How Informed is Informed Consent? Experiences of Research Participants at the KAVI-Institute of Clinical Research, Kenya

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Summary

INTRODUCTION

Informed consent (IC) is a key yardstick for the ethical and legal conduct of clinical research involving human subjects. However, the extent to which it meets its obligations in low-income settings remains under-examined. This study explored the views and experiences of informed consent among research participants at the KAVI-Institute for Clinical Research, Nairobi, Kenya.

MATERIALS AND METHODS

A mixed-methods study was conducted between March and June 2014. Participants were drawn from six selected KAVI-ICR studies. Data collection involved a survey questionnaire with 164 participants and in-depth interviews with 44 participants purposively selected from the survey questionnaire respondents. Descriptive statistics via SPSS and thematic analysis via Atlas *Ti* were used, for quantitative and qualitative data analysis respectively.

RESULTS

The majority of participants had learnt about the KAVI studies from friends (41%) and community mobilisers/ peer educators (47%). The information relayed by these relations regarding participation had led some participants to reach their decisions before undergoing the informed consent process. All participants reported attending information meetings, passed the assessment of understanding tests, and autonomously gave their written consent. Incomplete understanding of research concepts such as randomization and associated terminologies, placebo, and vaccine-induced positivity were expressed.

CONCLUSIONS

Beyond understanding the information received before enrolment, participants' decisions are shaped by individual and community factors as well as trust relations with trial staff and own friends. There is, therefore, a need for innovative approaches to implementing and evaluating informed consent in low-resource settings.

Keywords: *Informed consent, volunteerism, clinical research, information, understanding, decision-making, vaccines*

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Introduction

Informed consent (IC) remains a key yardstick for ethical conduct in clinical research involving human subjects. Rooted in the Nuremberg Code, the Helsinki Declaration, the Belmont Report, and other codes of conduct, informed consent is a widely recognised legal, moral and regulatory requirement for the conduct of clinical research involving human subjects.(1–3) As a

principle and a process, informed consent is actualized through adequate information disclosure to individuals with legal and mental capacity to understand the information provided, can exercise decision autonomy, and offer voluntary participation. (4)

Despite the known goals of informed consent, its implementation faces ethical, cultural, and practical complexities.(5–7) In many low-income settings, including sub-Saharan Africa, rarely are the goals met.(8,9) Evidence has shown participants to have incomplete understanding of the many facets of informed consent (9,10) and yet claim to understand. These discrepancies are due to individual and community-level factors such as low literacy, poor socio-economic status, and cultural impediments, as well as clinical trial staff competencies.(11–15) As a result, efforts to improve informed consent delivery and efficacy in Kenya and other low-income settings, have included simplifying and translating research information into local languages.(16–19)

Studies conducted among populations on the Kenyan Coast have shown challenges in obtaining informed consent to include: language barriers, mistrust, and concerns about research procedures such as blood sampling.(12,13,20) Follow-up studies have recommended community engagement as a means of improving the quality of informed consent, simplifying research information, and tiered information delivery that starts from the community before eventual consenting.(21,22)

The studies discussed above, highlight challenges and potential opportunities for improving informed consent delivery in low-income settings. However, other studies have also argued for the assessment of participants' perceptions and experiences on how aspects such as accuracy of transfer of information, voluntariness, and safety are accomplished in the clinical research process can help researchers meet ethical obligations.(23)

In this paper, we describe research participants' experiences from the point of learning about the KAVI studies, through to the informed consent process and the role of social-relational factors in their decision-making to participate in clinical research. The findings are based on a mixed-methods phenomenological study that explored the perceptions of clinical research participation among volunteers at the KAVI-Institute of Clinical Research in Nairobi, Kenya.

