al.* 2007; Hill *et al.* 2008; Oduro *et al.* 2008; Taiwo & Kass 2009; Ellis *et al.* 2010; Saidu *et al.* 2013), eight in East Africa (Molyneux *et al.* 2004; Pace *et al.* 2005; Tekola *et al.* 2009; Vallely *et al.* 2010; Hussein & Ahmed 2011; Kiguba *et al.* 2012; Vreeman *et al.* 2012; Oria *et al.* 2013) and nine in Southern Africa (Abdool Karim *et al.* 1998; Joubert *et al.* 2003; Moodley *et al.* 2005; Minnies *et al.* 2008; Chaisson *et al.* 2011; Friedland *et al.*, 2011a,b; Ciampa *et al.* 2012; Ndebele *et al.* 2012). Despite adoption of official languages of former colonial masters, countries in each subregion share similar socio-cultural factors that may influence informed consent comprehension (Angell 1997; Annas 2009). Therefore, this review focused on a regional comparison rather than the adopted official languages.

We extracted information on the type and sites of the studies, the sample size, definition of understanding/comprehension as provided by the authors, method and timing of evaluation of participants' comprehension. Also retrieved were data on participants' understanding/comprehension of study information including key concepts of informed consent: study nature and purpose, blinding, placebo, randomisation, voluntariness, rights of withdrawal, benefits/risks and adverse events. We performed

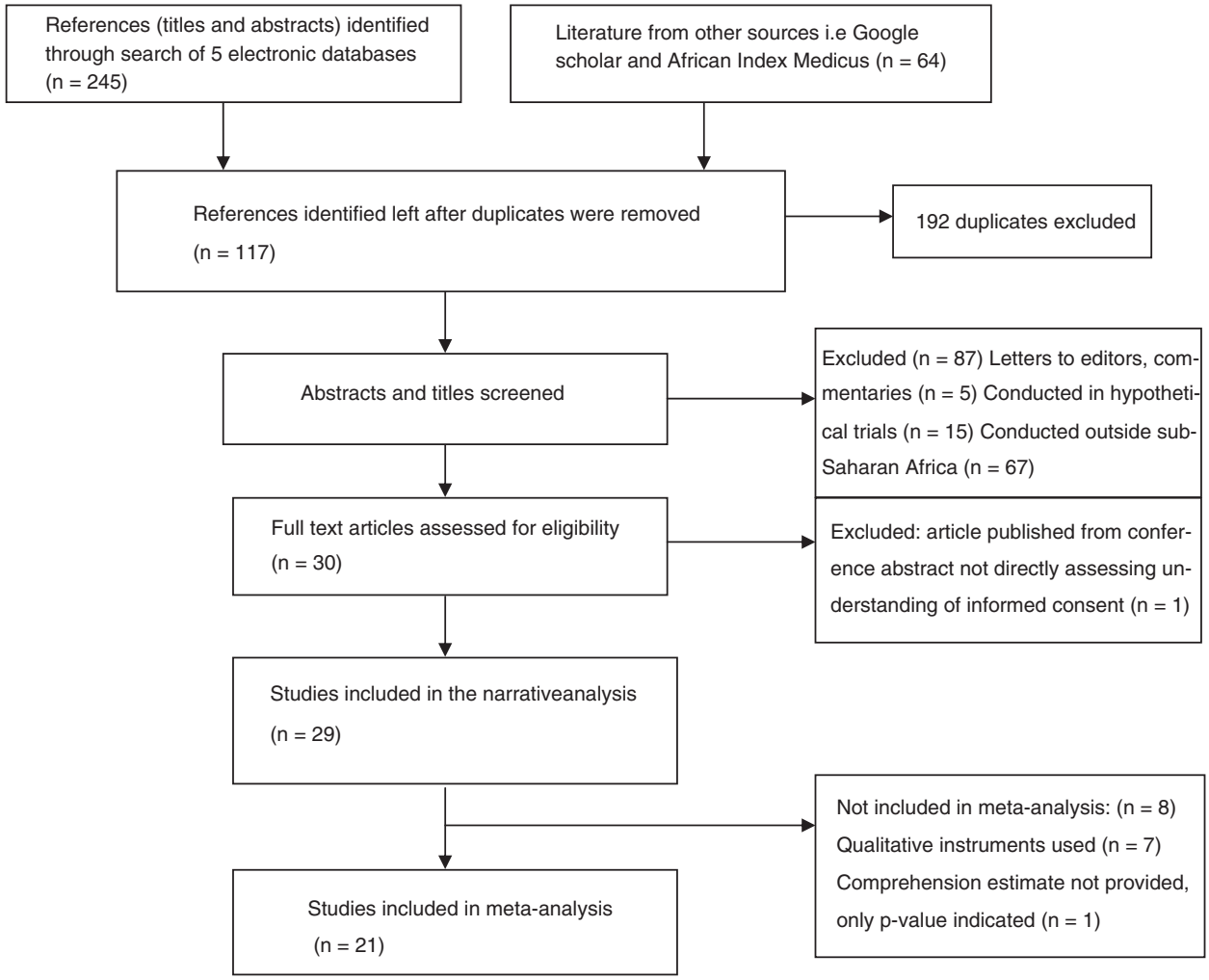

Figure 1 PRISMA flow chart showing inclusion process of papers for the review.

a detailed descriptive analysis and head-to-head comparison of study design, timing of informed consent, categories of participants recruited, instruments used for assessments and domains of informed consent assessed in each study (see Table 2).

Because only three authors provided a full questionnaire in their papers (Krosin *et al.* 2006; Minnies *et al.* 2008; Ellis *et al.* 2010), we did not analyse the few questionnaires for data extraction. We based our comparison on results provided in the papers included in this review.

Meta-analysis

We conducted meta-analyses of summary statistics from 21 studies (Abdool Karim *et al.* 1998; Joubert *et al.* 2003; Ekouevi *et al.* 2004; Moodley *et al.* 2005; Pace *et al.* 2005; Krosin *et al.* 2006; Marshall *et al.* 2006; Manafa *et al.* 2007; Minnies *et al.* 2008; Oduro *et al.* 2008; Taiwo & Kass 2009; Ellis *et al.* 2010; Vallely *et al.* 2010; Chaisson *et al.* 2011; Friedland *et al.*, 2011a, b; Hussein & Ahmed 2011; Kiguba *et al.* 2012; Ndebele *et al.* 2012; Oria *et al.* 2013; Saidu *et al.* 2013) which provided comprehension or understanding levels of participants on different domains of informed consent. Studies which used qualitative methods for assessments of comprehension (n = 7; Préziosi *et al.* 1997; Leach *et al.* 1999; Coulibaly-Traore *et al.* 2003; Molyneux *et al.* 2004; Hill *et al.* 2008; Tekola *et al.* 2009; Vreeman *et al.* 2012) and one with insufficient information (Ciampa *et al.* 2012) were excluded from the meta-analysis.

Table 2 Summary of studies on comprehension of informed consent information among research participants in sub-Saharan Africa

Authors	Country	Type of clinical research	Sample size	Method of evaluation	Outcome measures	Domains of IC understanding targeted
Studies in Anglophone countries						
Saidu *et al.* (2013)	The Gambia	Pneumoprotein vaccine trial	1200 mothers of study infants	Closed-ended study quiz	Comprehension measured by percentage of study mothers who demonstrated understanding	Study purpose, study procedure, voluntary participation, confidentiality
Oria *et al.* (2013)	Kenya	Knowledge assessment to seasonal influenza vaccination	5284 parents for pre-assessment and 5755 parents for post-assessment	Pre- and post-assessment questionnaires; focus group discussions	Percentage of respondents who had knowledge of the vaccination	Reason for influenza vaccination
Vreeman *et al.* (2012)	Kenya	Community perspectives on informed consent and research participation	108 community members	Community group discussions	Proportions of respondents who demonstrated knowledge	Knowledge, attitude, community consent
Ndebele *et al.* (2012)	Malawi	Microbicide trial	36 women	Structured interviews with a questionnaire 8 months after completion of parent trial	Understanding measured by percentage of correct responses to the questionnaire	Randomisation, blinding, placebo
Kiguba *et al.* (2012)	Uganda	Eight clinical trials and seven observational studies	600 men and women	Semistructured interviewer-administered questionnaires	Satisfaction with informed consent process measured on a visual analogue scale (0–10 arbitrary scores)	Study purpose, study procedures, discomfort/risk, potential benefit, confidentiality, compensation, voluntary participation
Chaisson *et al.* (2011)	Botswana	Isoniazid prevention therapy trial	1995 men and women	20-item true/false quiz administered at enrolment, 2 years after enrolment and at subsequent 6 month visits	Passing scores of ≥16 correct responses of 20 questions	Study purpose, study procedures, randomisation, placebo, adverse events, blinding, compensation, voluntariness, risks
Friedland *et al.* (2011b)	Swaziland	Male circumcision scale-up	953 men	10-item questionnaire prior to surgery; qualitative interviews 1 week post-surgery	Comprehension about key informed consent measured by percentage of correct answers to true/false question items	Study procedure, motivating factor for undergoing the procedure, decision-making, post-operative care and complication

(continued)

Table 2 (*Continued*)

Authors	Country	Type of clinical research	Sample size	Method of evaluation	Outcome measures	Domains of IC understanding targeted
Friedland *et al.* (2011a)	Zambia	Male circumcision scale-up	290 men	10-item questionnaire prior to surgery; qualitative interviews 1 week post-surgery	Comprehension about key informed consent measured by percentage of correct answers to true/false question items	Study procedure, motivating factor for undergoing the procedure, decision-making, post-operative care and complication
Hussein and Ahmed (2011)	Ethiopia	HIV voluntary and counselling testing for PMTCT	422 pregnant women	Pre- and post-test questionnaire adapted from UNAID tool	Comprehension about VCT and PTMCT by percentage of participants who reported understanding	Comprehension and satisfaction about VCT and PTMCT
Vallely *et al.* (2010)	Tanzania	Placebo controlled microbicide trial	1146 women had comprehension assessment through checklist, while a subsample of 99 women completed in-depth interviews	Comprehension checklist administered at screening, enrolment, 12-, 24-, 40- and 50-week follow-up visits during the trial. In-depth interviews conducted immediately with a semistructured standardised interview guide after 4-, 24- and 52-week follow-up visits	Comprehension and retention of key messages evaluated through participants' internalisation of the messages and how understanding was incorporated into their beliefs, perceptions, risks and hopes of effectiveness of the gel	Understanding of three key messages was examined: (i) therapeutic misconception, that is, the microbicide gel may not protect against HIV acquisition, (ii) that consistent condom use would prevent HIV infection; (iii) discontinuation of microbicide gel in the event of pregnancy
Taiwo and Kass (2009)	Nigeria	Oral health research	113 men and women	Qualitative and quantitative instruments	Understanding of key informed consent concepts measured by proportion of participants who gave correct responses	Involvement in research, benefits, contacts, confidentiality and voluntariness
Tekola *et al.* (2009)	Ethiopia	Pilot study to develop appropriate informed consent procedure	27 men and 19 women	Qualitative instrument: in-depth interview and focus group discussion	Community understanding of participation in research	Therapeutic misconception

(continued)

Table 2 (*Continued*)

Authors	Country	Type of clinical research	Sample size	Method of evaluation	Outcome measures	Domains of IC understanding targeted
Oduro *et al.* (2008)	Ghana	Paediatric trials evaluating immune correlates of protection against malaria	270 mothers	Semistructured questionnaire administered at the end of the study	Comprehension measured by percentage of correct scores to the question items	Understanding about study procedure, selection criteria, study risks/ benefits, rights of withdrawal, confidentiality
Hill *et al.* (2008)	Ghana	Vitamin A supplementation trial	1971 men and women	60 semistructured interviews and 12 FGDs after consent. Survey carried out to explore knowledge of treatment allocation	Participants' perception and knowledge of the trial evaluated by correct description of study purpose and whether they received active medication or placebo	Knowledge about study purpose and placebo used in the trial
Minnies *et al.* (2008)	South Africa	Paediatric case–control trial of immune correlates of childhood TB	192 mothers	9-item questionnaire on 'recall' and 8-item questionnaire on 'understanding' administered within 1 h of consent	'Recall' measured by success in selecting the correct answers in the question items on voluntary participation, confidentiality, risks/ benefits. 'Understanding' evaluated as correctness of interpretation of statements presented in the question items	Question items covered voluntary participation, confidentiality, risks and benefits
Manafa *et al.* (2007)	Nigeria	Antiretroviral trial	88 men and women	Questionnaire with structured and unstructured items	Understanding assessed by selecting correct responses to the question items	Study purpose, participants' eligibility, risks/benefits, rights of refusal, right of withdrawal
Marshall *et al.* (2006)	Nigeria	Genetic studies of hypertension	307 men and women	3-item survey questionnaire and in-depth interviews at variable time after consent	Understanding of study purpose and voluntary participation measured by participants' responses to question items in the survey questionnaire and responses by participants at in-depth interviews	Question items covered study purpose and voluntary participation

(continued)

Table 2 (*Continued*)

Authors	Country	Type of clinical research	Sample size	Method of evaluation	Outcome measures	Domains of IC understanding targeted
Moodley *et al.* (2005)	South Africa	Influenza vaccine trial	334 men and women	6-item semistructured questionnaire administered. 4–12 months post-trial. Separate questionnaires for treatment and placebo group	Understanding and perception measured by participants' correct responses to the question items	Therapeutic misconception, study purpose, voluntary participation, right to withdraw, randomisation, placebo and compensation
Pace *et al.* (2005)	Uganda	Paediatric malaria treatment study	347 parents	In-person interview immediately after consent. 60-item questionnaire covering six key domains of IC	Comprehension of study information measured by correct responses to question items	Study purpose, study risks, number of clinic visits, ways treatment were assigned, option of quitting the study
Molyneux *et al.* (2004)	Kenya	One field-based and two hospital-based studies involving blood sampling	30 patients admitted to paediatric ward and 1600 adults and children in the field	Semistructured interviews, informal interviews and structured observation of the consent process	Perceptions and understanding explored through participant responses	Reasons for collecting blood samples, therapeutic misconception, risks/benefits
Joubert *et al.* (2003)	South Africa	Vitamin A trial for prevention; of mother-to-child HIV transmission	92 women	Interviewer-administered structured questionnaire at a median of 14 months after consent	Knowledge and perceptions regarding the trial measured by proportions of participants who gave correct responses at the interview	Medications used in the trial, reasons for administering medications, duration of follow-up visits, perceptions about HIV counselling and trial participation
Leach *et al.* (1999)	The Gambia	Paediatric trial of *Haemophilus influenza* type B conjugate vaccine	137 mothers who gave consent and 52 mothers who declined consent	Semistructured interview conducted in local languages within a week of consent. Interview about recall took place 1 week of joining the study	Knowledge/understanding and motive for joining the study were evaluated by participants' responses at the interview	Study purpose, risks/benefit, placebo, motives for participation, people involved in decision-making were explored at the interviews

(continued)

Table 2 (*Continued*)

Authors	Country	Type of clinical research	Sample size	Method of evaluation	Outcome measures	Domains of IC understanding targeted
Abdool Karim *et al.* (1998)	South Africa	Perinatal HIV transmission trial	Evaluation group: 56 women; control group: 56 women	Questionnaire administered before and after HIV counselling and consent	Knowledge and voluntariness of participation were measured by participant responses to the question items	Perception about study purpose, implications of positive HIV test result, voluntary participation, rights of withdrawal
Studies in Francophone countries						
Ellis *et al.* (2010)	Mali	Phase I malaria vaccine trial	89 men and women; 700 parents	9-item questionnaire administered before consent	Understanding measured by percentage of correct responses to the question items	The questionnaire focused on study design, study procedures, risk, benefit, right of withdrawal, randomisation
Krosin *et al.* (2006)	Mali	Paediatric malaria vaccine trial	163 parents	9-item questionnaire administered within 48 h after consent	Comprehension and recall of key messages were measured by correct responses to the question items	Question items covered study purpose, voluntary participation, compensation, rights of withdrawal, randomisation, risks/ benefits
Ekouevi *et al.* (2004)	Cote d'Ivoire	Prevention of mother-to-child transmission trial	55 men and women	Interviewer-administered questionnaire at a median of 136 days after consent	Perception and understanding measured by proportions of participants who gave correct responses to the questionnaire	Rights of withdrawal, knowledge of informed consent process, for example receiving, understanding consent information
Coulibaly-Traore *et al.* (2003)	Cote d'Ivoire	Prevention of mother-to-child transmission of HIV	57 women	In-depth interviews and structured interviews	Percentages of women who showed understanding	Study purpose, randomisation, placebo, motivation for participation
Préziosi *et al.* (1997)	Senegal	Pertussis vaccine trial	2071 mothers	Group consensus meetings	Refusal rates before and after introduction of individual informed consent	Study rationale, blinding, adverse events
Study in a Lusophone country						
Ciampa *et al.* (2012)	Mozambique	Association of HIV knowledge with literacy and numeracy levels of rural women	3557 women	Validated measure of literacy and numeracy	Participants' scores assessed by correct responses to the validated test	Knowledge of HIV testing, prenatal care, PTMCT

Owing to differences in methods of outcome assessments (understanding scores or percentages of participants who demonstrated understanding), we generated the proportions of participants who had 'understanding' and 95% confidence intervals (95% CI) for each domain of informed consent. Random effects meta-analysis was used to pool the estimates of proportions across the studies because heterogeneity of study participants, study designs and assessment tools was envisaged. We estimated heterogeneity statistically using I squared statistics, which is the proportion of true heterogeneity that could be explained by chance (Higgins *et al.* 2003). Expectedly, I squared statistics revealed a substantial heterogeneity in all domains of informed consent assessed (I^2 = 98–99%, $P < 0.0001$). Tables 3 and 4 summarise the meta-analytic results. The meta-analysis was conducted using MedCalc statistical software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org, 2013).

Table 3 Meta-analytic results of studies examining comprehension of 'generic' domains of informed consent

Domain	Studies	Total sample size	Proportion (%)	95% CI
Compensation (n = 3)	Chaisson *et al.* (2011) Oduro *et al.* (2008) Krosin *et al.* (2006)	2428	76.2	39.0–98.5
Voluntariness (n = 8)	Chaisson *et al.* (2011) Oduro *et al.* (2008) Krosin *et al.* (2006) Taiwo *et al.* (2009) Kiguba *et al.* (2012) Moodley *et al.* (2005) Joubert *et al.* (2003) Abdool Karim *et al.* (1998)	3679	78.6	63.1–90.8
Right of withdrawal (n = 13)	Ekhuoevi *et al.* (2004) Oduro *et al.* (2008) Saidu *et al.* (2013) Krosin *et al.* (2006) Ellis *et al.* (2010) Abdool Karim *et al.* (1998) Manafa *et al.* (2007) Marshall *et al.* (2006) Minnies *et al.* (2008) Pace *et al.* (2005) Joubert *et al.* (2003) Friedland *et al.* (2011) Moodley *et al.* (2005)	4183	56.7	33.3–78.6
Right of refusal (n = 6)	Ekhuoevi *et al.* (2004) Manafa *et al.* (2007) Kiguba *et al.* (2012) Moodley *et al.* (2005) Minnies *et al.* (2008) Taiwo *et al.* (2009)	1382	48.6	25.6–71.9
Therapeutic misconception (n = 5)	Ekhuoevi *et al.* (2004) Krosin *et al.* (2006) Taiwo *et al.* (2009) Moodley *et al.* (2005) Manafa *et al.* (2007)	753	30.1	4.6–66.7
Confidentiality (n = 4)	Oduro *et al.* (2008) Minnies *et al.* (2008) Saidu *et al.* (2013) Taiwo *et al.* (2009)	1775	55.4	11.1–94.7

Table shows that about 80% of study participants across the studies understood compensation and voluntariness, while only 30% understood therapeutic misconception, 55% understood confidentiality and <60% understood right to withdraw.