Materials and Methods

Setting

The study was conducted at the KAVI-Institute of Clinical Research sites in Nairobi, Kenya. The sites are KAVI-KNH housed at the University of Nairobi, Faculty of Health Sciences at the Kenyatta National Hospital, and KAVI-Kangemi within the Kangemi County Health facility. For two decades, KAVI-ICR has conducted Phase 1 HIV vaccine trials, drug trials, observational epidemiologic studies, an Ebola vaccine trial, and several other trials including the COVID 19 vaccine trials underway. Efforts to improve clinical research practise have included community engagement strategies and assessment of individuals' understanding of trials' information before securing written consent as reported in other research settings.(24)

Sampling

The sampling of participants and data collection process were sequentially conducted, giving prominence to the qualitative component.(25) Initially, quantitative data were collected with 164 participants from the six selected studies via a survey questionnaire. The results from the qualitative data were used to refine the in-depth qualitative interview tool and guide the purposive sampling of 44 willing participants to provide in-depth rich accounts of their experiences.

Participants

Participants were male and female and were drawn from four phase 1 HIV vaccine trials (B002, B003, S001and HIVCORE); one PrEP study; and a Protocol J observation study Participants' ages ranged from 18-49 years. Participants enrolled in the vaccine trials were low-risk and HIV uninfected, while Protocol J had a mix of low- and high-risk uninfected, and HIV-positive participants. Participants from the PrEP study were classified as high-risk and all were seronegative. Recruitment was undertaken with the help of trial staff who provided contacts to the lead author for follow-up interview scheduling. The inclusion criteria for participants included all those who had been enrolled in the selected studies and were willing to be interviewed in this study.

Data collection

The study was conducted between April and September 2014. The data collection involved the lead author with the support of three experienced social science research assistants. Quantitative data were collected using a survey questionnaire. The questionnaire explored the socio-demographic and economic characteristics of the participants. Additionally, participants' experiences and perceptions of various levels of research participation were captured using closed-ended questions. Qualitative data were collected via in-depth interview tools. Participants were asked to describe their experiences from the point of learning about the studies at the KAVI-ICR, various forms of information received, and how it had shaped their decision making to participate in the studies, including their overall experience with the informed consent process.

Before the data collection, the study tools were pre-tested with ten female participants enrolled in a double-blind randomized trial that gave a monthly treatment of Metronidazole and Miconazole Co-formulated suppositories versus placebo for preventing vaginal infections, at the Kariobangi Sex Workers Outreach Program (SWOP) clinic in Nairobi. Responses were reviewed to ensure tool effectiveness.

Both the administering of the survey questionnaires and in-depth interviews were conducted in private and quiet rooms at the trial sites. English and Kiswahili languages were used according to the participants' preferences. The average time for administering either the survey questionnaire or the in-depth interviews was one hour. All in-depth interviews were audio-recorded and interview notes were taken appropriately.

Data analysis

Survey data were cleaned and entered into SPSS Version 17.0 for descriptive statistical analysis. Audio recorded in-depth interviews were transcribed verbatim and translated into English where the Kiswahili language had been used. All transcripts were read in their entirety for a holistic sense of the interview content and themes to inform the development of the codebook. The transcripts were manually coded and subsequently entered into Atlas Ti for management and analysis. Meaning units reflecting individuals' experiences were outlined and transformed into sensitive statements for the synthesis of the general structure of the participants' experiences.

Ethical considerations

Study ethical approval was obtained from the Kenyatta National Hospital Ethics Research Committee (KNH-ERC- ref P298/05/2013). All study participants gave their written consent before data collection. Participants' confidentiality was safeguarded by separating individual identities from the data and assigning identifiers for ease of retrieval and analysis. A sum of Kshs.500 was reimbursed to participants to cover their transport costs to and from the research sites.

Results

Participants' characteristics

A majority of the participants were of low socio-economic status and were either unemployed or daily wage earners engaged in petty businesses. Their ages ranged from 20 to 40+ years. There were 112 (68%) males and 52 (32%) females, thus reflecting the sex differences of the volunteers who enrolment in the clinical studies from which we recruited our participants.

Their sexual orientation ranged from self-identified heterosexual (90%), homosexual (6%), and bisexual (4%). Table 1 describes the participants' socio-demographic characteristics.

Learning about the KAVI-ICR studies

The most common sources of information about trials taking place at the KAVI-ICR were friends (41%) and the KAVI-ICR community mobilizers/peer educators (47%). A few participants reported learning from trial staff following random walk-ins and VCT counsellors outside of KAVI that were aware of the ongoing recruitments. More than half of the PrEP, B002, and S001 participants had learned from friends; while those in the B003, HIVCORE, and Protocol J studies, were from the community mobilisers/peer leaders. Table 2 summarizes the sources of information by study type, sex, and marital status.

Table 1:

Socio-Demographic Characteristics of the Participants

Characteristics	**n =164 (%)**
Age in years (mean = 29.5; median = 29)	
20 – 29	84 (51%)
30 – 39	71(43%)
40+	9 (6%)
Sex	
Male	112 (68%)
Female	52 (32%)
Marital status	
Single	86 (52%)
Married	63 (38%)
Widowed	6 (4%)
Divorced	9 (6%)
Educational attainment	
Primary incomplete	6 (4%)
Primary completed	50 (31%)
Secondary complete	63 (38%)
College/University	45 (27%)
Occupation/Employment	
Unemployed	20 (12%)
Student	12 (7%)
Casual worker	56 (34%)
Small Business	37 (23%)
Permanently employed	39 (24%)
Monthly income (Kshs.)	
None	32 (20%)
Below 5,000	41 (25%)
Between 5,000-10,000	46 (28%)
Above 10,000	45 (27%)

Table 2:
Participants' Learning about KAVI by Study Type and Demographic Characteristics

	Study Name	Friends (n = 68)	Relatives (n = 4)	Community Mobilizers/ Peer leaders (n = 77)	Other (n = 15)	Totals N = 164
Study	B002	18	2	15	1	36
	B003	14	0	26	1	41
	HIV-CORE 004	13	1	15	6	35
	PrEP	9	0	2	2	13
	Protocol J	3	1	10	5	19
	S001	11	0	9	0	20
Sex	Female	19	1	30	2	52
	Male	49	3	47	13	112
Marital status	Single	36	3	41	6	86
	Married	26	1	30	6	63
	Divorced	4	0	3	2	9
	Widowed	2	0	3	1	6

The content and detail of information shared about trial recruitment varied from one individual to another, depending largely on who had contacted them. For instance, for those recruited by peer educators, theirs was just an invitation to attend information seminars, while those contacted by friends additionally included study-specific information on what to expect when joining a clinical study, as explained in the following two excerpts:

The peer educator asked if I had ever participated in any trials with KAVI but I told him I did not even know what KAVI was. He directed me to a venue in the community where I found doctors teaching and I was impressed. (36-year old female, B003 trial participant).

A friend of mine told me there was research for high-risk people; they will collect blood samples and monitor our health, we should try out (33-year old MSM, Protocol J Participant)

There were variations in the interpretations of information received among participants. For example, transport reimbursement was seen as payment, as detailed below:

My friend told me that KAVI was conducting research and needed people to volunteer. Those participating were to be paid. There were to be 24 visits and we were to receive the drug in the process; we were also to receive phones and 400 Kshs worth of airtime per month (31-year old MSM, PrEP trial participant)

Information received during the seminars

Prior to enrolment, participants across the six studies reported attending a series of meetings, in their communities and at the KAVI-ICR trial sites. These were organized by KAVI-ICR peer educators and facilitated by the KAVI-ICR community liaison staff. At the community level, participants received general HIV information, about KAVI-ICR and its activities; information about the studies, and their inclusion criterion. Those showing interest in learning more about the studies were listed and invited to the trial sites for more sessions. From the participants' perspectives, the information received at the trial sites was broad and detailed in aspects that HIV transmission and prevention; HIV clinical research, development of vaccines, voluntarism, and study-specific information.