Table 4 Meta-analytic results of studies examining comprehension of 'trial-specific' domains of informed consent

Domains	Studies	Total sample size	Proportion (%)	95% CI
Risks (n = 10)	Minnies *et al.* (2008) Abdool Karim *et al.* (1998) Oduro *et al.* (2008) Pace *et al.* (2005) Krosin *et al.* (2006) Vallely *et al.* (2010) Ellis *et al.* (2010) Taiwo and Kass (2009) Marshall *et al.* (2006) Ndebele *et al.* (2012)	3419	51.3	32.1–70.2
Benefits (n = 5)	Oduro *et al.* (2008) Taiwo and Kass (2009) Pace *et al.* (2005) Vallely *et al.* (2010) Friedland *et al.* (2011a,b)	2829	72.1	42.0–94.0
Placebo (n = 6)	Moodley *et al.* (2005) Vallely *et al.* (2010) Chaisson *et al.* (2011) Pace *et al.* (2005) Ndebele *et al.* (2012) Manafa *et al.* (2007)	3946	47.9	19.0–77.5
Blinding (n = 4)	Chaisson *et al.* (2011) Ndebele *et al.* (2012) Pace *et al.* (2005) Vallely *et al.* (2010)	3524	68.8	55.7–80.6
Randomisation (n = 4)	Ellis *et al.* (2010) Krosin *et al.* (2006) Moodley *et al.* (2005) Pace *et al.* (2005)	1633	46.6	13.9–80.9
Study purpose (n = 17)	Saidu *et al.* (2013) Minnies *et al.* (2008) Abdool Karim *et al.* (1998) Pace *et al.* (2005) Marshall *et al.* (2006) Taiwo and Kass (2009) Krosin *et al.* (2006) Joubert *et al.* (2003) Ekouevi *et al.* (2004) Ndebele *et al.* (2012) Friedland *et al.* (2011a) Friedland *et al.* (2011b) Ellis *et al.* (2010) Manafa *et al.* (2007) Chaisson *et al.* (2011) Hussein and Ahmed (2011) Oria *et al.* (2013)	12 382	64.8	34.9–89.4

(continued)

Table 4 (*Continued*)

Domains	Studies	Total sample size	Proportion (%)	95% CI
Study procedure (n = 13)	Chaisson *et al.* (2011) Saidu *et al.* (2013) Oduro *et al.* (2008) Ellis *et al.* (2010) Manafa *et al.* (2007) Taiwo and Kass (2009) Kiguba *et al.* (2012) Pace *et al.* (2005) Friedland *et al.* (2011a) Friedland *et al.* (2011b) Abdool Karim *et al.* (1998) Minnies *et al.* (2008) Joubert *et al.* (2003)	6985	72.9	55.2–87.4

Table shows that about 50% of participants across various studies understood placebo, randomisation and risks, while higher proportions (about 70%) understood benefits, blinding and study procedure.

Results

Study characteristics and design

Twenty-nine studies conducted in 20 countries from SSA examined participants' comprehension of informed consent information in clinical research on vaccines, tuberculosis treatment in HIV-infected patients, HIV prevention trials, male circumcision scale-up, oral health, vitamin A supplementation, immune correlates in paediatric age group and genetic studies of hypertension (Table 2). The number of study participants in the studies ranged from 36 to 5755. Of the studies, 17 interviewed participants close to the time of consent (Abdool Karim *et al.* 1998; Leach *et al.* 1999; Coulibaly-Traore *et al.* 2003; Pace *et al.* 2005; Fairhead *et al.*, 2006a,b; Krosin *et al.* 2006; Hill *et al.* 2008; Minnies *et al.* 2008; Taiwo & Kass 2009; Tekola *et al.* 2009; Ellis *et al.* 2010; Hussein & Ahmed 2011; Ciampa *et al.* 2012; Kiguba *et al.* 2012; Vreeman *et al.* 2012; Saidu *et al.* 2013); interviews were conducted 1–14 months after participants gave consent in six studies (Joubert *et al.* 2003; Ekouevi *et al.* 2004; Moodley *et al.* 2005; Hill *et al.* 2008; Vallely *et al.* 2010; Ndebele *et al.* 2012) and longer than 14 months in two studies (Oduro *et al.* 2008; Chaisson *et al.* 2011); pre- and post-assessments were carried out in two studies (Préziosi *et al.* 1997; Oria *et al.* 2013), while baseline and repeated assessments of understanding were carried out in another two studies (Vallely *et al.* 2007; Chaisson *et al.* 2011). Six studies interviewed the mothers of study children (Préziosi *et al.* 1997; Leach *et al.* 1999; Minnies *et al.* 2008; Oduro *et al.* 2008; Oria *et al.* 2013; Saidu *et al.* 2013); nine studies interviewed adult male and female participants (Joubert *et al.* 2003; Ekouevi *et al.* 2004; Moodley *et al.* 2005; Marshall *et al.* 2006; Hill *et al.* 2008; Tekola *et al.* 2009; Vallely *et al.* 2010; Friedland *et al.*, 2011a,b), seven interviewed only female participants (Abdool Karim *et al.* 1998; Coulibaly-Traore *et al.* 2003; Joubert *et al.* 2003; Vallely *et al.* 2010; Hussein & Ahmed 2011; Ciampa *et al.* 2012; Ndebele *et al.* 2012), two interviewed only male participants (Friedland *et al.*, 2011a,b) and five studies interviewed both parents and adult participants (Molyneux *et al.* 2004; Pace *et al.* 2005; Krosin *et al.* 2006; Ellis *et al.* 2010; Vreeman *et al.* 2012).

Measurement tools

Sixteen studies used questionnaires to assess participants' comprehension (Abdool Karim *et al.* 1998; Joubert *et al.* 2003; Ekouevi *et al.* 2004; Moodley *et al.* 2005; Krosin *et al.* 2006; Manafa *et al.* 2007; Minnies *et al.* 2008; Oduro *et al.* 2008; Ellis *et al.* 2010; Chaisson *et al.* 2011; Hussein & Ahmed 2011; Ciampa *et al.* 2012; Kiguba *et al.* 2012; Ndebele *et al.* 2012; Oria *et al.* 2013; Saidu *et al.* 2013); six employed in-depth qualitative interviews (Leach *et al.* 1999; Coulibaly-Traore *et al.* 2003; Molyneux *et al.* 2004; Pace *et al.* 2005; Hill *et al.* 2008; Tekola *et al.* 2009) and five used both qualitative and quantitative methods (Marshall *et al.* 2006; Taiwo & Kass 2009; Vallely *et al.* 2010; Friedland *et al.*, 2011a,b) and two used community group discussions

(Préziosi *et al.* 1997; Vreeman *et al.* 2012). The majority of the questionnaires used closed-ended response formats. The questionnaires varied significantly in the number of items, and the domains addressed by these items. The authors indicated the number of question items in eight studies (Moodley *et al.* 2005; Krosin *et al.* 2006; Marshall *et al.* 2006; Minnies *et al.* 2008; Ellis *et al.* 2010; Chaisson *et al.* 2011; Friedland *et al.*, 2011a,b); the number ranged from 3- to 20-item quiz. The items in the questionnaire could be classified into two broad domains: generic and trial-specific questions (Joffe *et al.* 2001). The generic questions focused on general aspects of research such as confidentiality, compensation, rights of withdrawal or refusal (Table 3), while the trial-specific questions focused on individual research-related domains such as study purpose, study rationale, study procedures, medications, risks and adverse events (Table 4). A complete questionnaire was included in the appendix in three papers (Krosin *et al.* 2006; Minnies *et al.* 2008; Ellis *et al.* 2010). Participants were assessed on several domains of informed consent, while two studies (Tekola *et al.* 2009; Vallely *et al.* 2010) focused only on participants' understanding of therapeutic misconception. The format adopted in the semistructured or in-depth interviews was not clearly discussed in most of the papers except one study (Vallely *et al.* 2010) which used a standardised interview guide.

Development of measurement tools

Only four manuscripts (Krosin *et al.* 2006; Vallely *et al.* 2010; Ciampa *et al.* 2012; Ndebele *et al.* 2012) provided an account of how the measurement instrument was developed. One study (Taiwo & Kass 2009) mentioned that the questionnaire was adapted from previously developed questionnaires such as the Quality Questionnaire of Informed Consent and the Deaconess Informed Consent Questionnaire. Another study (Ciampa *et al.* 2012) adapted and validated its questionnaire from the Wide Range Achievement Test. Ten reported that they translated and back-translated the questionnaires from foreign languages to participants' local languages (Joubert *et al.* 2003; Moodley *et al.* 2005; Pace *et al.* 2005; Krosin *et al.* 2006; Marshall *et al.* 2006; Oduro *et al.* 2008; Chaisson *et al.* 2011; Ciampa *et al.* 2012; Kiguba *et al.* 2012; Ndebele *et al.* 2012). Significant linguistic diversity made it costly and logistically challenging to translate informed consent documents from English, French or Portuguese into effective written versions of several local languages of participants in each country (Préziosi *et al.* 1997; Tekola *et al.* 2009; Chaisson *et al.* 2011; Ciampa *et al.* 2012; Ndebele *et al.* 2012).

In three studies, participants' comprehension was measured by the proportion of correct responses to the question items (Krosin *et al.* 2006; Oduro *et al.* 2008; Ellis *et al.* 2010), while other studies assessed proportions of participants who gave correct responses to questionnaires and interviews (Joubert *et al.* 2003; Ekouevi *et al.* 2004; Moodley *et al.* 2005; Marshall *et al.* 2006). Additionally, terms such as 'understanding', 'comprehension', 'knowledge', 'remembering', 'retention', 'recall, 'awareness' or 'recognition' were used interchangeably without clear definitions. Only one study (Minnies *et al.* 2008) defined the outcome variables: recall as 'success in selecting the correct answers in the question items' and understanding as 'correctness of interpretation of statements presented in the question items'. There was also no consensus on the time points to measure comprehension as participants (Pace *et al.* 2005; Krosin *et al.* 2006; Marshall *et al.* 2006; Sand *et al.* 2010; Friedland *et al.*, 2011a,b) were evaluated at different times.

Comprehension of informed consent information

This section focuses on the meta-analytic results on 21 studies (Abdool Karim *et al.* 1998; Joubert *et al.* 2003; Ekouevi *et al.* 2004; Moodley *et al.* 2005; Pace *et al.* 2005; Krosin *et al.* 2006; Marshall *et al.* 2006; Manafa *et al.* 2007; Minnies *et al.* 2008; Oduro *et al.* 2008; fTaiwo & Kass 2009; Ellis *et al.* 2010; Vallely *et al.* 2010; Chaisson *et al.* 2011; Friedland *et al.*, 2011a,b; Hussein & Ahmed 2011; Kiguba *et al.* 2012; Ndebele *et al.* 2012; Oria *et al.* 2013; Saidu *et al.* 2013) and complementary narrative comparison of all eligible studies.

Study purpose. Meta-analytic results showed that 65% of a total of 12 382 participants in 17 studies (Abdool Karim *et al.* 1998; Joubert *et al.* 2003; Ekouevi *et al.* 2004; Pace *et al.* 2005; Krosin *et al.* 2006; Marshall *et al.* 2006; Manafa *et al.* 2007; Minnies *et al.* 2008; Taiwo & Kass 2009; Ellis *et al.* 2010; Chaisson *et al.* 2011; Friedland *et al.*, 2011a,b; Hussein & Ahmed 2011; Ndebele *et al.* 2012; Oria *et al.* 2013; Saidu *et al.* 2013) understood the purpose of the studies they were involved in (95% CI 34.9–89.4%). Furthermore, on descriptive comparison, comprehension of study purpose assessed in 18 studies (Préziosi *et al.* 1997; Abdool Karim *et al.* 1998; Leach *et al.* 1999; Coulibaly-Traore *et al.* 2003; Joubert *et al.* 2003; Ekouevi *et al.* 2004; Molyneux *et al.* 2004; Moodley *et al.* 2005; Pace *et al.* 2005; Krosin *et al.* 2006; Marshall *et al.* 2006; Manafa *et al.* 2007; Hill *et al.* 2008; Taiwo & Kass 2009; Chaisson *et al.* 2011; Ciampa *et al.* 2012; Kiguba *et al.* 2012; Saidu *et al.* 2013) was markedly high among participants in southern Africa (Minnies *et al.* 2008;

Chaisson *et al.* 2011; Friedland *et al.*, 2011a,b). This ranged from 88% to 98.7%, while East and West African participants had comprehension rates between 8% and 47% (Joubert *et al.* 2003; Molyneux *et al.* 2004; Taiwo & Kass 2009; Kiguba *et al.* 2012). Most participants in countries with poorer comprehension had a low level of education. Endemicity of the conditions studies also explained the disparities in the observed responses. For instance, there were marked differences in comprehension of the causes, routes of transmission and prevention of HIV by pregnant women in Cote d'Ivoire and South Africa, with most participants in Cote d'Ivoire demonstrating poor understanding of the study rationale (Coulibaly-Traore *et al.* 2003; Ekouevi *et al.* 2004). Similarly, poor comprehension was observed in participants enrolled in an oral health study in Nigeria (Taiwo & Kass 2009).

Voluntary participation. About 80% of 3679 participants across eight studies (Abdool Karim *et al.* 1998; Joubert *et al.* 2003; Moodley *et al.* 2005; Krosin *et al.* 2006; Oduro *et al.* 2008; Taiwo & Kass 2009; Chaisson *et al.* 2011; Kiguba *et al.* 2012) demonstrated comprehension about voluntariness towards participation (95% CI 39.0–98.5%), with perceived medical benefit cited as a main determinant (Leach *et al.* 1999; Pace *et al.* 2005; Oduro *et al.* 2008). Inadequate access to health care and other poor socio-economic factors in developing countries were reported as strong motives for joining clinical trials (Préziosi *et al.* 1997; Leach *et al.* 1999). Severity of diseases also contributes to the sense of compulsion to participate. In a Kenyan study, only 4% of mothers of seriously ill children agreed that participation was voluntary, while most participants believed that they would have been chased away if they refused to join the study (Molyneux *et al.* 2004). In contrast, 97% of mothers whose children were less seriously sick in the same study reported voluntary participation during admission; 14% spontaneously reported this on discharge and 59% after prompting (Molyneux *et al.* 2004).

Right of withdrawal. Of 4183 participants across 13 studies (Abdool Karim *et al.* 1998; Joubert *et al.* 2003; Ekouevi *et al.* 2004; Moodley *et al.* 2005; Pace *et al.* 2005; Krosin *et al.* 2006; Marshall *et al.* 2006; Manafa *et al.* 2007; Minnies *et al.* 2008; Oduro *et al.* 2008; Ellis *et al.* 2010; Friedland *et al.*, 2011a; Saidu *et al.* 2013), 57% understood right of withdrawal (95% CI 33.3–78.6%). Further descriptive comparison of findings in seven studies (Abdool Karim *et al.* 1998; Ekouevi *et al.* 2004; Pace *et al.* 2005; Krosin *et al.* 2006; Manafa *et al.* 2007; Oduro *et al.* 2008; Ellis *et al.* 2010) showed that understanding of the right to withdraw from a study was low among most study participants across West African subregion. In a Malian trial (Krosin *et al.* 2006), participants believed that leaving before the end of the study would be disrespectful to the investigators who might consequently deny them medical benefits associated with participation. Their counterparts from a South African (Abdool Karim *et al.* 1998) study showed better comprehension of their rights to stop participation. Similar trends were observed for rights of refusal to participate. Taiwo and Kass (2009) reported that social status in the study community might positively influence a participant to enrol in a study. One example was cited of a highly educated community officer who enrolled in a trial so as not to discourage other community members from joining the trial. Participants in a Gambian study (Leach *et al.* 1999) also expressed the fear of serious, unknown side effects of an experimental vaccine as a major reason for declining to enrol in the study.

Confidentiality. Meta-analytic results showed that 55% of a total of 1775 participants in four studies (Minnies *et al.* 2008; Oduro *et al.* 2008; Taiwo & Kass 2009; Saidu *et al.* 2013) did not understand the concept of confidentiality. However, descriptive comparison showed a high level of comprehension in two studies (Minnies *et al.* 2008; Saidu *et al.* 2013), but in other two studies (Taiwo & Kass 2009; Kiguba *et al.* 2012), participants were not aware of how their research records would be kept.

Compensation. Across three studies (Krosin *et al.* 2006; Oduro *et al.* 2008; Chaisson *et al.* 2011) involving 2428 participants, 76% understood compensation (95% CI 39.0–98.5%). Understanding of compensation associated with participation was largely dependent on how the questions were framed and presented to the participants, who generally considered personal benefit a high priority. Participants in two studies (Oduro *et al.* 2008; Chaisson *et al.* 2011) misunderstood reimbursement of transport fares as payment for study participation.

Risks. About 51% of 3419 participants understood risks involved in study participation (95% CI = 32.1–70.2%) in 10 studies (Leach *et al.* 1999; Molyneux *et al.* 2004; Pace *et al.* 2005; Krosin *et al.* 2006; Manafa *et al.* 2007; Minnies *et al.* 2008; Taiwo & Kass 2009; Ellis *et al.* 2010; Chaisson *et al.* 2011; Kiguba *et al.* 2012). This was found to be better among participants from southern Africa (Minnies *et al.* 2008; Chaisson *et al.* 2011) than among participants in West African studies (Krosin *et al.* 2006; Taiwo & Kass 2009).

Therapeutic misconception. Only 30% of 753 participants across five studies (Ekouevi *et al.* 2004; Moodley *et al.* 2005; Krosin *et al.* 2006; Manafa *et al.* 2007; Tai-

wo & Kass 2009) understood the concept of therapeutic misconception. This occurs when participants believe that the study is solely aimed at providing health care rather than generating research data. It featured prominently among West African participants (Ekouevi *et al.* 2004; Krosin *et al.* 2006; Manafa *et al.* 2007; Taiwo & Kass 2009), while a South African study (Moodley *et al.* 2005) reported that a significant proportion of participants recognised they were participating in a research as opposed to seeking medical care.