Table 3:
Participants' Levels of Understanding Consent Information by Educational Attainment

Education Attainment	Very well	Well	Average	Not well	Totals
Some primary education	4 3.97 (0.00)	3 2.48 (0.11)	0 0.47 (0.47)	0 0.09 (0.09)	7
Completed Primary	18 27.79 (3.45)	23 17.33 1.86)	6 3.29 (2.24)	2 0.60 (3.29)	49
Secondary Completed	40 35.73 (0.51)	20 22.28 (0.23)	3 4.23 (0.36)	0 0.77 (0.77)	63
College/ University	31 25.52 (1.18)	12 15.91 (0.96)	2 3.02 (0.34)	0 0.55 (0.55)	45
Totals	93	58	11	2	164

$\chi^2 = 16.402$, df = 9, χ^2/df =1.82, P ($\chi^2 > 16.402$) = 0.0590

Several participants reported immense learning in the process as explained in the following excerpt:

I learnt a lot because they were teaching

Participants in the vaccine-based studies were advised to avoid pregnancy occurrence as the safety of the unborn babies had not been ascertained. Both male and female participants were therefore required to adopt safe and effective methods of contraception.

A male participant explained:

"They said that once you have received the vaccine, you use a condom every time you have sex to avoid getting your partner pregnant as they do not know how the vaccine will react on the unborn baby." (21-year old male, HIVCORE trial participant)

They also reported learning about the study schedules, benefits of participation, including free healthcare during participation:

".... The consent had information about the vaccine and its benefits, and it contained how our appointments would be and what we had to do when we came, and the amount of blood to be taken". (35- year old female, HIVCORE trial participant)

about the vaccine itself and HIV and how to maintain low-risk behaviour, so I can say that I learnt a lot (22- year old female, B002 trial participant)

Understanding the information

Participants across the six studies reported high levels of understanding as gauged, with ratings ranging from '*very well'* to '*not well'*. More than 56 % of the participants rated their understanding of the information as '*very well',* 35% as '*well',* and less than 8% as '*average'* or limited understanding. A Chi-square statistical analysis, revealed differences in the levels of understanding between individuals that varied significantly with the level of education ($\chi 2$ test; p=0.059) as shown in table 3 below.

Findings from the qualitative interviews revealed that for most participants the field of clinical research and human trials was a grey area. This was evident in their grasp of the various scientific terminologies in use. A B003 study male participant said "*I had never heard of something like a placebo in my life. We were also told that this group and this group will receive this… the placebo is this…., you know."* However, through continued education and engagement with trial staff, participants reported gaining knowledge about vaccine development and the rationale for

conducting human trials. To ensure comprehension, information was packaged and conveyed in English and Kiswahili languages. To improve communication and understanding analogies such as *askari* (*meaning soldiers)* were applied to explain antibody vaccine response, as narrated below:

> *...we understood that there was a vaccine on trial. It had passed two trials; the first one was about safety, ….and it produces antibodies for fighting against the HIV virus… (26-year old male, BOO2 trial participant).*

Despite the high levels of understanding reported, there were instances of incomplete understanding by more than a quarter of participants. These were related to the following aspects: placebo, vaccine, and randomization (n = 30); scientific terminologies (n = 14); false-positive after receiving the trial vaccine (n = 10); and rationale for mucosal sampling (n = 4) and blood sampling (n = 5). Participants in vaccine-based studies and PrEP expressed difficulties in comprehending the randomization groupings and what the terms assigned to each meant.