Randomisation and placebo. Of 1633 participants in four studies (Moodley *et al.* 2005; Pace *et al.* 2005; Krosin *et al.* 2006; Ellis *et al.* 2010), 47% demonstrated understanding about randomisation (95% CI = 13.9–80.9%). Similarly, 48% of 3946 participants in six studies (Moodley *et al.* 2005; Pace *et al.* 2005; Manafa *et al.* 2007; Vallely *et al.* 2010; Chaisson *et al.* 2011; Ndebele *et al.* 2012) had understanding of placebo (95% CI 0.19.0–77.5%). Descriptive comparison showed that methods employed in explaining the concepts of randomisation and use of placebo during informed consent process influenced participants' understanding. Malawian participants (Ndebele *et al.* 2012) demonstrated good understanding of randomisation when a locally designed narrative was used to illustrate the research terms. About 75–78% of these participants comprehended randomisation and placebo, while 10–19% of East and West African participants demonstrated good understanding of the concepts (Leach *et al.* 1999; Pace *et al.* 2005; Hill *et al.* 2008).

Autonomy/decision-making. Seven studies (Leach *et al.* 1999; Coulibaly-Traore *et al.* 2003; Ekouevi *et al.* 2004; Molyneux *et al.* 2004; Krosin *et al.* 2006; Friedland *et al.*, 2011a,b) assessed this concept. Ninety-nine percentage of Gambian participants (Leach *et al.* 1999) submitted that parents and village leaders were involved in decision-making. Similar patterns were reported in East and other West African studies (Ekouevi *et al.* 2004; Molyneux *et al.* 2004; Krosin *et al.* 2006), while individual decision-making was common in southern African countries (Friedland *et al.*, 2011a,b).

Predictors of comprehension. In most studies reviewed (Oduro *et al.* 2008; Taiwo & Kass 2009; Chaisson *et al.* 2011; Kiguba *et al.* 2012; Ndebele *et al.* 2012), demographic variables like age and literacy did not show statistical significance, but male sex was reported as the only independent predictor of higher comprehension scores in one study (Ellis *et al.* 2010). Conversely, primary education and residence in urban areas were predictors of understanding among women (Hill *et al.* 2008). Similarly, another study (Krosin *et al.* 2006) reported higher comprehension scores in most urban participants than their rural counterparts. Among Mozambican participants, numeracy level was significantly associated with comprehension of study purpose and this was independent of respondent's age, income, distance from the hospital and the language of survey administration (Ciampa *et al.* 2012). Moodley *et al.* (2005) also reported a positive linear correlation between participants' comprehension scores and their mini-mental state examination scores.

Discussion

To our knowledge, this is the first comparison of participants' comprehension of informed consent information in studies conducted across SSA. Previous reviews have either concentrated on informed consent comprehension in developed countries (Sand *et al.* 2010) or compared the quality of informed consent between Western and developing countries in Africa and Asia (Mandava *et al.* 2012).

Our review reveals that the methods used for assessing participants' comprehension differed significantly. Such variations in methodology limited comparison of findings and raise challenges about how to measure comprehension of informed consent information. Very few studies (Ciampa *et al.* 2012; Ndebele *et al.* 2012) described the format and justifications for deciding to use a set of question items. A sizeable proportion of the tools were developed ad hoc for each study without following standard guidelines of instrument development and validation.

We also identified a lack of a uniform definition of comprehension as studies in the review used the term 'comprehension' to mean 'understanding' or 'recall' or 'retention' or 'knowledge'. It is important to establish a distinction between these terms as it would help in developing a uniform definition for the concept. This effort is capable of providing an acceptable method for determining how an instrument can be constructed, implemented, interpreted and applied to measure the concept (Spreitzer & Sonenshein 2004).

The domains of informed consent assessed by the studies also vary considerably with little regard to the crucial information that could engender comprehension. There is a need to develop guidelines that define the most crucial information relevant for comprehension of informed consent in African research settings as well as the best way this information should be communicated.

Most study participants in this review did not understand the distinction between research participation and seeking medical care. This concept of therapeutic misconception has been documented among participants in resource poor settings where inadequate access to health

care exists (Appelbaum *et al.* 1982; Préziosi *et al.* 1997). This is due to a mix of heavy burden of disease, poor access to health care, poor education, low literacy levels and the overriding impact of illness, suffering and poverty on decision-making. A National Bioethics Advisory Commission reported that therapeutic misconception does not imply that participants will most likely get adequate clinical care during research, but subsists when participants believe that the sole aim of clinical trials is to provide treatment rather than collect data (NBAC 2001). Consequently, African researchers should strive to harmonise the research of essential medicines with the ethical requirements of making them accessible. Improved access to such care could reduce vulnerability and ultimately improve comprehension of African participants.

The time interval between informed consent process and assessment of comprehension in most of the studies was long, some more than 14 months after the trials have ended. Given the background of low literacy among participants, and not being familiar with research terms, it is very unlikely that reliable inferences can be drawn from assessments carried out after such long periods. There are no existing guidelines on the timing of such assessments as these are likely to be study or context specific.

Availability of the questionnaires in local languages was reported to aid participants' understanding in few countries (Chaisson *et al.* 2011; Ndebele *et al.* 2012). However, this is not always possible as some African languages are spoken and do not have standardised writing formats. Translations and back-translation of informed consent documents are practically challenging in the Gambia for this reason.

A major strength of this review is the combination of meta-analytic results with the narrative comparison of the findings. This provided a robust summary of the findings on informed consent comprehension despite significant disparities in methodologies and heterogeneity of the data. Further contributing to this, we excluded participants in hypothetical studies so that our findings could reflect true clinical research situations as much as possible. We also included studies where participants were legally and cognitively competent, to remove factors which might confound our findings.

Limitations

Very few of the studies included in this review provided adequate information on the instruments employed to assess comprehension of informed consent. This did not permit analysis of wordings of the questionnaires to establish what the authors actually explored in their studies. Such analysis could have provided useful insights that might have contributed to appropriate interpretations of findings of the studies.

Also, findings of this review need to be cautiously interpreted because majority of the quantitative instruments used in this review contained closed-ended questionnaires, which are known to be an imperfect method of assessing comprehension, because respondents could guess answers correctly or provide socially desirable responses. This could have over-estimated the comprehension levels, thereby leading to inaccuracies in our findings. Studies (OnvomahaTindana *et al.* 2006; Ndebele *et al.* 2012) have shown that requesting participants to explain, using their own words, their comprehension of study information may truly manifest what participants understand.

It could also be inferred that studies in this review examined the 'performance' of participants, but apparently did not evaluate the communication skills of the researchers administering the consent; and this plays a key role for comprehension. This may represent an asymmetry, where researchers ask 'why participants do not comprehend' but we do not ask ourselves 'why are we not good at explaining crucial information to our participants?'

Nevertheless, the representativeness of studies in this review provides a comprehensive knowledge base for setting research agenda and plans.

Conclusions

Our review confirmed the findings of previous reviews that comprehension of informed consent in Africa settings varies from country to country with relatively better comprehension among participants in southern Africa. Tools for measuring participants' comprehension are neither validated nor standardised. To overcome potential pitfalls in effectiveness of conventional informed consent procedures in African research settings, it is crucial to engage a body of knowledge on the development of clear guidelines to design adequate tools for improving informed consent comprehension and maximise the voluntariness of the choice to participate in clinical trials. Such tools should translate the respect for fundamental ethical principles, by taking into considerations local cultural values and constraints.

Furthermore, due to wide linguistic variability that made effective translations of informed consent documents to local languages challenging, appropriately developed tools using orally interpreted procedure with non-verbal support like video and animations may improve the comprehensibility of unfamiliar research concepts among African participants. Experts who are familiar with the local context and influence of communication and

demographic factors on informed consent process need to be involved in the design. This multidisciplinary approach should harmonise local contextual and behavioural factors, including the expectations of the community, in developing comprehensible consent tools.

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Digitised audio questionnaire for assessment of informed consent comprehension in a low-literacy African research population: development and psychometric evaluation

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ABSTRACT

Objective: To develop and psychometrically evaluate an audio digitised tool for assessment of comprehension of informed consent among low-literacy Gambian research participants.

Setting: We conducted this study in the Gambia where a high illiteracy rate and absence of standardised writing formats of local languages pose major challenges for research participants to comprehend consent information. We developed a 34-item questionnaire to assess participants' comprehension of key elements of informed consent. The questionnaire was face validated and content validated by experienced researchers. To bypass the challenge of a lack of standardised writing formats, we audiorecorded the questionnaire in three major Gambian languages: Mandinka, Wolof and Fula. The questionnaire was further developed into an audio computer-assisted interview format.

Participants: The digitised questionnaire was administered to 250 participants enrolled in two clinical trials in the urban and rural areas of the Gambia. One week after first administration, the questionnaire was readministered to half of the participants who were randomly selected. Participants were eligible if enrolled in the parent trials and could speak any of the three major Gambian languages.

Outcome measure: The primary outcome measure was reliability and validity of the questionnaire.

Results: Item reduction by factor analysis showed that 21 of the question items have strong factor loadings. These were retained along with five other items which were fundamental components of informed consent. The 26-item questionnaire has high internal consistency with a Cronbach's α of 0.73–0.79 and an intraclass correlation coefficient of 0.94 (95% CI 0.923 to 0.954). Hypotheses testing also showed that the questionnaire has a positive correlation with a similar questionnaire and discriminates between participants with and without education.

Conclusions: We have developed a reliable and valid measure of comprehension of informed consent information for the Gambian context, which might be easily adapted to similar settings. This is a major step towards engendering comprehension of informed consent information among low-literacy participants.

Strengths and limitations of this study

- Our study demonstrates that a locally appropriate informed consent tool can be developed and scientifically tested to ensure an objective assessment of comprehension of informed consent information among low and non-literate research participants.
- This is capable of minimizing participants' vulnerability and ultimately engenders genuine informed consent.
- Our findings are based on data collected from specific research context in a small country with three major local languages. Further research is needed to validate this tool in other settings.

INTRODUCTION

Conduct of clinical trials in developing countries faces considerable ethical challenges.[1 2] One of these constraints includes ensuring that informed consent is provided in a comprehensible manner that allows potential participants to freely decide whether or not they are willing to enrol in the study. According to the Helsinki Declaration[3] and other internationally agreed guidelines,[4 5] special attention should be given to the specific information needs of potential participants and to the methods used to deliver the information. This implies, among other things, that the information must be provided in the participant's native language. If

the informed consent documents have been originally written in one of the major international languages, they must be translated to the local languages of potential study participants.[6 7] The translated documents are subsequently back-translated by another independent group to the initial language to confirm that the original meaning of the contents of the document is retained.

In sub-Saharan Africa, this process may become extremely challenging because many research concepts such as randomisation and placebo do not have direct interpretations in the local languages.[8] Furthermore, in some African countries, local languages exist only in oral forms and they do not have standardised writing formats, which makes written translation and back-translations of informed consent documents not only impractical, but also less precise.[9] Further adding to these difficulties are the high rates of illiteracy and functional illiteracy in such contexts, which may contribute to the socioeconomical vulnerability of these research populations.[10]

Nevertheless, it remains crucial to ensure an understanding of vulnerable participants about study information because the voluntary nature of informed consent could be easily jeopardised by cultural diversity, an incorrect understanding of the concept of diseases, a mix of communal and individual decision-making, huge social implications of some infectious diseases and inadequate access to care.[11] Use of an experiential model at the pre-enrolment, enrolment and postenrolment stages of clinical research[11] as well as tailoring of cultural and linguistic requirements to the informed consent process has been reported to improve comprehension of basic research concepts.[12]

Furthermore, international guidelines[3–5] emphasise that informed consent must be based on a full understanding of the information conveyed during the consent interview. In contexts characterised by high linguistic variability and illiteracy rates, the use of tools to ascertain comprehension of study information conveyed during the informed consent process may be recommended. These tools could vary from a study quiz to complex questionnaires.[13 14] Tools that have been used extensively to assess informed consent comprehension include Brief Informed Consent Evaluation Protocol (BICEP),[15] Deaconess Informed Consent Comprehension Test (DICCT)[16] and the Quality of Informed Consent test (QuIC).[17] These tools were limited in usability across other studies because they were developed for specific trials. In addition, because they were designed for the developed world, they are not easily adaptable to African research settings. To the best of our knowledge, there is no published article to support the availability of an appropriate measure of informed consent comprehension in African research settings. To comply with the ethical principle of respect for persons,[4] a systematically developed tool could contribute to achieving an adequate measurement of comprehension of study information among the vulnerable research population in Africa. This is consistent with a framework incorporating aspects that reflect the realities of participants' social and cultural contexts.[11]

This study was designed to develop and psychometrically evaluate an informed consent comprehension questionnaire for a low-literacy research population in the Gambia, for whom English is not the native language. This is the first step towards contextualising strategies of delivering study information to research participants; objectively measuring their comprehension of the information using a validated tool and, based on this, improving the way information is delivered during informed consent process.

DISEASE PROFILE IN THE GAMBIA AND RESEARCH ACTIVITIES OF THE MEDICAL RESEARCH COUNCIL UNIT, THE GAMBIA

The Gambia is one of the smallest West African countries with an estimated population of 1.79 million people.[18] According to the 2012 World Bank report, Gambia's total adult literacy rate was 45.3% while the adult literacy rate of the female population, which constitutes a large majority of clinical trial participants, was 34.3%.[19]

Three major ethnolinguistically distinct groups, Mandinka, Fula and Wolof, populate the country. The languages do not have standardised writing formats and they are not formally taught in schools. The ethnic groups have similar sociocultural institutions such as the extended family system and patrilineal inheritance. Health-seeking behaviour is governed by traditions rather than modern healthcare norm. Because the people live in a closely knit, extended family system, important decisions like research participation is taken within the kinship structure.[20]

Like other low-income countries characterised by social and medical disadvantages,[21] infectious diseases such as malaria, pneumonia and diarrhoea constitute major reasons for hospital presentations in the Gambia.[22] In addition to the high disease burden, low literacy, a high poverty rate and inadequate access to healthcare tend to make the people vulnerable to research exploitation.[21]

The Medical Research Council (MRC) Unit in the Gambia was established to conduct biomedical and translational research into tropical infectious diseases. The institute has key northern and southern linkages and a track record of achievements spanning over 67 years. The research portfolio of MRC covers basic scientific research, large epidemiological studies and vaccine trials. Important recent and current vaccine trials include those on malaria, tuberculosis, HIV, *Haemophilus influenzae* type B, measles, pneumococcal and the Gambia Hepatitis Intervention study. Preventive research interventions include intermittent preventive treatment with sulfadoxine-pyrimethamine versus intermittent screening and treatment of malaria in pregnancy, a cluster randomised controlled trial on indoor residual spraying plus long-lasting insecticide impregnated nets. Ethical conduct of these studies takes place through

sustained community involvement and engagement of participants as research partners.[20]

METHODS

Study design

Questionnaire development

The items on the questionnaire were generated from the basic elements of informed consent obtained from an extensive literature search on guidelines for contextual development of informed consent tools,[23–32] international ethical guidelines[3–5] and operational guidelines from the Gambia Government/Medical Research Council Joint Ethics Committee.[33]

We identified and generated a set of question items on 15 independent domains of informed consent. These domains are voluntary participation, rights of withdrawal, study knowledge, study procedures, study purpose, blinding, confidentiality, compensation, randomisation, autonomy, meaning of giving consent, benefits, risks/adverse effects, therapeutic misconception and placebo.

Because evidence has shown the deficiencies of using one question format in assessing comprehension of informed consent information,[30] we developed a total of 34 question items under three different response formats. These response options are a combination of Yes/No/I don't know, multiple choice and open ended with free text response options. The inclusion of the 'I don't know' option was meant to avoid restricting participants to only two options of 'yes or no', which is capable of inducing socially desirable responses and also helps to reduce guesswork.

The questionnaire was made up of five sections: the first section contains 10 closed ended and 7 follow-up question items; the second section has 6 single choice response items; the third section has 4 multiple choice response items; the fourth section has 7 free-text open-ended question items. The last section has 9 questions on sociodemographic information of participants and these were not included in the psychometric analysis of the questionnaire.

The follow-up question items were included in the first section to ensure that the responses given by participants truly reflected their understanding as asked in the closed-ended questions, for example, "*Have you been told how long the study will last?*" was followed by "*If yes, how many months will you be in this study?*". No response options were given and the participants were expected to give the study duration based on their understanding of information given during the informed consent process. The order of responses to the questions was reversed for some items to avoid participants defaulting to the same answer for each question.

The use of multiple choice and open-ended response items was meant to explore participants' 'actual' understanding of study information, because this could not be adequately measured using the closed-ended response options.

To enable non-literate participants understand how to answer questions under multiple and open-ended response options, we included locally appropriate sample question items before the main questions. For example, *'Domoda' soup is made from: a. Bread, b. Groundnut, c. Yam, d. Orange*. Groundnut is the correct response and participants were directed to choose only one correct response in the question items that followed the sample question. For items with multiple response options, we included: "*Which of these are Gambian names for a male child: a. Fatou, b. Lamin, c. Ebrima, d. Isatou*." The correct responses are Lamin and Ebrima; participants were directed to choose more than one correct response that applies to the question items.

As the questionnaire was intended to be used across different clinical trials, we developed question items that aimed to be applicable to most clinical trials and yet specific to individual trials. This was achieved with the inclusion of open-ended question items in which participants could give trial-specific responses. An example of this was: "*What are the possible unwanted effects of taking part in this study?*" which allowed participants to explain in his/her words the adverse events peculiar to the clinical trials in which he/she is participating.

Face and content validity

Face validity was performed to assess the appearance of the questionnaire regarding its readability, clarity of words used, consistency of style and likelihood of target participants being able to answer the questions. Content validity was performed to establish whether the content of the questionnaire was appropriate and relevant to the context for which it was developed.[34] After generating the question items, we requested five researchers: two from the London School of Hygiene and Tropical Medicine UK (LSHTM) and three from MRC, the Gambia, who are experienced in clinical trials methodology, bioethics and social science methods to review the English version of the questionnaire for face and content validity. All of them agreed that essential elements of informed consent information were addressed in the questionnaire, and that the items adequately covered the essential domains of informed consent, with special attention to those whose understanding may be especially challenged in African research settings. They also supported the use of multiple response options as being capable of eliciting appropriate responses that might reflect a true 'understanding' of participants. One of the reviewers recommended presenting the item in the form of a question instead of a statement, for example, "*I have been told that I can freely decide to take part in this study*" was changed to "*Have you been told you can freely decide to take part in this study?*". The response option was also changed from True/False to Yes/No.

We further gave the revised English version of the questionnaire to three experienced field assistants at MRC and three randomly chosen laypersons to assess the clarity and appropriateness of the revised question items and their response options. The laypersons were

selected randomly from a list of impartial witnesses by choosing one person each from three ethnolinguistic groups in the Gambia. They independently agreed that the questions were clear, except for three items addressing confidentiality, compensation and the right to withdraw. On the basis of these feedbacks, we reworded the question items to improve clarity. The question on confidentiality was reframed from "Will non-MRC workers have access to your health information?" to "Will anyone not working with MRC know about your research information?". Similarly, "Will you be rewarded for taking part in this study?" was changed to "Will you receive money for taking part in this study?".

Audiorecording in three local languages and development into a digitised format

Owing to the lack of acceptable systems of writing Gambian local languages, the question items were audiorecorded in three major Gambian languages, Mandinka, Wolof and Fula, by experienced linguistic professionals who are native speakers of the local languages and are also familiar with clinical research concepts. Audio backtranslations were made for each language by three independent native speakers and corrections were made in areas where translated versions were not consistent with the English version. A final audio proof was conducted by three clinical researchers (native speakers) who independently confirmed that the translated versions retained the original meaning of the English version.

The revised questionnaire was developed into an audio computer-assisted interview format at the School of Medicine, Tufts University, Boston, USA. In conjunction with the MRC community relations officer, we identified and selected locally acceptable symbols and signs, for example, star, moon, house, fish, bicycle, to represent the response options. The question items were serially developed into the digitised format and draft copies were sent to the first author, MOA, for review at each stage. After ensuring that the wordings of the paper questionnaire were consistent with the digitised version, translated audios in Mandinka, Wolof and Fula were subsequently recorded as voice-overs on the digitised questionnaire, which will be subsequently referred to as the Digitised Informed Consent Comprehension Questionnaire (DICCQ) in this manuscript.

Piloting

On completion of the initial development, DICCQ was piloted among 18 mothers of infants participating in an ongoing malaria vectored vaccine trial at the MRC Sukuta field site (ClinicalTrials.gov NCT01373879). The field site is located about 5 km from the MRC field site targeted for field testing of the questionnaire. DICCQ was administered through an interviewer (MOA) on a computer laptop in a private consultation room within the Sukuta field site. After entering the participant's assigned identification number and interviewer's initials into DICCQ, the participant's local language of choice was selected on the computer screen. Operated by MOA, the question items were serially read aloud to the participants in the local language with the click of a button on the lower toolbar of the computer screen and a 'forward arrow' button to move to the next question item. Participants answered either by vocalising their responses or by pointing to the symbols on the computer screen that corresponded to their choice of responses. The participants generally reported the questionnaire to be clear and easy to follow. The audio translations were also accepted as conforming with the dialects spoken by the majority of Gambians. The average administration time was 29.4 min. Suggestions were made to include 'backward', 'repeat' and 'skip' function buttons in the computer toolbar. These amendments were incorporated into the final version of the digitised questionnaire.

Field testing

The final version of DICCQ (see online supplementary appendix 1) was tested sequentially among participants in two clinical trials. The two sites were selected for field testing of the questionnaire based on some similarities of the clinical trials taking place simultaneously at the two diversely distinct research communities within the Gambia.

The first field test took place from 4 to 20 February 2013 among mothers of children enrolled in an ongoing randomised controlled, observer blind trial that aimed to evaluate the impact of two different formulations of a combined protein-polysaccharide vaccine on the nasopharyngeal carriage of *Streptococcus pneumoniae* in Gambian infants at the Fajikunda field site of MRC (ClinicalTrials.gov NCT01262872). The site is located within an urban health centre, about 25 km south of the capital, Banjul. A total of 1200 infants were enrolled in the trial and mothers brought their children for a total of six study visits over a period of one year.

The second field test took place from 22 February to 15 March 2013 in villages around Walikunda, about 280 km east of Banjul, among participants in an ongoing randomised controlled, observer blind trial (http://www.who.int/whopes/en/). The study was designed to compare the efficacy of two different doses of a newly developed insecticide with the conventional one, used for indoor residual spraying for malaria vector control in the Gambia. Over 900 households in 18 villages around the Walikunda field station of MRC were randomly selected to receive any of the three doses of insecticides. Household participants gave informed consent before indoor spraying of the insecticides. Entomologists visited the households every month for 6 months to collect mosquitoes and interviewed the participants for perception of efficacy and adverse effects of the insecticides.

In the two studies, written informed consent was obtained based on the English version of the respective study information sheets. These were explained in the

local languages by trained field staff, in the presence of an impartial witness in case of illiteracy. Similarly, prior to administering DICCQ at each trial site, written informed consent was obtained from participants or their parents. One week after first administration, DICCQ was readministered to the randomly selected group among the participants.

After obtaining a written informed consent, trained interviewers administered DICCQ on a laptop computer to each participant in his/her preferred local language in noise-free consulting rooms at the MRC facility located within the Fajikunda Health Centre and at designated areas within the households in Walikunda villages. In addition, at the end of the first questionnaire administration, each participant in the two sites was administered an Informed Consent Questionnaire (ICQ),[35] which has been validated in a different context. Briefly, ICQ consists of two subscales: the 'understanding' subscale, which has four question items, and the 'satisfaction' subscale, which has three question items on satisfaction with study participation (see online supplementary appendix 2). The questionnaire was validated in English among participants in a randomised clinical trial of Gulf War veterans' illnesses. ICQ exhibited good psychometric properties following standard item-reduction techniques.[35] Similar to DICCQ, the 'understanding' subscale of ICQ covers the domain on the meaning of consenting, benefits and risks of trial participation. However, unlike ICQ, the 'study expectation' domain was not covered by DICCQ. ICQ was orally translated to Mandinka, Fula and Wolof by three independent native speakers who confirmed consistency with the original English version. To establish construct validity, the participants' scores on ICQ were compared with their scores on DICCQ.

Sample size estimation

Sample size for validation studies is usually determined with the aim of minimising SE of the correlation coefficient for reliability test. Also, 4–10 participants per question items are recommended to obtain a sufficient sample size in order to ensure stability of the variance–covariance matrix in factor analysis.[36 37] Based on these recommendations, we chose seven participants per question items. DICCQ has 34 question items (excluding the first 9 questions on sociodemographic data and information on previous clinical trial participation) to give 34×7=238 participants. Allowing for a 5% non-response rate, the sample size was approximated to 250. Half of these participants (n=125) were invited 1 week after first administration of the questionnaire for a retest. Written informed consents were obtained from each consenting participant. Participation was voluntary and confidential.

Scoring system for the questionnaire

The scoring algorithm consistent with the level of increasing difficulty of the question items is summarised in table 1. In designing the scoring algorithm, we considered the possibility that certain question items should attract greater weight than others in determining the summated scores. For example, closed-ended question items were scored 0–3, question items with multiple response options were scored 0–4 and open-ended question items with no response option were scored 0–5. The first author, MOA, scored all participants to avoid inter-rater variations. Participant scores on closed-ended question items were summed up as the 'recall' scores while participant scores on open-ended question items were summed as the 'understanding' scores. The total sum of 'recall' and 'understanding' scores for each participant constitutes the 'comprehension' scores[38] (not shown in this manuscript).

For ICQ,[35] responses were scored as follow: 3 for 'Yes, completely', 2 for 'Yes, partially', 1 for 'I don't know' and 0 for 'No'. The first author, MOA, assigned the scores based on the responses ticked by trained assistants who administered the questionnaire to the participants.

Data analysis

Data were retrieved from the in-built database of DICCQ and converted to the Microsoft Excel format. Analysis was performed with Stata V.12.1 (College Station, USA) and the Statistical Package for Social Sciences software V.20.0 (Chicago, Illinois, USA). The significance of

Table 1 Scoring of question items

Closed-ended question items in the first section	Each correct answer was scored 3; wrong answer was scored 0 and responses with 'I don't know' were scored 1
Open-ended question items which are follow-up questions to the closed-ended question items in the first section	Each correct answer was scored 5, partially correct answer was scored 3, incorrect answer was scored 0, while 'I don't know' responses were scored 1
In the second section, participants chose one correct answer out of four option responses	Each correct answer was scored 3, incorrect answer was scored 0 and 'I don't know' responses were scored 1
In the third section, participants chose more than one correct answers from four option responses	Full correct answers were scored 4, partially correct answers were scored 2, wrong answers were scored 0 and 'I don't know' answers were scored 1
In the fourth section, participants responded using their own words to open-ended question items	Full correct answer was scored 5, partially correct answers were scored 3, wrong answers were scored 0 and 'I don't know' responses were scored 1

group differences was tested by Mann-Whitney U tests for demographic variables with p<0.05 (two-tailed) considered as significant. Psychometric properties of DICCQ were evaluated in terms of reliability and validity using the following steps:

Steps in validation analysis

Construct validity: Construct validity refers to the degree to which items on the questionnaire relate to the relevant theoretical construct. It represents the extent to which the desired independent variable (construct) relates to the proxy independent variable (indicator).[39 40] For example, in DICCQ, 'recall' and 'understanding' were used as indicators of comprehension. This is based on an earlier study[41] which defined 'recall' as success in selecting the correct answers in the question items and 'understanding' as correctness of interpretation of statements presented in the question items. When an indicator consists of multiple question items like in DICCQ, factor analysis is used to determine construct validity.[39 42]

To verify construct validity, the design of DICCQ was analysed in a stepwise procedure. First, we tested whether the sample size of 250 was sufficient to perform factor analysis of the 34-item DICCQ according to the Kaiser-Meyer-Olkin (KMO) coefficient (acceptable value should be >0.5). In a second step, we conducted a principal component analysis (PCA) to derive an initial solution. Third, we determined the number of factors to be extracted according to three different criteria: (1) eigenvalue >1, (2) Cattell's scree plot and (3) the number of factors identical with the proposed number of subscales (ie, the 'recall' and 'understanding' subscales).[34 43] In the last step, we compared the unrotated and the rotated factor solutions. The rationale of rotating factors is to obtain a simple factor structure that is more easily interpreted and compared. We chose the varimax rotation as the most commonly used orthogonal rotation undertaken to rotate the factors to maximise the loading on each variable and minimise the loading on other factors.[34 43 44]

Furthermore, owing to a lack of a specific 'gold standard' tool to measure informed consent comprehension, we could not examine concurrent (criterion) validity in which participants' scores on DICCQ could be compared with the participants' scores on the 'gold standard' obtained at approximately the same point in time (concurrently). Nevertheless, construct validity provided evidence of the degree to which participants' scores on the questionnaire were consistent with hypotheses formulated about the relationship of DICCQ with the participants' scores on other instruments measuring similar or dissimilar constructs, or differences in the instrument scores between subgroups of study participants.[40] Two forms of construct validity based on hypothesis testing were examined:

1. *Convergent validity*: A good example of an instrument measuring the same construct as DICCQ is ICQ which contains four question items on 'understanding' subscale and three items on 'satisfaction' subscale.

   The following a priori hypotheses were made: convergent validity—participants' scores on DICCQ will correlate positively with their scores on 'understanding' subscale of ICQ because both constructs relate to informed consent comprehension in clinical trial contexts. However, the correlation is not expected to be high, because DICCQ covers more domains of informed consent comprehension than the ICQ subscale.
2. *Discriminant validity* which examines the extent to which a questionnaire correlates with other questionnaires of construct that are different from the construct the questionnaire is intended to assess. To determine this, it was hypothesised that participants' scores on DICCQ will correlate negatively with the 'satisfaction' subscale of ICQ because DICCQ does not include the 'satisfaction' domain about study participation. Spearman's correlation coefficients were used because the data of the questionnaires (DICCQ and ICQ) were not normally distributed.
3. To establish further evidence of construct validity, we examined the *discriminative validity* in which participants' scores on DICCQ were compared between subgroups of participants who differed on the construct being measured. Using the Mann-Whitney U test, the differences of participants' scores on DICCQ were compared based on their demographic variables (ie, gender, place of domicile: urban vs rural and education status).

Reliability

After completing item reduction in the validity analysis, the item-reduced DICCQ was investigated for reliability. Reliability describes the ability of a questionnaire to consistently measure an attribute and how well the question items conceptually agree together.[34 45] Two commonly used indicators of reliability, internal consistency and test–retest reliability were employed to examine the reliability of DICCQ. Cronbach's α was computed to examine the internal consistency of the questionnaire. Because the questionnaire contains the 'recall and understanding' subscales, Cronbach's α was computed for each subscale as well as for the entire scale. An acceptable value for Cronbach's α was ≥0.7.[37 39]

Test–retest reliability was examined by administering the same questionnaire to half of the study participants who were randomly selected on two different occasions, one week apart. This is based on the assumption that there would be no substantial change in the comprehension scores of participants between the two time points.[34 46] A high correlation between the scores at the two time points indicates that the instrument is stable over time.[34 46] Analysis of participants' scores between the test and retest was conducted by estimating the intraclass correlation coefficients and 95% CI.

RESULTS

Two hundred and fifty participants consisting of 130 participants from the clinical trial in the urban setting and another 120 clinical trial participants in the rural setting were interviewed. To address the missing data, participants (n=3) who did not respond to three or more items (5%) in DICCQ were excluded from further analysis.[44] Those with one or two missing items (n=6) were replaced with the mean value of the participant scores for the question item.[44] Thus, data from 247 participants were included in the final analysis. The mean age was 37.06 ±15 years; there were 129 participants (52.2%) in the urban group and 118 participants (47.8%) in the rural group. The overall mean time of administration of the questionnaire was 22.4±7.4 min while the overall mean time for retest of the questionnaire was 18.5±5.4 min. The reduction in duration of administration of the questionnaire might be because a majority of the participants became familiar with the question items as a result of the short interval of one week between the first and second administration.

The sociodemographic characteristics of the study participants are summarised in table 2.

Table 2 shows that a majority of the participants (about 27%) were in the age group 18–25 years; about 63% were women and about 40% had no formal education. The index trial was the first clinical exposure in 81% of the participants, while the rest had participated in at least one trial apart from the current trial.

Table 2 Sociodemographic characteristics of study participants

Characteristics	Frequency (%; N=247)
Age group (years)	
18–25	67 (26.8)
26–33	65 (26.0)
34–41	40 (16.0)
42–49	23 (9.2)
>49	55 (22.0)
Gender	
Female	156 (63.2)
Male	91 (36.8)
Domicile	
Urban	129 (52.2)
Rural	118 (47.8)
Occupation	
Farming	80 (32.3)
Trading	39 (15.8)
Artisans	7 (2.8)
Civil servant	18 (7.3)
Housewife	94 (38.2)
Schooling	4 (1.6)
Unemployed	5 (2.0)
Education group	
Had western education	62 (25.1)
Had no western education	185 (74.9)
Religious affiliation	
Islam	239 (96.8)
Christianity	8 (3.2)
Previous clinical trial participation	
Only one	200 (81.0)
More than one	47 (19.0)

Factor analysis

The KMO coefficient for DICCQ was 0.62 (acceptable value was >0.5), confirming a sufficient degree of common variance and the factorability of the intercorrelation matrix of the 34 items. The first PCA yielded a total variance of 69.02%, which implied that at least 50% of the variance could be explained by common factors, and this is considered acceptable. This initial solution after PCA revealed 13 components with eigenvalues >1. However, the scree plot began to level off after two components, consistent with the number of subscales (figure 1). As the scree plot is considered more accurate in determining the numbers of factors to retain especially when the sample size is ≥250, or the questionnaire has more than 30 items,[42] a two factor solution with varimax rotation was considered conceptually relevant and statistically appropriate for DICCQ. To give the correct explanation, the values of factor loadings were checked using Steven's guideline of acceptable value of 0.29–0.38 for a sample size of 200–300 participants.[42] As the sample size used in this study was 250, eight items: two items on study duration, four items on the funder/sponsor of the study and two items on the number of study participants with factor loadings of <0.3, were deleted. Five items: voluntary participation, rights of withdrawal, placebo, blinding and study purpose, were retained despite low factor loadings because they were theoretically important components of informed consent. The final PCA of the two-factor solution with 26 items (corresponding to 'recall and understanding' themes) accounted for 60.25% of the total variance. The factor loadings of the final PCA and their factorial weights are shown in table 3.

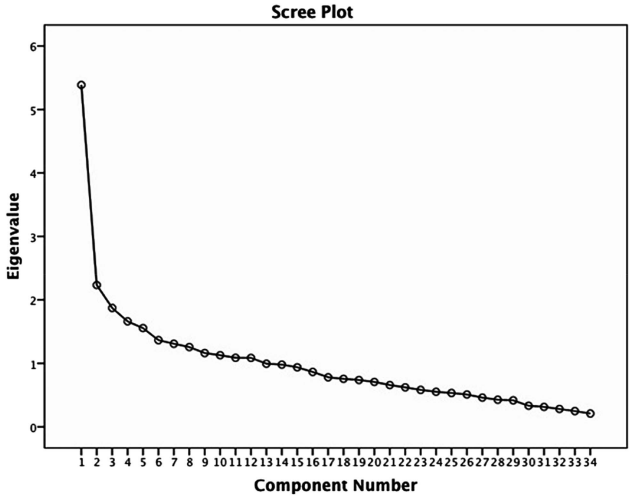

Figure 1 Cattell's scree plot for the item-level factor analysis.

Table 3 shows that the factorial weights of each item of the two components are greater than 0.3 and that Cronbach's α coefficient of each component is greater than 0.7, suggesting high internal consistency.

Internal consistency reliability

Cronbach's α computed for the item-reduced DICCQ was 0.79 and 0.73, respectively, for 'recall and understanding' domains. This indicates a high correlation between the items and that the questionnaire is reliable.

Test–retest reliability

One hundred and twenty-six (51%) of 247 participants completed the second questionnaire at a mean of 7.5 days after the first administration. The mean age of respondents who had a retest was 36.9±15.1 years; 77 (60.6%) were women and 50 (39.4%) were men; 60 (47.2%) were from a rural setting while 67 (52.8%) lived in the city. The average time of administration was 18.5 ±5.4 min (range 9–39 min). An intraclass correlation coefficient of 0.94 (95% CI 0.923 to 0.954) was obtained, showing that the questionnaire was consistently reliable over the two periods of administration.

Validity

Convergent validity

To test the expected relationships between DICCQ and ICQ, we correlated total DICCQ scores with ICQ scores in the sample population (n=247). As expected, DICCQ was significantly positively correlated with the 'understanding' subscale of ICQ (r=0.306, p<0.001). These findings provide some evidence of convergent validity.

Discriminant validity

Also as predicted, DICCQ was significantly negatively correlated with the 'satisfaction' subscale of ICQ (r=−0.105, p=0.049), providing evidence of discriminant validity.

Discriminative validity

Expectedly, there was a significant statistical difference in the comprehension scores on DICCQ among female and male participants (z=8.8, p<0.001), rural and urban participants (z=−11.1, p<0.001) and educated and non-educated participants (z=4.27, p<0.001). This provides further evidence of construct validity (table 4).

Table 4 shows that there were significant differences in the comprehension scores of participants based on gender, place of domicile and education status.

Table 3 Principal component analysis (PCA) with varimax rotation: final two-component solution and Cronbach's α of each component

	PCA factor loadings
Recall items (n=17): closed-ended and multiple choice response formats (Cronbach's α=0.79)	
Told I can freely take part	0.719
Told I can withdraw anytime	0.314
Will know the study drug/vaccine	0.552
Unauthorised person will not know about my participation	0.372
Told the contact person	0.540
My participation can be stopped without my consent	0.420
Will I be paid for taking part	0.395
How were participants divided into groups	0.403
At what point can I leave the study	0.371
Meaning of signing/thumb-printing consent form	0.390
How I decided to take part	0.429
What will I receive as compensation	0.520
What will happen if I decide to withdraw	0.464
Reason for doing the parent study	0.393
Which are the study procedures	0.489
Which are the study activities	0.617
Which are the main benefits of taking part	0.390
Understanding items: open-ended response format (n=9; Cronbach's α=0.73)	
Describe the function of the study drug/vaccine	0.647
Mention the name of the contact person	0.451
Tell what researchers want to find in this study	0.312
Number of study visits	0.492
Tell what were done during the study visits	0.498
Describe how participants were divided	0.689
Tell the difference between taking part in a study and going to hospital	0.464
What are the possible unwanted effects of a study drug/vaccine	0.388
Why were participants given different drugs/vaccines	0.437

Table 4 Discriminative validity showing differences of comprehension scores by participants' demographic variables

	Rank sum	Expected	Significance
Gender			
Male (n=91)	5765.5	11 284	z=8.80,
Female (n=156)	24 862.5	19 344	p<0.001
Domicile			
Urban (n=129)	7640.5	14 632	z=−11.1,
Rural (n=118)	22 987.5	15 996	p<0.001
Education status			
Educated (n=62)	9765	7688	z=4.27,
No western education (n=185)	20 863	22 940	p<0.0001

DISCUSSION

This study reports the psychometric properties of a digitised audio informed consent comprehension questionnaire when tested in a sample of clinical trial participants in urban and rural settings in the Gambia. This is the first validation process of the questionnaire and the results suggest that it has good psychometric properties. The digitised audio questionnaire in local languages could be useful as a measure of comprehension of informed consent. DICCQ demonstrated good internal consistency and convergent, discriminant and discriminative validity. This study adds to knowledge by demonstrating that the digitised questionnaire can be developed and psychometrically evaluated in three different oral languages.

Expectedly, DICCQ scores were significantly positively correlated with the 'understanding' subscale of ICQ, and significantly negatively correlated with the 'satisfaction' subscale of the questionnaire. These significant correlations are evidence of convergent and discriminant validity of DICCQ, because DICCQ scores correlated with scores on ICQ in the theoretically expected directions. Furthermore, there were significant statistical differences in the participants' scores on DICCQ based on their gender, domicile and education status (p<0.0001), providing evidence of the discriminative validity of the questionnaire. Taken together, these findings establish a construct validity of DICCQ.

This innovative approach of developing and delivering questions has enabled a rapid measurement of informed consent comprehension in rural, remote and urban research settings. It overcomes the obstacles of multiple written translations, which are quite challenging in some African countries due to the lack of standardised written languages and low literacy. The use of orally recorded interpretations of the questionnaire and delivery through a digitalised format ensured that the questions were consistently presented to all participants. Given that the communication skills of an interviewer could influence comprehension of the information, it was important that we used experienced native speakers to interpret the English version of the questionnaire to Gambian local languages that were understandable to the participants in rural and urban settings.

Nevertheless, we fully recognise that it could be counterproductive to depend solely on the technology of a tool to meet the comprehension assessment of participants during informed consent process; hence, we involved trained interviewers to administer the audio computerised questionnaire to the participants. In our study, we ensured that the research team had sufficient time to discuss participants' concerns about the research, in addition to the use of the comprehension tool. Thus, we believe that the overall acceptance and success of the tool will ultimately depend on a well-balanced combination of the technology and human elements.[38]

The questionnaire software also has an in-built database which minimises errors in data entry and reduces data entry time. This improves the accuracy and quality of the data and ultimately the psychometric properties of the questionnaire.

Another important strength of this study is the reasonable sample sizes used in the rural and urban populations. Almost 99% of the participants for the first and retest questionnaires completed the study. The representative sample and high response rates could be due to the fact that the participants were recruited from ongoing clinical trials with regimented study visits. Also, the strategy used in administering the questionnaire in the local languages of choice of the participants encouraged greater participation and high retention rates.

A major limitation could be that this experience is very specific to the Gambia, a relatively small country with three major local languages. It may be challenging to translate this experience to other contexts. Also, the scoring of all participant assessments by a single researcher eliminated inter-rater variability, which could create a possibility of error that might lead to underestimation or overestimation of participants' comprehension scores. Nevertheless, this effort represents an important development towards improving informed consent comprehension. Until now, a lot of literature has explained the challenges of informed consent comprehension in resource-poor contexts, but few concrete recommendations have improved it. If DICCQ can help to identify elements of informed consent which are less understood in a specific context, then further work could be carried out with a multidisciplinary team and the community for developing better approaches, wordings and examples for describing those aspects which are more difficult to understand in that very context. This will, in addition to improving participants' comprehension, protect their freedom to decide, and also potentially improve the quality of data and outcome of the research.

Another limitation of this study is that known group validity and sensitivity to change could not be determined. This is because known group validity requires a

strong a priori hypothesis that groups differ on the construct. There is insufficient previous research on informed consent comprehension to develop strong a priori expectations about differences in comprehension levels between different subgroups of participants. There is an expectation of higher comprehension levels when the tool is used following an intervention, which will make a preintervention and postintervention comparison test a test of sensitivity to change and of known group validity. This will be explored in a future study where the ability of the questionnaire to detect changes in the participants' level of comprehension will be calculated by determining the effect size and the standardised response means.

CONCLUSIONS

DICCQ was developed using a combination of international and local guidelines. The present study suggests that the questionnaire has two factors, consistent with the definition proposed by Minnies *et al*[41] suggesting comprehension as comprising recall and understanding components.

We conclude that DICCQ not only has good psychometric properties, but also has potential as a useful measure of comprehension of informed consent among clinical trial participants in low-literacy communities. As with all psychometric instruments, the evidence for the psychometric properties and usefulness of DICCQ for evaluating informed consent comprehension will be strengthened by further research. In particular, it will be important to (1) test the psychometric properties of the questionnaire in other African populations, (2) conduct long-term follow-up studies and (3) explore the properties of DICCQ in different phases of clinical trials, in particular preventive and therapeutic trials. This will enable predictive testing including further tests of known group validity; overall, it will also provide us with more reliable information to improve the process of informed consent in African contexts, in a relationship of mutual partnership between study participants and researchers.

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Contributors MOA conceived, designed and conducted the study and also drafted the manuscript. KB, UD'A, MOCO, EBI, RR, HJL, NM and DC made substantial inputs to the analysis and interpretation of data, revision of the article and approved the final version of the manuscript.

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Multimedia Informed Consent Tool for a Low Literacy African Research Population: Development and Pilot-Testing

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Abstract

Background—International guidelines recommend the use of appropriate informed consent procedures in low literacy research settings because written information is not known to guarantee comprehension of study information.

Objectives—This study developed and evaluated a multimedia informed consent tool for people with low literacy in an area where a malaria treatment trial was being planned in The Gambia.

Methods—We developed the informed consent document of the malaria treatment trial into a multimedia tool integrating video, animations and audio narrations in three major Gambian languages. Acceptability and ease of use of the multimedia tool were assessed using quantitative and qualitative methods. In two separate visits, the participants' comprehension of the study information was measured by using a validated digitised audio questionnaire.

Results—The majority of participants (70%) reported that the multimedia tool was clear and easy to understand. Participants had high scores on the domains of adverse events/risk, voluntary participation, study procedures while lowest scores were recorded on the question items on randomisation. The differences in mean scores for participants' 'recall' and 'understanding' between first and second visits were statistically significant ($F(1,41)=25.38$, $p<0.00001$ and ($F(1, 41) = 31.61$, $p<0.00001$ respectively.

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Conclusions—Our locally developed multimedia tool was acceptable and easy to administer among low literacy participants in The Gambia. It also proved to be effective in delivering and sustaining comprehension of study information across a diverse group of participants. Additional research is needed to compare the tool to the traditional consent interview, both in The Gambia and in other sub-Saharan settings.

Keywords

Informed consent; Video; Technology; Vulnerable population; Development; The Gambia

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Introduction

Informed consent is a practical application of respect for person which is a fundamental principle of research [1]. The process of informed consent is meant to ensure that the decision to participate in clinical research is freely made after an individual has received, considered and understood fully the complete study information without being coerced, induced, unduly influenced or intimidated [2]. For informed consent to fulfil its goals researchers must not only provide full disclosure of study information but they must also ensure full comprehension of the information to potential study participants. Informed consent must be provided in the languages and terminologies understandable to the participants to allow him/her understand the study information to make an informed decision on whether or not to participate [2,3].

Comprehensive systematic reviews [4,5] of clinical research conducted in sub-Sahara Africa showed that participants often demonstrated poor comprehension of various domains of informed consent. For example, only 10% of mothers of study children in The Gambia [6] and 20% of Ghanaian women [7] demonstrated good comprehension of the concept of placebo. Similarly, participants from Ivory Coast [8], Nigeria [9], Senegal [10], Kenya [11], Uganda [12] and Ethiopia [13] had sub-optimal comprehension of voluntary participation, autonomy, risks/benefits, randomisation and blinding. These unacceptably low levels of comprehension may be due to a combination of factors. These include poor communication between the participants and the persons administering the consent (e.g. due lack of time and power imbalance making the participants not to ask necessary questions).

Furthermore, central to this problem is the almost exclusive reliance on written information document in research settings where many study participants are unable to read and understand documents written either in foreign or local languages [5,14,15]. In such situations, the World Medical Association Declaration of Helsinki recommends the use of appropriate alternative informed consent procedures that will engender adequate comprehension of the study information [16,17].

Nishimura et al. [18] in a recently published systematic review identified several effective strategies for improving informed consent process including enhanced consent forms, extended discussions and multimedia. Enhanced consent form involved the use of simplified paper consent document with revised layout, text styling, and sometimes with added pictures. In extended discussion, a study team member engaged participants in additional discussions and, multimedia approach involved presentation of study information through

combined use of video, audio and animations [19]. A meta-analysis showed a modest but statistically non-significant increase in comprehension scores of participants randomised to a multimedia-based consent approach when compared to their counterparts randomised to control consent approach (Standardised Mean Difference [SMD]=0.30, 95% CI, −0.23 to 0.84). Similar comparison of enhanced consent form and extended discussion with control consent increased the comprehension scores significantly (SMD 1.73, 95% CI, 0.99 to 2.47; SMD 0.53, 95% CI, 0.21 to 0.84 respectively [18]. These findings raise concerns about the impact of multimedia in informed consent process, although, previous studies reported its usefulness in promoting retention of consent information longer than one week [20,21].

An earlier review by Flory and Emanuel [19] also showed that multimedia tools are not significantly effective in aiding participants' comprehension. This submission agreed with the conclusions of a Cochrane review [22] that 'the empirical literature is not yet sufficiently developed to draw definitive conclusions about the general effectiveness of or value derived from multimedia consent tools'**.** Nevertheless, critics argue that the reported limited usefulness of multimedia tool is untenable because the effectiveness of multimedia consent approach was evaluated in studies with considerable methodological flaws. For example, some of the studies had no standard controls, and in others, informed consent documents were merely presented on computer screens for participants to read [18]. Apart from these, the studies included in the systematic reviews [18,19,22] were conducted in developed countries where literacy rates were high. Consequently, the conclusions of lack of effectiveness of multimedia approach may not be applicable to low literacy populations in sub-Saharan Africa. Although no study from sub-Saharan Africa is yet to report the potential usefulness of multimedia for delivering study information during informed consent process; media-based technology is becoming cheaper to implement, readily available and more manageable in Africa [18,23]. Thus, assessing the effectiveness of a multimedia informed consent tool for improving the consenting process is becoming increasingly crucial in low literacy research settings in Africa.

As a first step, we describe here how we developed and pilot-tested a multimedia tool to provide information for a clinical trial scheduled to take place among low and non-literate participants in The Gambia. This study was also aimed at gathering preliminary data to determine the effectiveness of a locally designed multimedia tool in aiding informed consent comprehension of participants in the low literacy research community.

Materials and Methods

The PRINOGAM Trial

The development of the multimedia tool was done using the informed consent document for PRINOGAM trial (ClinicalTrials. gov NCT01838902). Briefly, PRINOGAM is an open-label, four-arm treatment trial, aimed at determining the lowest possible primaquine dose to obtain a substantial gametocytocidal effect in asymptomatic malaria infected individuals, as this may reduce the risk of harmful effects in Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency.

The trial was planned to take place concurrently at Basse and Jahaly areas of The Gambia where level of literacy of the inhabitants is low. The Gambia is one of the smallest West African countries with a population of 1.79 million people and adult literacy rate of less than 30% [24]. Mandinka, Fula and Wolof are three major ethno-linguistically distinct groups populating the study areas. In previous studies [6,25] conducted in Gambian communities, the local ethic committees recommended that oral interpretations of the English version of written informed consent documents should be provided to potential participants by trained field staff who are native speakers of the local languages [26]. This is because, in addition to low literacy rate, no written translation of consent documents to local languages is possible as no standardised written format for the local languages exist [25,27]. Because most participants are not literate, they gave consent by thumb-printing the consent form in the presence of an impartial witness.

This pilot study of the multimedia consent tool was conducted among healthy volunteers in Basse, an area which shares similar epidemiologic and demographic features with Jahaly.

Development of multimedia tool from informed consent document of PRINOGAM

We worked with a multimedia expert who had extensive training and experience in motion graphics and interactive media design to develop the participant information document of PRINOGAM trial. The information document was earlier written by the Principal Investigator of the trial with technical support from the Medical Research Council (MRC) Clinical Trials Support Manager who ensured that all relevant information was adequately and comprehensibly presented in the document. The document were submitted along with the study protocol to an independent body of scientists who reviewed and confirmed that information contained in the document was satisfactory to engender informed decision-making by potential study participants. The information document was further submitted to the local ethical committee who also reviewed and approved the document as conforming to internationally agreed ethical requirements for conduct of clinical trials.

The approved information document contained 11 sections namely: *introduction, reason for the study, what is G6PD, how to take part, what would happen if one took part in the study, what blood tests would be done, what are the side effects and possible risks of taking part, potential benefits, would taking part in this study be kept confidential, who has reviewed this study, who can be contacted if one has questions?* The messages in each section were graphically translated into a context-specific visual story. We serially reviewed these storyboards to confirm appropriateness to Gambia research setting. The stories were acted in role-plays by members of the clinical trial team after undergoing several training and rehearsals. The final role-play on each section of information sheet was serially video-recorded by the multimedia expert.

Three experienced linguistic professionals who are native speakers of the three major Gambian languages and are also familiar with clinical research concepts were contracted to audio-translate each section of the participant information document. The audio-translations were confirmed to be consistent with the English version by another three native speakers of the languages. The audio-translations were recorded as voice-over on the video-recorded role-plays by the multimedia expert. Sections which could not be visually conveyed in the

role-plays e.g symptoms of adverse events of study drugs like headache, diarrhoea, passage of dark-coloured urine were graphically represented with animations.

Review of multimedia tool

The first draft of the multimedia tool in a Digital Video Disc (DVD) was given to two qualified lay persons and two experienced researchers to confirm whether the contents of the tool was consistent with the contents of the participant information document of PRINOGAM trial. They all agreed that the tool included all essential information on the study as requested by ethical and Good Clinical Practice (GCP) guidelines, and that it used dialects that were well understandable to general populace. In very few areas, one of the narrators wrongly used a local language *'biir bumuti'* which means 'lower abdominal pain' to describe 'abdominal pain' as one of the adverse effects of the investigational products. This was corrected with appropriate word '*nahl bumuti'*. Also, omission of '*hel butey'* meaning 'nausea' was discovered and this was included in the revised version. Non-inclusion of dark coloured urine as a major complication of G6PD deficiency was pointed out by one of the researchers and this was included in the revised version.

Pilot-testing

A purposive sample of 42 healthy male and female volunteers aged 18-49 years was recruited to pilot-test the multimedia informed consent tool. The upper limit of the age range (49 years) was based on data from previous studies [28,29]. The lower age limit (18 years) was chosen to avoid the logistical challenges associated with obtaining informed consent from under-aged participants. Participants were recruited from the north and south parts of Basse to ensure representation. Despite being representative of the PRINOGAM trial population and participants could in the future become eligible, they were not screened for PRINOGAM when the pilot-testing was carried out. After obtaining a written informed consent, we played the multimedia tool on a laptop computer for each participant in his/her preferred local language in noise-free consulting rooms at MRC facilities located within Basse Major Health Centre. The participants were requested to ask questions if they were not clear about the contents of the multimedia tool.

To assess acceptability and ease of use of the multimedia tool, an 8-item questionnaire was adapted from a similar study conducted in South Africa [30]. The original questionnaire contained 15 question items on acceptability and ease of use of an alternative informed consent tool. The relevant part of the question items were retained e.g. "*do you like the pictures in the tool*" while non-relevant questions were removed e.g "*do you know how to replace the battery of the tool*". After watching the multimedia video and participants confirmed they had no questions, the 8-item questionnaire was administered to each participant to assess acceptability and ease of use of multimedia tool. Participants responded by indicating either 'yes' or 'no' to each question item. Following the questionnaire administration, we assessed the participants' comprehension using a Digitised Audio Informed Consent Comprehension Questionnaire (DICCQ) that was previously validated in low literacy Gambian populations. The development and psychometric evaluation of DICCQ has been described elsewhere [31]. Briefly, DICCQ is a 26-item questionnaire consisting of a combination of closed-ended, multiple choice and open-ended question

items. Psychometric evaluation of DICCQ done in urban and rural Gambian populations showed that the questionnaire was reliable and valid [31]. The question items in DICCQ are consistent with the elements of informed consent required to ensure understanding of potential participants according to international ethical guidelines [2,32]. The following domains of informed consent are covered in the DICCQ: voluntary participation (Q1), rights of withdrawal (Q2,8,11,15), study procedures (Q17, 18,21,22), study purpose (Q16,20), blinding (Q3,4), confidentiality(Q5), compensation (Q9,14), randomization (Q10,23), autonomy (Q13), meaning of giving consent (Q12), benefits (Q19), risks/adverse effects (Q25), therapeutic misconception (Q24), placebo (Q26). The question items in DICCQ are listed in Table 4.

We further assessed acceptability and ease of use of DICCQ using the questionnaire adapted from the South African study described above [30].

To assess how much of the study information was retained, the participants were recalled one week after first administration and the digitised comprehension questionnaire was re-administered to the participants.

Focus group discussions

During the second visit, selected participants were invited for Focus Group Discussions (FGD) to further explore acceptability and ease of use of multimedia consent tool and digitised informed consent comprehension questionnaire. A separate group of six men and women were invited for the FGD sessions. Participants were segregated by sex to ensure homogeneity and open discussions in each group. A purpose-designed FGD guide was used and the first author, MOA, served as the facilitator of the discussions. The proceedings were audio-taped after verbal consent was obtained from the participants. These were transcribed into English texts by two independent native speakers. We identified the main themes of the transcribed texts and content analysis of these themes was performed.

Ethical consideration

Ethical approvals were obtained from the ethics committees of London School of Hygiene and Tropical Medicine, UK and Gambia Government/Medical Research Council Joint Ethics Committee. Due to absence of standardised writing formats for Gambian languages and high illiteracy rates, informed consent was obtained from the participants in this study by trained field assistants who were native speakers of the local languages. The trained assistants provided oral interpretations of the study information to the participants in the local languages he/she understood. After the potential participants had agreed to join the study, literate participants (about 10% in this study) signed the consent form while the majority (about 90%) thumb-printed the consent form in the presence of an impartial witness. Participation was voluntary and confidential.

Scoring system—The scoring system used in previous validation work of DICCQ [31] was applied:

Closed ended question items in the first section	Each correct answer was scored 3; wrong answer was scored 0 and responses with 'I don't know' were scored 1
Open-ended question items which are follow-up questions to the closed ended question items in the first section	Each correct answer was scored 5, partially correct answer was scored 3, incorrect answer was scored 0, while 'I don't know' responses were scored 1
In the second section, participants chose ONE correct answer out of FOUR option responses	Each correct answer was scored 3, incorrect answer was scored 0 or 'I don't know' responses were scored 1
In the third section, participants chose more than one correct answers from FOUR option responses	Full correct answers were scored 4, partially correct answers were scored 2, wrong answers were scored 0 and 'I don't know' answers were scored 1
In the fourth section, participants responded using their own words to open-ended question items	Full correct answer was scored 5, partially correct answers were scored 3, wrong answers were scored 0 and 'I don't know' responses were scored 1

Data analysis

Data on acceptability and ease of use of multimedia tool and digitised questionnaire were entered on Microsoft Excel while data on participant comprehension were retrieved from the in-built database within DICCQ and exported into Microsoft Excel. Acceptability and ease of use were assessed by calculating the percentage of 'yes' responses indicated by participants on the questionnaire. Mean participants' scores (and standard deviations) on DICCQ were calculated to determine the domains of informed consent which were most or least understood by the participants.

Further analysis was done by adopting the definition of comprehension used by Minnies et al. [33] which consists of two components: recall and understanding. 'Recall' was defined as correct answers to the close-ended and multiple choice questions while 'understanding' was correct responses given to the open-ended questions [33].

Repeated measures analysis of variance model was done to determine the effect of the multimedia and the effect of time on the participants' recall and understanding scores at the two study visits. Pair-wise comparison of the mean difference of participants' scores between first and second visits was performed and appropriate Bonferroni corrections were made to allow for multiple comparisons. Analysis was done with Stata version 12.1 (College Station, USA) with $p<0.05$ (two-tailed) considered significant.

Results

Forty-two participants consisting of 20 females and 22 males were recruited. Table 1 shows socio-demographic characteristics of the study participants. The median age was 34.5 ± 11; (range, 18-48 years), 90% were Mandinka and less than 10% had Western education. Each playing session of the multimedia tool lasted an average of 20 minutes, while questionnaire administration through DICCQ took an average of 32 minutes.

All participants liked the features of the multimedia tool, would like to use it again, and wanted future study information delivered using the tool (Table 2). About 70% reported that they were comfortable with the tool and that it was easy to follow. However, about 10% of participants suggested changes to the Fula translation of the tool. The dialect (Fula Puta)

used in the tool was not generally acceptable to the participants. Fula Torah was suggested as the appropriate dialect.

The colour, pictures and voices used in the DICCQ were acceptable to the participants (Table 3). About 60% reported it was easy to follow and 70% were comfortable with it. About 17% suggested changes to the tool mainly on reducing administration time (8%) and waiting time (9%).

Table 4 shows that the mean participants' scores were high on the question items on adverse event/risk (4.36 ± 1.21), voluntary participation (2.86 ± 0.65), meaning of giving consent (2.93 ± 0.46), study procedures (3.33 ± 0.95) while lowest mean scores were recorded on the two question items about randomisation (0.02 ± 0.15) and (0.88 ± 1.13).

The differences in the mean scores for participants' recall between first and second visits were statistically significant [F (1,41)=25.38, p<0.00001] (Table 5). Similarly, the mean scores for participants' understanding between first and second visits were statistically significant [F (1,41)=31.61, p<0.00001]. Pair-wise comparison of the significance levels for the time difference of the participants' recall scores at the two study visits showed a mean time difference of 2.33, standard error of 0.463 and p<0.0001, 95% CI (1.398-3.269). The participants' understanding scores showed a mean time difference of 3.60, standard error of 0.639 and p<0.0001, 95% CI (2.304-4.887).

Findings of FGDs

Acceptability

Overall, there is a consensus that the multimedia tool was clear, helpful, informative, easy to follow and understand. Most of the participants were excited about watching the video and hearing their local languages being used to explain the study information. One male participant expressed that the tool was capable of improving understanding of study information as follows: '*I have been coming to this hospital for over 10 years; I have never seen a thing like this. The sound is very good and clear to me, I am sure this thing will help to improve understanding. I am happy (and) like to join (PRINOGAM) study*'.

A female participant commented: '*Though I have taken part in MRC studies before, but this one will be different. The picture and the information are clear, I am very impressed. My concern is if I get pregnant before the time this study starts, how will I take part?*'

Ease of use

The majority of the participants admitted that they could not used a computer, but could use mobile phones on daily basis, which they claimed made the multimedia and DICCQ tools easy to follow and use. One of the participants noted: '*I must thank you people for thinking of this very nice thing. Although, I am not used to a computer, I can use mobile phones very well. (So), I can follow and even use this computer easily*'.

Suggested changes to multimedia and DICCQ

One participant said: '*The video is fine but it will be better if background music is reduced*'. A male participant suggested reducing the time to administer the DICCQ and reduction in overall waiting time. '*I am happy with this tool,*' he said, '*but you have to do something about the time (administration and waiting time), so that we can return quickly to our places of work*'.

Discussion

This study evaluated a multimedia tool developed to obtain informed consent from low literacy participants who were potentially eligible to enrol in a clinical trial. Despite the fact that only 10% of the study population had formal education, the computerised tool was well received and easy to administer. Similarly, a digitised audio comprehension questionnaire developed in a previous study [31] was also acceptable to these participants. The participants expressed satisfaction with the tools and wanted future studies to adopt them. However, they suggested reducing the administration time for the digitised questionnaire, overall waiting time and background music in the multimedia.

The mean participants' scores were relatively high on the question items about adverse events/risk, voluntary participation, meaning of giving consent and study procedures, implying that the participants understood these elements better. Conversely, the scores were lowest on the items on randomisation showing that the participants had least understanding on this domain. Illustrations of the study information using a combination of video, animations and oral explanation in local languages could have contributed to the high comprehension scores recorded by participants in this study. This finding represents a new insight into the use of multimedia tool to deliver consent information to low literacy participants in sub-Saharan Africa.

Furthermore, the multimedia tool increased significantly both recall and understanding scores of the participants and this is consistent with the results from some previous studies [34-38]. The increase in participants' recall and understanding scores observed after one week period could be explained by the quiz/feedback strategy adopted in the digitised questionnaire. This introduced the possibility of enhancement or practice effect due to memorisation which might occur when participants gave correct answers or when the researchers clarified area of concerns. To minimise the memorisation or practice effect, the digitised questionnaire used closed ended, multiple-choice and open-ended items which were likely to elicit responses that truly reflect participants' comprehension of the information.

A major benefit of the multimedia tool is that it consistently provides the same research information to all participants in the same manner. This strategy removes inter-person variations in translations of informed consent information to the low literacy research participants. This becomes crucial as a participant's comprehension is influenced by the communication skills of the person administering the consent. This is truer in contexts like the Gambia, where there is no standard writing format for the local languages and the person administering the consent plays a key role in translating it orally. It was therefore critical

that we employed the services of experienced linguistic professionals who were native speakers to translate the written English version of the informed consent document to the audio forms of three major Gambian languages.

Furthermore, the development of the multimedia tool involved many technical processes including graphical translation of elements of the informed consent document to appropriate visual stories. These were further acted in role-plays by trained individuals before video, animations and audio-translations in local languages are systematically added. Some researchers have argued that the time and cost involved in the production of a multimedia tool might further add to logistic challenges of the conduct of clinical trials [39,40]. However, the ultimate benefits of ensuring well-informed research participants through the use of multimedia intervention could, in addition to improving participants' comprehension, protect their freedom to decide, and also potentially improve the quality of data and outcome of the research. This remains a worthy venture even if it requires spending a little more than expected.

The use of a multimedia tool to deliver study information during informed consent process may weaken compassionate human interactions that form the basis of research ethics [41]. Therefore, it could be counter-productive to depend solely on the technology to meet the information needs of participants during the informed consent process. The research team need to keep enough time in discussing the participants' concerns about the research, in addition to the multimedia. The multimedia could in fact replace the first part of 'traditional' consent interview. It could be followed by an interview where the participants would still be free to ask clarification questions. Thus, the overall acceptance and success of the tool will ultimately depend on a well-balanced combination of the technology and human elements.

Although both quantitative and qualitative assessments adopted in our study consistently revealed improvements in participants' comprehension scores, caution is required in interpreting these observations because our study targeted healthy volunteers who were not enrolled in any study. The simulated trial situation might have over-estimated the advantages of the multimedia tool and under-estimated other factors which would be present in real life, e.g. the participants' anxiety and haste to get enrolled. Nevertheless, increases in participants' comprehension scores over a one-week period were consistent with the design of this study. The use of repeated measures design allowed the study participants to serve as their own control. This improves the precision of the study by reducing the size of the error variance.

Another limitation of our study may be due to the fact that it reflects the situation in The Gambia, where local languages do not have written standardised forms. Consequently, we suggest that the tool should be later tested and adapted in different sub-Saharan African contexts.

Our study provides important information on the development and evaluation of a multimedia strategy for improving comprehension in research informed consent to low literacy individuals. Information shared on processes involved in the development will serve as a useful guide for investigators in similar settings. Another study comparing the

multimedia consent to the ‘conventional’ consent procedure among participants enrolled for the parent trial is currently ongoing. We hope findings of the study will shed more lights on the efficacy of multimedia in a real-life setting.

Conclusions

This study developed and evaluated a multimedia informed consent tool for improving the informed consent procedure, and noteworthy comprehension, in low literacy participants in The Gambia. We carried out an initial assessment of the strength of the tool and identified areas for further research and improvement. This study represents an important step towards institutionalising a context-specific informed consent tool. Future work is needed but there was enthusiasm for this modality and potential to improve the informed consent process, leading in turn to a better and more solid partnership between the community and the clinical researchers in The Gambia.

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Table 1

Socio-demographic characteristics of the study participants.

Characteristics	Frequency (%) N=42
Age group	
18-25 years	4(9.5)
26-33 years	16(38.1)
34-41 years	13(31.0)
42-49 years	9(21.4)
Sex	
Female	20(47.6)
Male	22(52.4)
Ethnicity	
Mandinka	38(90.5)
Fula	4(9.5)
Highest level of education attained	
Primary	2(4.8)
Secondary	2(4.8)
Arabic	29(69.0)
Vocational education	1(2.4)
No formal education	8(19.0)
Occupation	
Artisan	7(16.7)
Farming	10 (23.8)
Housewife	17(40.5)
Schooling	1 (2.4)
Trading	7(16.7)
Area of domicile	
Basse North	20(47.6)
Basse South	22(52.4)

Table 2

Participants' responses to questions on acceptability and ease of use of multimedia informed consent tool.

1. Overall, how much do you like the following features of the multimedia tool?	**Like (N=42)**	**Dislike (N=42)**	**I don't know (N=42)**
Colour	42(100.0)	0(0.0)	0(0.0)
Pictures	42(100.0)	0(0.0)	0(0.0)
Voices	42(100.0)	0(0.0)	0(0.0)
Duration	42(100.0)	0(0.0)	0(0.0)
2. Do you think the tool provide enough information about the study?	**Yes**	**No**	**I don't know**
	42(100.0)	0(0.0)	0(0.0)
3. Overall, how comfortable are you with the information in the tool?	**Comfortable**	**Very comfortable**	**Not comfortable**
	30(71.4)	12(28.6)	0(0.0)
4. Overall, how easy or difficult did you find the Information provided In the tool	**Easy**	**Very easy**	**Difficult**
	30(71.4)	12(28.6)	0(0.0)
5. Will you like to use it again?	**Yes**	**No**	**I don't know**
	42(100.0)	0(0.0)	0(0.0)
6. Would you want future study information delivered through this tool?	**Yes**	**No**	**I don't know**
	42(100.0)	0(0.0)	0(0.0)
7. Do you want any changes to the tool?	**Yes**	**No**	**I don't know**
	4(9.5)	38(90.5)	0(0.0)

Table 2 shows that all participants liked the features of the multimedia tool, about 70% found it easy to follow and 10% suggested some changes to the tool

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Table 3

Participants' responses to questions on acceptability and ease of use of digitised comprehension questionnaire (DICCQ).

1. Overall, how much do you like the following features of DICCQ?	**Like (N=42)**	**Dislike (N=42)**	**I don't know (N=42)**
Colour	42(100.0)	0(0.0)	0(0.0)
Pictures	42(100.0)	0(0.0)	0(0.0)
Voices	42(100.0)	0(0.0)	0(0.0)
Duration	39(92.9)	3(7.1)	0(0.0)
2. Overall, how easy or difficult did you find the questions provided In the tool	**Easy**	**Very easy**	**Difficult**
	24(57.1)	18(42.9)	0(0.0)
3. Overall, how comfortable are you with the information in the tool?	**Comfortable**	**Very comfortable**	**Not comfortable**
	30(71.4)	11(26.2)	1(2.4)
4. Will you like to use it again?	**Yes**	**No**	**I don't know**
	42(100.0)	0(0.0)	0(0.0)
5. Would you want future study questionnaires delivered through this tool?	**Yes**	**No**	**I don't know**
	42(100.0)	0(0.0)	0(0.0)
6. Do you want any changes to the tool?	**Yes**	**No**	**I don't know**
	7(16.7)	35(83.3)	0(0.0)

Table 3 shows that majority of the participants liked the features of the audio questionnaire, about 60% found it easy to follow and 17% suggested changes to the tool

Table 4

Descriptive statistics of participants' scores on the audio digitised comprehension questionnaire (DICCQ).

Section A: Choose only one right answer		Mean	SD*	Minimum	Maximum
1.	Have you been told that you can freely decide to take part in this study?	2.86	0.65	0	3
2	Have you been told you can withdraw from this study anytime?	2.74	0.83	0	3
3.	During the study, will you know the drug you or your child is receiving?	2.86	0.52	1	3
4.	If yes, describe or mention what the drug is doing?	2.95	1.10	1	5
5.	During the study, will anyone not working with MRC know about your health information?	2.29	1.23	0	3
6.	Have you been given the name and phone number of the person to contact if you have any questions about the study?	2.50	0.99	0	3
7.	If yes, mention the name of the person?	2.07	1.30	0	3
8.	Can your participation in the study be stopped without your consent?	1.49	1.49	0	3
9.	Will you receive money for taking part in the study?	2.52	0.94	0	3
Section B: Answer the following questions by circling the right answer					
10.	How were participants divided into different groups in this study?	0.02	0.15	0	1
11.	At what point can you leave the study?	2.02	1.41	0	3
12.	What does it mean when you sign or thumbprint the study consent form?	2.93	0.46	0	3
13.	How did you decide to participate in this study?	1.79	1.49	0	3
14.	What will you receive as a reward for taking part in the study?	2.79	0.78	0	3
15.	What will happen if you decide to stop taking part in this study?	2.71	0.89	0	3
Section C: You will need to circle more than one correct answers in this part					
16.	Which of the following describes why the primaquine study is being done?	2.95	1.01	2	4
17.	Which procedures were you asked to take part in?	3.33	0.95	2	4
18.	Which activities were you asked to complete?	2.76	0.98	2	4
19.	Which describes the main benefits of taking part in the study?	3.04	1.01	2	4
Section D: In this section, you are requested to provide answers that are specific to the study you are currently participating.					
20.	Please tell me what the researchers want to find out in the study?	2.92	0.78	0	5
21.	How many times do you have to come to the clinic for a visit during the study?	3.17	2.17	0	5
22.	Tell me what will be done during the study visits?	2.92	1.26	0	5
23.	How are participant assigned into different groups this study?	0.88	1.13	0	3
24.	What is the difference between taking part in this study and going to see a doctor for treatment?	2.97	2.48	0	3
25.	What are the possible unwanted effects of taking part in this study?	4.36	1.21	0	5
26.	Why do you think some of the study participants were given different medicine?	2.98	2.48	0	3

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Table 5

Repeated measures analysis of variance of participants' recall and understanding scores.

	'Recall' scores (N=42)	'Understanding' scores (N=42)
1st visit	25.62±4.4	55.00±5.58
2nd visit	27.95±4.8	58.5952±7.06
Within-participant effects	F-test=25.38 P<0.001	F-test=31.61 P<0.001
Between-participant effects	F-test=1588.91 P<0.0001	F-test=3743.267 P<0.0001
Pairwise comparison of significance levels for the time difference	Mean time difference =2.33 S.E=0.463, P<0.0001 95% CI (1.398-3.269)	Mean time difference= 3.60 S.E=0.639, P<0.0001 95% CI (2.304-4.887)

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Participation in medical research as a resource-seeking strategy in socio-economically vulnerable communities: call for research and action

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Abstract The freedom to consent to participate in medical research is a complex subject, particularly in socio-economically vulnerable communities, where numerous factors may limit the efficacy of the informed consent process. Informal consultation among members of the Switching the Poles Clinical Research Network coming from various sub-Saharan African countries, that is Burkina Faso, The Gambia, Rwanda, Ethiopia, the Democratic Republic of Congo (DRC) and Benin, seems to support the hypothesis that in socio-economical vulnerable communities with inadequate access to health care, the decision to participate in research is often taken irrespectively of the contents of the informed consent interview, and it is largely driven by the opportunity to access free or better quality care and other indirect benefits. Populations' vulnerability due to poverty and/or social exclusion should obviously not lead to exclusion from medical research, which is most often crucially needed to address their health problems. Nonetheless, to reduce the possibility of exploitation, there is the need to further investigate the complex links between socio-economical vulnerability, access to health care and individual freedom to decide on participation in medical research. This needs bringing together clinical researchers, social scientists and bioethicists in transdisciplinary collaborative research efforts that require the collective input from researchers, research sponsors and funders.

keywords research ethics, clinical trials, informed consent, developing countries, vulnerable populations, equity, health inequalities

Introduction

Ensuring free decision-making when deciding to be part of medical research is a complex subject, particularly in socio-economically vulnerable communities. For instance *comprehension*, one of the cornerstones of the consent procedure may be impaired by illiteracy (Chaisson *et al.* 2011), as well as by a lack of consideration for the local socio-cultural context when informing potential study subjects (Tekola *et al.* 2009; Bull *et al.* 2012; Vreeman *et al.* 2012). But in addition to the information provided during the consent process, other factors may influence people's decision to participate in research, possibly limiting the importance of the informed consent process.

In a recent anthropological study in a semiurban setting in Burkina Faso, Pare Toe *et al.* (2013) reported that

most parents of children enrolled in a malaria paediatric clinical study had taken the decision of participating before starting the informed consent process. Their individual decision was based on information that informally spread through the community and was mainly motivated by the possibility of accessing free and good quality health care during the study period.

The study raises the question whether this also occurs in other African contexts and trials and how these findings relate to potential risk in research participation and to free decision-making. We discussed this question within the Switching the Poles Clinical Research Network (http://www.itg.be/itg/GeneralSite/Default.aspx?L=E&WPID=705&MIID=670, last accessed on 17th August 2014; Tinto *et al.* 2013). This network brings together research institutions from South-East Asia, sub-Saharan Africa and Latin America, with the objective of developing clinical research policies that are compliant with appropriate ethical and methodological standards and that are feasible in resource-constrained settings and programmes. Since the start of the network's activities in 2008, the informed consent process in vulnerable populations was identified as a major challenge by all members, and this resulted in the Institut de Recherche en Science de la Santé (IRSS)/Centre Muraz (Burkina Faso) taking the lead on this topic and carrying out the above-mentioned study (Pare Toe *et al.* 2013).

Besides the IRSS/Centre Muraz, the institutions that participated in the discussion leading to this manuscript were the Medical Research Council Unit (The Gambia), Rinda Ubuzima (Rwanda), the Institute National de Recherche Biomédicale and the University of Kinshasa (DRC), the Centre de Recherches Entomologiques de Cotonou (Benin), the Addis Ababa University School of Public Health (Ethiopia) and the Institute of Tropical Medicine (Belgium).

Clinical research and access to medical benefits

All the participating researchers agreed that in settings with inadequate access to health care, the opportunity of receiving free medical care is often a strong incentive to participation in clinical studies and may result in 'pro-active strategies' for being recruited, independent of the researchers' best efforts to accurately inform potential participants and to underline the experimental nature of the study.

In The Gambia, for instance, exhaustive information about new trials is carefully 'cascaded' through the community hierarchy. The study is first introduced to the village heads (the '*Alkalo*'), who subsequently convey the information to household heads and religious leaders. Additional community sensitisation is organised to provide feedback on findings of previous studies, as well as to introduce the new trial (Afolabi *et al.* 2014). Nevertheless, mothers still actively seek to find out whether their children can be enrolled in any other trials, in order to increase their chances of obtaining the study-related benefits (such as better access to care).

During a study on family planning in Rwanda, women sought out the research site with the specific purpose of being recruited, even without having attended any information sessions in the community or even if knowing that they did not meet the inclusion criteria. The women's willingness to participate seemed to be independent of the detailed information they would later receive during the consent process, as enrolment allowed access to cervical cancer screening and to free testing and treatment for sexually transmitted infections.

In Ethiopia, researchers observed high levels of implicit expectation from research at personal and community level among residents in rural and socio-economically poor communities. In a recent qualitative assessment conducted in the rural area of Butajira, members of the community expressed their disappointment about a prospective cohort study, as part of the community felt excluded from the benefits allocated to the households included in the cohort, that is medical and school support for children. The project data collectors also iterated that poor rural households tended to consent to participate in the research more rapidly than those with higher socio-economic status.

During a prospective cohort clinical study conducted in lagoon area in Benin, (Nahum *et al.* 2007) many parents who had initially refused to consent for their children, at a later stage reported to the study team, volunteering for recruitment. The researchers observed that this change of attitude was linked to the wish to access the free care benefits provided to recruited children.

In such poor communities, besides the personal benefits, trial participation may be seen as an opportunity for other family members to access better health care. In a malaria study conducted in Kinshasa (Muhindo *et al.* 2013), for instance, some mothers reportedly attempted to obtain additional concomitant medications for recruited children, which in reality they intended to use for some of their sick but not recruited children. The view of the clinical study as a means to access to health benefits is echoed by the observations of researchers in the DRC, who reported a 'selective recall' of the informed consent information: many potential participants focused on the fact that the study team would take care of adverse events and medical problems occurring during the study, while they tended to ignore the

experimental nature and the potential risks attached. In addition, participants from socio-economically vulnerable communities, for example Kasaï province of DRC, are reported to decide on trial participation primarily or solely on the trust they place in their medical caregivers, that is nurses and doctors, believing they will always make the best individually tailored decision for them.

Beside the direct medical benefits, monetary reimbursements for the travel to the study clinic for scheduled and unscheduled study visits also are an incentive for trial participation, as observed by researchers in Burkina Faso, Rwanda, Benin, Ethiopia and DRC. In DRC, this also applied to the reimbursement of food expenses incurred during a study visit or the period of hospitalisation as part of the study. Researchers even noticed that some parents seemed unsatisfied when the trial team announced that their child had successfully completed the follow-up, potentially because of the end of the benefits. Noteworthy, these monetary reimbursements had been approved – and in some cases explicitly required – by the concerned Ethics Committees(s) that considered them fair, that is not representing an undue inducement. The researchers' observations, however, show that for individuals and families living in a disadvantaged socio-economic situation, they were still an incentive to participate. From this perspective, trial participation can be seen as a strategic choice based on a 'risk-benefit assessment' that goes beyond the purely medical and technical aspects of the research.

Informed consent in vulnerable communities: a way forward?

Overall, these anecdotal observations in different settings in sub-Saharan Africa seem to confirm that in socio-economically vulnerable communities, the decision to participate in research is often taken prior to and irrespectively of the contents of the informed consent interview, and it is largely driven by the opportunity to access free and/or better quality care and other indirect benefits.

Populations' vulnerability due to poverty and/or social exclusion should not lead to exclusion from medical research and, as such, research is most often crucially needed to address their specific health problems. The goal therefore is to strive for a balance between the risk of exploitation and the relevance of the research implemented in these populations (Ravinetto *et al.* 2013). To reduce the possibility of exploitation, explorative research is ongoing in our network, addressing certain challenges related to illiteracy and poor comprehension in the informed consent process, for example the development of multimedia tools for delivering the informed consent information (Afolabi *et al.* 2014), or of context-adapted assessments of understanding before confirming enrolment (Saidu *et al.* 2013; Afolabi *et al.* 2014). However, achieving full comprehension is essential but not sufficient to secure the freedom to decide, as in many contexts, the risks related to the research intervention –even if well explained and well understood – are overshadowed by the risk of not being included in the research and losing the related benefits. In other words, for these vulnerable communities, the study-related benefits (including, but not limited to, free access to quality health care during the study period) remain a strong incentive to study participation, irrespective of the accuracy of the informed consent procedure and despite other local cultural concerns (Peeters Grietens *et al.* 2014). As suggested, the participation in the trial becomes a pro-active strategic choice to secure otherwise unavailable health and non-health resources, and it is not necessarily based on poor comprehension of the study risks, but on a 'risk-benefit assessment' that takes into consideration factors other than those usually considered in the protocol design.

There is therefore the need to further investigate the complex links between socio-economical vulnerability, access to health care and individual freedom to decide on participation in medical research. This goes beyond the simple improvement of the informed consent procedure and requires an interdisciplinary approach that includes clinical researchers, social scientists and bioethicists, as well as the collective input from researchers, Ethics Committees, sponsors and funders.

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Evaluation of the effectiveness of a multimedia consent tool among low literacy research participants in The Gambia: a randomised controlled trial

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Abstract

Objective: To compare the effectiveness of a novel multimedia consent tool with standard 'written' informed consent among participants with low literacy in a clinical trial.

Methods: A multimedia consent tool and a digitised audio comprehension questionnaire were previously developed and evaluated in a Gambian research population. Individuals eligible to be recruited in a malaria drug trial were randomised to receive the information for their informed consent either through the multimedia tool (intervention) or the 'standard' procedure (control). Assessments of participant comprehension in both study arms were done at baseline and follow-up visits using the digitised audio questionnaire. Acceptability and ease of use of the multimedia tool were assessed using qualitative method.

Findings: The multimedia tool was clear and easy to understand for most participants (70%) in the intervention arm. Participants in the intervention arm had significantly higher comprehension scores than those in the control arm at baseline and follow-up visits. Higher comprehension scores were associated with being a male participant (p=0.03), resident in a peri-urban area (p=0.02) and having basic formal education (p=0.005). Male participants (OR = 0.29, 95% CI: 0.12-0.70, p=0.006), living in Basse (OR= 0.33, 95% CI: 0.13-0.82, p=0.017) remained independent predictors of comprehension after controlling for the effects of other co-variables. Survival analysis showed that participants in the intervention arm took longer time to drop to 50% of the baseline comprehension score than those in the control arm (hazard ratio 0.22, 95% CI: 0.16-0.31).

Conclusions: The multimedia tool significantly improved the comprehension and retention of consent information compared to the 'standard' consent procedure. Further research is needed to compare the tool with conventional consent method in other sub-Saharan Africa settings.

Introduction

Many clinical trial participants in sub-Saharan Africa including The Gambia often show limited understanding of study information given during informed consent. This is largely due to poor literacy among potential study participants and difficulty in providing an information sheet in the local languages because the latter lack standardised writing formats (1, 2). International ethical guidelines (3, 4) require that informed consent must be given in a manner that engenders comprehension by an individual to voluntarily decide on study participation. The current Declaration of Helsinki emphasises that special attention should be given to the specific information needs of potential participants and to the methods used to deliver the information (4). This suggests that study information must be provided in a medium and language understood by a potential participant. However, informed consent documents are usually written in the official national language, often one of the common international languages. In countries such as The Gambia where local languages do not have a standardised writing format, the approach of translation of informed consent documents (to the local language) and back-translation (to the national language) to check consistency, is not only impractical but also less accurate (2).

Comprehension of consent information is essential for protecting participants' rights and for complying with the principles of good clinical practice in clinical trials. In sub-Saharan Africa, where an increasing number of clinical trials are conducted among populations that are vulnerable to exploitation because of poverty, illiteracy, social exclusion or poor access to health care(5, 6). Illiterate participants are particularly vulnerable to research exploitation because of their inherent poor comprehension of research concepts which undermines the freedom of informed choices and jeopardise giving a truly informed consent (5). Improving comprehension of the study information is therefore extremely important and may be achieved by exploring new approaches that ensure participant comprehension and ultimately lead to obtaining truly informed consent in this population.

Multimedia consent tools have been reported to be effective in communicating crucial research information in developed countries (7-9). Empirical studies also suggest that a multimedia tool could serve as an alternative medium for delivering study information to vulnerable groups (10, 11). Nevertheless, the effectiveness of multimedia consent tools have not been determined among low literacy clinical trial participants in Africa.

We previously developed and validated a multimedia tool for delivering study information to clinical trial participants (12) and a digitised audio questionnaire for assessment of comprehension of informed consent in The Gambia (13). We now report the implementation of the multimedia tool, its acceptability, ease of use and effectiveness among Gambian participants enrolled in a malaria drug trial.

Methods

Study design, participants and recruitment

This randomised controlled trial was conducted in Basse and Jahaly provinces in the Upper and Central River Regions of The Gambia respectively, from 15 August 2013 to 12 March 2014. Most residents in the study areas are subsistence farmers, and the literacy rate among adults was about 50% (14). The trial was nested within a parent study (PRINOGAM) which is an open-label four-arm treatment trial aimed to determine the optimal dosage of primaquine required for gametocytocidal and transmission blocking effects in asymptomatic malaria carriers treated with dihydroartemisinin-piperaquine. (ClinicalTrials.gov NCT01838902). Participants in the parent trial were ≥1 year of age, and were seen at Days 0 (the day of inclusion), 3, 7, 14, 21, 28, 35 and 42.

To be eligible for the multimedia trial, participants must be eligible for the parent trial; speak and understand any of the three major Gambian languages (Mandinka, Fula or Wolof); should not have obvious communication, visual or cognitive impairment.

Sample size

A systematic review showed that comprehension levels on basic research concepts among most African study participants averaged 47% (1). We estimated that a study with 90% power for detecting a 20% difference at 5% significance level (two-sided) between the intervention and control arms would require 137 participants in each arm. Adding a 10% attrition rate, an approximate sample size of 150 participants was required in each group.

Randomisation

An independent statistician used RANDI3, (http://dschrimpf.github.io/randi3/), a web-based open source application to generate the randomisation list for each trial site. Participants were stratified by age groups and gender. Randomisation was done on a 1:1 ratio across intervention and control arms with a block size of four.

Interventions

Multimedia consent tool

The development and validation of the multimedia tool and digitised comprehension questionnaire have been reported elsewhere (12, 13). Briefly, the multimedia tool contained information in the PRINOGAM consent document which was written under the following headings : *introduction, reason for the study, what is Glucose-6-Phosphate Dehyrogenase deficiency (G6PDd), how to take part, what would happen if one took part in the study, what blood tests would be done, what are the side effects and possible risks of taking part, potential benefits, would taking part in this study be kept confidential, who has reviewed this study, who can be contacted if one has questions?* The messages in each section were graphically translated into a context-specific visual story. A multimedia expert recorded the stories acted by members of the clinical trial team after undergoing several training and rehearsals. Audio-translation of the information was done in the three Gambian languages and then recorded as voice-overs on the video. Symptoms of adverse events of study drugs like headache, diarrhoea, passage of dark-coloured urine which could not be adequately captured in the role-plays were graphically represented with animations(12). The tool was tailored

to the cultural and linguistic diversities of the Gambian populace and its potential to improve comprehension of informed consent was demonstrated in a pilot-study (12). The three language versions were recorded in one digital video disc (DVD) and uploaded onto computer laptops. Following randomisation to the intervention arm of this study, a trained field assistant selected a local language preferred by a prospective participant from the multimedia DVD menu and this was played individually to the participant on a computer laptop in a quiet room at the trial sites. If participants agreed to join the trial, he/she confirmed consent by signing or thumb-printing the consent form. Literate participants confirmed consent by signing the consent form while non-literate participants provided a thumb-print on the consent form in the presence of an impartial witness.

Digitised audio informed consent comprehension questionnaire (DICCQ)

Our previous work showed that DICCQ is a reliable and valid tool to measure comprehension of informed consent among Gambian trial participants (13). It is a 26-item audio questionnaire consisting of a combination of closed ended, multiple choice and open ended question formats. The operational definition of comprehension in DICCQ includes 'recall' and 'understanding' (15), where 'recall' is measured by success in selecting correct answers to the closed ended and multiple choice question items and 'understanding' is measured by correct interpretations or responses to the open-ended question items.

Control arm

The control arm in this study employed the current 'standard' practice accepted by the ethics committee in The Gambia for presenting clinical trial information to potential participants (16). As there is no acceptable written version of the local languages, experienced field staffs who are native speakers of the major local languages were trained by the study's principal investigator on the correct interpretation of the contents of English version of the participant information sheet. The trained staff delivered the study information verbally to the prospective participants during informed consent discussion. The procedure described above on signing or thumb-printing the

consent form was also done for the participants in the control arm (2, 17).

Primary outcome: Comprehension of consent information as measured by the total test scores of participants who succeed in selecting correct answers to the closed ended and multiple choice question items and give correct interpretations or responses to the open-ended question items on DICCQ at Day 0 visit.

Secondary outcomes: Comprehension of consent information as measured by total test scores of participants who succeed in selecting correct answers to the closed ended and multiple choice question items and give correct interpretations or responses to the open-ended question items on DICCQ at Days 7,14,21 and 28 after Day 0 visit .

Data collection

Participants were seen for a total of seven times during the parent trial. The randomisation to the multimedia arm of the nested trial occurred at Day 0, at the same time when randomisation to the treatment arm was done in the parent trial. A first comprehension assessment was done at Day 0 and at subsequent visits, i.e. Days 7, 14, 21 and 28, using DICCQ. In addition, focus group discussions (FGD) were held among randomly selected participants from the enrolment register (n=119) during the Day 35 visit to explore their 'actual' understanding of the parent trial. Acceptability and ease of use of multimedia tool were also explored during the FGD sessions. Ten FGD sessions were held in Basse while six sessions were held among Jahaly participants due to the relatively small number of participants at Jahaly site. Seven to eight men and women were invited for each session. The FGD participants were segregated by gender to allow free expression of views. A purpose-designed FGD guide was used to facilitate these sessions (Supplementary Table S1).

Statistical analysis

Statistical analyses were conducted using STATA version 12.1 (College Station, USA). Because the data were not normally distributed, we calculated the median participant comprehension scores and inter-quartile ranges at each visit and compared these across the study arms. The association

between participant characteristics and baseline comprehension scores was assessed using Mann-Whitney U test (2 categories), or Kruskal-Wallis test (>2 categories). A multivariate logistic regression (using comprehension scores dichotomised at the median values with variables selected by a forward-stepwise method) was undertaken to examine which participant characteristics were independently associated with baseline comprehension. Because participants were recruited from two different sites (Basse and Jahaly), we investigated the effect of clustering on participant comprehension levels using mixed-effects model. Survival analysis was used to determine the extrapolated drop in participant comprehension scores beyond the study follow-up. Statistical significance was defined as $p<0.05$.

Focus group discussions

The audio recordings of the FGD sessions were transcribed into English by three translators and the consistency of the English transcription with the local languages was confirmed by another set of independent translators fluent in local languages and English. The transcribed texts were entered into NVivo software version 10.0 and the main themes that emerged were coded line-by-line to elucidate the meanings. The themes were subsequently sorted and collated into categories and sub-categories. The relationships among themes from the two sites were compared, integrated and refined. Final comparisons of themes on understanding of consent information expressed by participants in the multimedia and 'standard' consent groups were illustrated using selected verbatim quotations from the participants. The findings of the FGD and quantitative data addressing similar concepts were triangulated.

Ethical consideration: Approvals were obtained from the ethics committees of the London School of Hygiene & Tropical Medicine, UK and Gambia Government/Medical Research Council Joint Ethics Committee. Written informed consent was obtained from each consenting participant. Participation was voluntary and confidential.

Results

Of 347 participants enrolled in the parent trial, 26 refused to take part (7.5 %) in the multimedia trial. A large proportion of those who refused the multimedia study cited not having time to wait as they had pressing domestic issues to attend. Another 10 participants (2.9%) insisted on having the study information through the multimedia tool without going through the formal randomisation process. These participants most likely knew about the multimedia tool through their friends or family members who were already enrolled in the study. As this would amount to selection bias, these 10 participants were excluded from the trial. A total of 311 participants were enrolled in the study and included in final analysis. Figure 1 shows the participants flow chart.

Excluding the question and answer sessions after each consent interview, the playing time for each language session of the multimedia DVD was 19.4 minutes while the 'standard' consent took about 30-35 minutes depending on the communication skills and experience of the research assistant providing the consent information to the potential participants.

Table 1 showed that there was no significant difference in the demographic characteristics of participants in both study arms at baseline.

There was statistically strong evidence of intervention among male participants (p=0.03), who resided in Basse (p=0.02) and had western education (p=0.005) (Table 2). Participant gender (p=0.006, 95% CI: 0.12-0.70) and domicile (p=0.017, 95% CI: 0.13-0.82) were independently associated with the baseline comprehension after controlling for the effect of other co-variables (Table 3). The median comprehension scores of participants in the multimedia arm were significantly higher than those in the control arm at all time points (Figure 2). The mixed- effects model showed that place of domicile is 0.85 times likely to account for variation in the comprehension levels between Basse and Jahaly participants (p=0.61) (Table 4).

Survival analysis showed that participant comprehension scores dropped more slowly in the intervention arm (hazard ratio 0.22, 95% CI: 0.16-0.31). Extrapolating beyond the study follow-up, the estimated median times to drop to 50% of baseline (Day 0) values, in the intervention and control arms, were 67 days and 40.6 days respectively (Table 5). The economic and financial costs of developing and administering the multimedia consent tool were summarised in supplementary table S2.

Findings of focus group discussions

Participants' ages ranged from 23-47 years. There were more female participants (39/56, 69.6%) at Basse site, while 63.4% (40/63) of Jahaly participants were male. The themes which emerged from the sessions are categorised as follows:

Comprehension of informed consent: There was general consensus that signing or thumb-printing consent forms implied commitment to participate in the research. A participant from Basse said: *'When you put your hand in that paper, then you have promised to be part of the study'*

Right of withdrawal: Understanding the right to withdraw after enrolment generated divergent opinions among the participants. While most participants in the 'standard' consent group strongly felt it was morally wrong for someone to stop participation before the end of the study, the majority of participants in the multimedia consent group stated that participants had freedom to leave the study at any time. A participant in the multimedia group said: '*What we always think is that our doctors will be angry if we leave before the end of the study, but I now know after watching the 'film' that we have freedom to leave at any time, without telling them the reason for this'*.....

Risks and benefits: Participants were unequivocal about the need to provide incentives to motivate them to join and be retained in the study. While the majority considered benefits as free medical care, a minority group described concrete benefits to include provision of fertilisers during farming seasons and sponsorship of their children's education. One of them said:

'*We appreciate all the good things you have done to care for us and our children, but the real help that we expect and will never be forgotten is to give us fertilisers for our crops and train our children to be like you*'...

When asked about their understanding of the risks involved in the trial participation, most participants in the 'standard' group could not mention any. They either said *'I do not know or I forgot'.* On further probe, one participant from Basse said:

'The frequent pricking of fingers (to collect blood) from my child is what I think is bad. At times, I am afraid to bring him to the clinic because of this'...

The participants in the multimedia group were able to give illustrative descriptions of the adverse events of the study medications. Four out of five in one of the sessions described the risks as follows*: 'If one takes the drug, it may cause headache, abdominal pain, vomiting and diarrhoea'...*

When asked about other possible adverse events following the study medication, only one participant in multimedia group in another session remembered 'passage of dark-coloured urine' which he described as urinating '*wonjo'. ' Wonjo*' is a popular local drink prepared from boiling hibiscus leaves in water. The participant likened the dark-red colour of the drink to passage of dark-coloured urine that is associated with haemolysis caused by intake of primaquine in G6PD deficient individuals.

Randomisation: A graphical illustration of the randomisation procedure was given by most participants in the multimedia group; although some participants in the 'standard' group also said randomisation was done to ensure participants had equal chance of participation. A participant in the multimedia group said:

'MRC wants to know the amount of primaquine that will work. Before giving someone the drug, MRC first checked that you are okay before you can take part, you'll be divided into groups , like tossing a coin, to make sure you have equal chance to take part'.....

Acceptability and ease of use of multimedia consent tool

A majority of participants (42/60, 70%) in the multimedia group felt that the pictures, voices, and study information delivered through the computer were clear and easy to understand. However, few of them expressed reservations about the tool. One of the participants in Jahaly said:

'Although I like the (computer) pictures and sounds, I prefer face-to-face talking. I can easily ask (the consenter) questions that are not clear to me and this will make me understand better'.

Another participant from Basse said: '*The Fula man (interpreter) on the computer (video) repeated the same information over and over, and this made everything boring to me'*.....

Discussion

The findings of this trial confirm that the multimedia consent method made study information more understandable to clinical trial participants than the 'standard' consent method. Also, the participants using the multimedia consent tool performed significantly better than participants in the 'standard' consent tool across all study visits.

Participants in the multimedia arm also retained the study information significantly longer than those in the control arm, and even beyond the length of the follow-up for the parent trial which ended at Day 42. Indeed, the median retention time for multimedia group, meaning the time at which participant comprehension drops below 50%, was 67.0 days as compared to 40.6 days in the control group. The latter indicates that those exposed to standard consent procedures would have forgotten half of the information before the end of the parent trial follow-up. This is a remarkable

finding in support of effectiveness of multimedia consent tool not only to improve comprehension but also retain the information for a reasonable period of time.

Although several factors such as education status, place of domicile and gender were associated with participants' comprehension scores at Day 0, only domicile and gender remained significantly associated with it after multivariate analysis. This differs from previous studies which reported level of education as a major independent predictor of comprehension (18, 19). This contrast may be explained by the fact that majority of our study participants had no formal education and this further strengthens the case for the use of interventions like the multimedia tool to deliver study information to low literacy participants.

The multimedia tool was well received by the participants. This became obvious during the recruitment when some participants insisted on being allocated to the multimedia group without undergoing formal randomisation. Also, during focus group discussions, participants expressed their preference for the pictures, sounds and information content of multimedia tool. This finding suggests that the tool has the potential to gain acceptance among participants in other similar research settings.

Our study adds to the emerging body of evidence that multimedia tools can improve participant comprehension as part of the informed consent process in the African settings (10, 11). Research concepts known to be difficult to understand were clearly illustrated in the tool with video and animations. The super-imposed audio narrations in three local languages also explained these concepts without ambiguities. Consequently, in low literacy research settings such as The Gambia, a multimedia tool integrating video, animation and audio narration of informed consent in the participants' local languages can be used an alternative informed consent tool. To our knowledge, no published studies have reported these findings in sub-Saharan Africa. Furthermore, previously reported studies conducted outside Africa adopted simulated study design, but this trial was nested

within a malaria drug trial to avoid the limitations of non-applicability of findings to real clinical trial situations.

One of the study limitations is that our centre has been conducting research projects in The Gambia for more than 60 years and the local populations are familiar with research projects. In other settings where populations are less familiar with research activities, the effectiveness of the multimedia tool may be different.

Also, there was some clustering of participants as about two thirds of participants were recruited in Basse, where the prevalence of asymptomatic malaria infection was higher than in Jahaly, though the two sites share similar socio-epidemiologic features. However, mixed-effects model showed that place of domicile accounted for an insignificant difference in participant comprehension, suggesting an insignificant clustering effect.

Conclusions

Multimedia tools improve participant comprehension and retention of consent information in low literacy settings in The Gambia. The tool addresses the fundamental ethical challenges of informed consent by improving participant comprehension. It has been demonstrated to be an acceptable medium for delivering clinical trial information to low literacy participants.

Contributors: MOA conceived, designed, conducted the study and drafted the manuscript. KB, UDA, BK, EBI, RMR, NA, HJL, NM and DC made substantial inputs to analysis and interpretation of data, revision of the article and approving the final version of the manuscript.

Competing interest: All authors declare no conflict of interest

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Result Legends

Figure 1: Participants flow chart

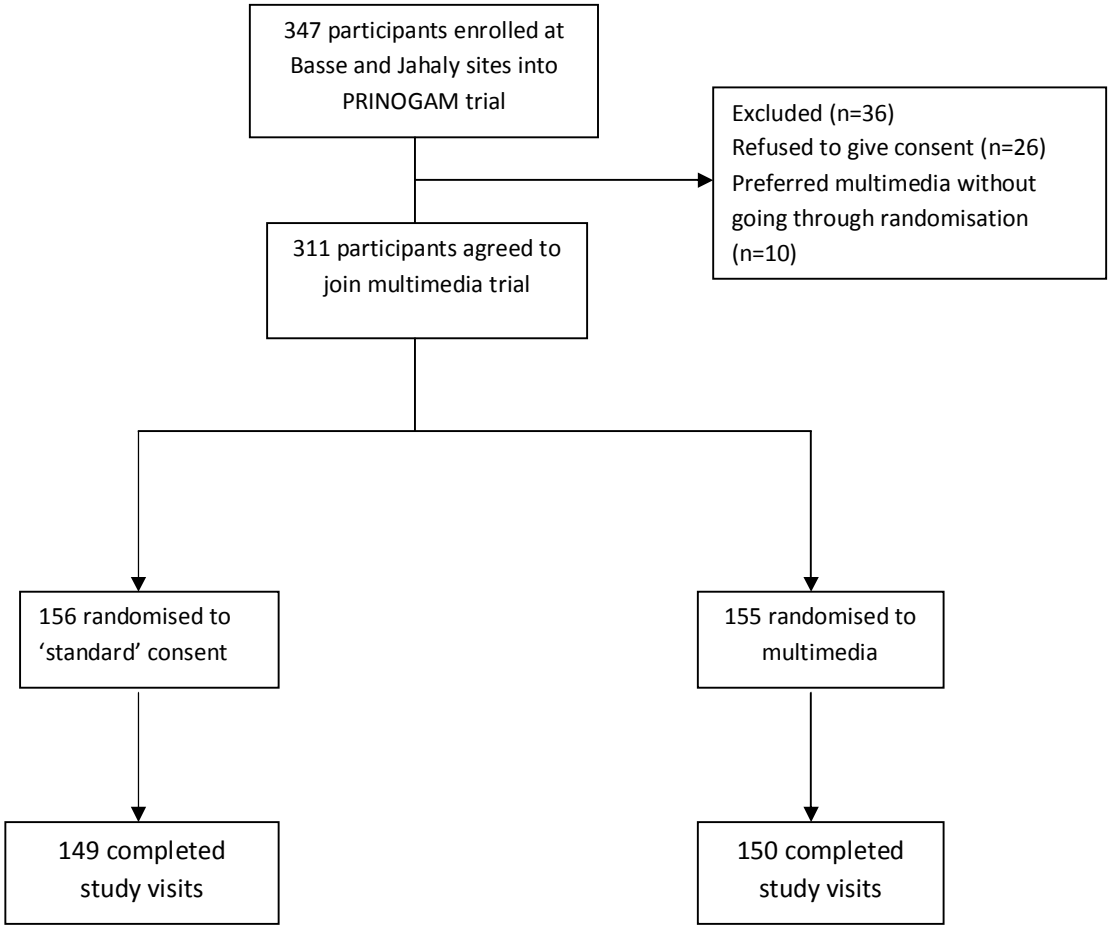


Table 1: Socio-demographic characteristics of study participants, Gambia, 2014

Characteristics	Study arms		
	Multimedia (n=155)%	Standard consent (n=156)%	Significance
Age group (years)			p=0.247
18-25	23(14.8)	35(22.4)	
26-33	50(32.3)	44(28.2)	
34-41	40(25.8)	35(22.4)	
42-49	28(18.1)	34(21.8)	
>49	14(9.0)	8(5.1)	
Gender			p=0.692
Female	96 (61.9)	100 (64.1)	
Male	59 (38.1)	56(35.9)	
Domicile			p=0.443
Basse	102 (65.8)	109(69.9)	
Jahaly	53(34.2)	47(30.1)	
Ethnicity			p=0.666
Mandinka	75(48.4)	81(51.9)	
Fula	66(42.6)	62 (39.7)	
Wolof	8(5.2)	5 (3.2)	
Sarahule	5(3.2)	7(4.5)	
Manjago	1(0.7)	0(0.0)	
Education group			p=0.097
Had Western* education	41(26.5)	29(18.6)	
Had no Western education	114(73.5)	127(81.4)	
Religious affiliation			p=0.995
Islam	153(98.7)	154(98.7)	
Christianity	2(1.3)	2(1.3)	
Previous clinical trial participation			p=0.071
Yes	14 (9.0)	28(18.0)	
No	140(90.3)	127(81.4)	
I don't know	1(0.7)	1(0.6)	

**For the purpose of this study, western education is defined as having basic formal education based on English curriculum i.e. completion of primary school education with or without three years of junior secondary school education*.

Table 2: Association between participants' characteristics and baseline comprehension scores, Gambia, 2014

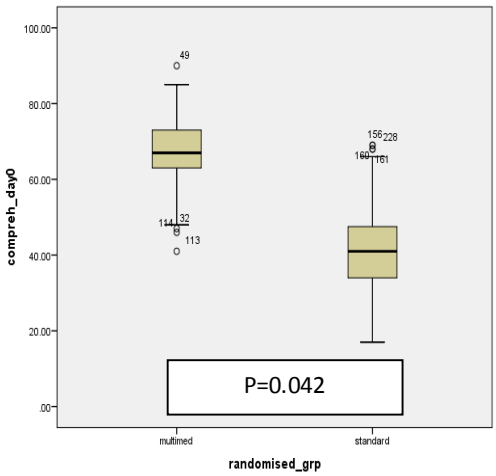
	Study arm		
Characteristics	**Multimedia (n=155) Median score (IQR)**	**'Standard' consent (n=156) Median score (IQR)**	**P value**
Age group (years)			0.5407*
18-40	63(68,73)	33.5(40.5,46.5)	
≥ 41	61(65.5,72)	35.5(43,53)	
Gender			**0.032***
Male	65 (68, 73)	38(45,51)	
Female	61 (67, 72)	33(39,46)	
Place of domicile			**0.0213***
Basse	63(67.5,73)	39 (44,51)	
Jahaly	61(67,74)	30 (33,38)	
Education status			**0.0049***
Had no Western education	61 (66.5,72)	33(40,48)	
Had Western education	65 (70,74)	40(45,47)	
Language of assessment			0.918‡
Mandinka	64(67,73)	33(41,47)	
Wolof	62(67.5,73)	35(42,50)	
Fula	61(69,74)	30(38,45)	
Previous clinical trial participation			
Yes	63(67,73)	34(41,48)	0.212‡
No	65(69,72)	33(40,47)	
I don't know	48(48,48)	43(43,43)	

*Mann-Whitney U test, ‡Kruskal-Wallis test

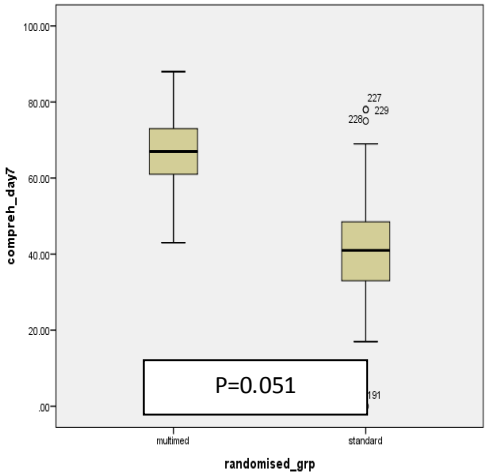
Table 3: Multivariate logistic regression analysis of predictors of comprehension, Gambia, 2014

	0dds ratio	95% CI	P value
Age group	1.41	0.62-3.21	0.42
Gender	0.29	0.12-0.70	**0.006**
Domicile	0.33	0.13-0.82	**0.017**
Education status	0.67	0.23-1.93	0.46
Assessment language	0.56	0.29-1.08	0.084
Previous trial participation	1.07	0.42-2.73	0.89

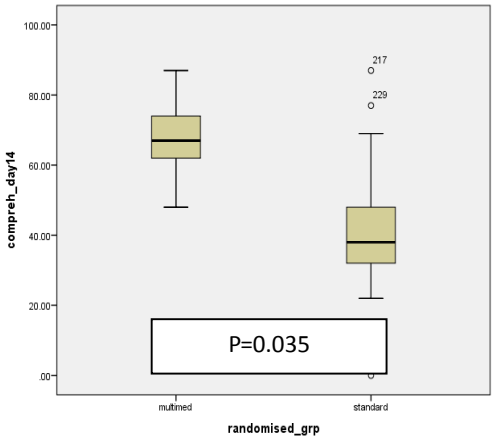
Figure 2: Box-plots showing comprehension scores of participants in multimedia and 'standard' consent arms at Days 0, 7, 14, 21 and 28



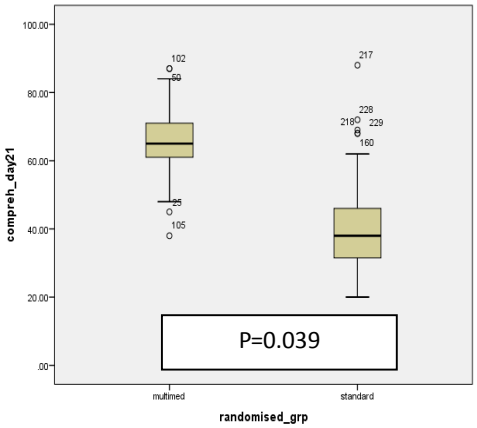
Day 0



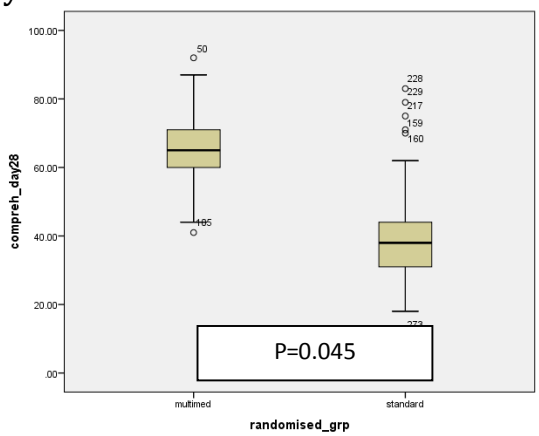
Day 7



Day 14



Day 21



Day 28

Table 4: Mixed-effects model estimating domicile effect on participant comprehension, Gambia, 2014

Comprehension level	Odds ratio	S.E	p	95% CI
Domicile	0.85	0.28	0.613	0.45-1.60
***Sigma_u**	1.91	0.99		0.69-5.31
‡rho	0.53	0.26		0.13-0.90

S.E= Standard error, Likelihood ratio test statistic=107.9, p=0.61

*Sigma_u is a measure of how much participant comprehension scores vary between Basse and Jahaly sites

‡rho is a measure of within-site correlation

Table 5: Extrapolated time to drop in participant comprehension scores to 50% of Day 0 values, Gambia, 2014

	Multimedia	'Standard' consent
Median drop time	67.0 days	40.6 days
Mean drop time	67.2 days	42.2 days
	95% CI: 65.9-68.5	95% CI: 40.5-43.8
Standard error	1.037	1.041
	95% CI: 65.0-69.0	95% CI: 39.0-43.0
Log rank test (with continuity correction	M=16.304	**p<0.0001**
Hazard ratio	0.22 (95% CI: 0.16-0.31)	