> *The information I did not understand…was those like A35 40, the groupings like AB, they said we would get the vaccine; they said in group A, everyone would receive a placebo. And the placebo I did not understand (28-year old male, HIVCORE trial participant)*

Participants also expressed limitations in understanding the concept of vaccine-induced seropositivity (VISP), a state in which individuals that receive a trial vaccine could test positive on standard HIV test kits even though not HIV infected. The caution not to take HIV tests outside KAVI had instead raised safety concerns, with some fearing a cover-up by trial staff. Other concerns were on how long the vaccine could remain in the body after participation, a question that the staff could not answer:

> *They said that the vaccine would produce antibodies to HIV. I did not understand why after the vaccination I would not be able to test for HIV anywhere and that it will show I am positive. I also asked for how long the vaccine would remain in the body because you might get injected and it stays in the body for forty years and they did not know yet (25-year old female, HIVCORE trial participant)*

Questions were also raised on the amounts and frequency with which blood was collected. Besides blood, male participants questioned the essence of collecting semen as some feared that perhaps, it was for sale to the sperm banks. The quotes below explain:

> *They were taking a lot of blood…if they could get just a little bit …… blood is usually a lot and we have never been told what they use it for. (29-year old male, S001 trial participant)*

> *I just felt uncomfortable giving the semen. I gave out saliva (26-year old male, B002, trial participant)*

Relevance of the information

Several participants reported gaining new knowledge and understanding about HIV and AIDS, the stages of developing vaccines, and their testing in human populations. One male participant explained how learning about how vaccines currently in use were developed and tested had helped him understand the role of human volunteers in HIV vaccines research as explained

> *They told us the way they got the polio vaccine and that they are doing the same to get the HIV vaccine. Therefore, I wanted to help get the cure. (34-year old male, HIVCORE trial participant)*

The information had also helped counter fears and misgivings initially held about the trials conducted at the KAVI-ICR. Initially, there were fears that the vaccines on trial contained components of the HIV virus. For some these had emanated from rumours in the community about KAVI trial staff plotting with foreigners to infect unsuspecting community members with the virus and that blood was being collected for sale:

> *Some people said that the Wazungu (whites) have come to infect us with the virus … There was no way of knowing if that was true, but we came to realise those were just rumours. (40-year old MSM, PrEP trial participant)*

> *… the outsiders told us that they (KAVI) would take 5 litres of blood, but I learnt that was not the case, though, the amounts varied from one group to another. Like in groups B and C they took 660ml and in group A 540ml. (34-year old male, HIVCORE trial participant)*

For others, the information had given them a sense of preparedness on what to expect at the various stages of research participation as explained below:

> *You will receive a vaccine. It will show if you have soldiers (antibodies) in your body… After receiving the vaccine…others will feel like vomiting, others tiredness and your hand will experience shock when being vaccinated. When they are done they use the other hand for like two times and then go back to the other hand. (24- year old female, HIVCORE trial participant)*

Through engagements with the trial staff, participants were aware that the products on trial did not have the potency of protecting them from contracting HIV and were, therefore, encouraged to maintain low-risk behaviours during participation and after:

> *The information I got during recruitment was good counsel. It was repeated repeatedly, such that even someone who did not understand, could understand that … "receiving the vaccine will not mean that now you are immune to HIV, so abstain or use protection" … I took it seriously. (26-year old S001 trial participant)*

Although participants were upon enrolment expected to remain in the studies till completion, they were also aware that participation was voluntary and that they had a right to decline or terminate their participation at any time. If they chose to participate, they could receive free medical care in the event of falling sick, as explained by a male participant below:

> *They told me the risks of joining the study..... I could withdraw at any time, and I felt secure. They told me, in case of any illness while participating I can walk to the facility for treatment. (22- year old male, BOO3 trial participant)*

Experiences with assessment of understanding (AoU)

All study participants were assessed for their understanding before providing written consent. This was conducted after a series of meetings that were followed by a period of 1-2 weeks to allow participants time to read and review the study information on their own and consult where necessary. The assessment entailed a set of questions posed by study doctors and an expected aggregate of at least eight out of ten correct answers. Those scoring below had an opportunity to repeat the test on a scheduled date. Although this process was to ensure their understanding, for some it had created feelings of anxiety, as it seemed like an examination. One participant explained:

It was like taking exams. Everyone went in and was asked questions. There were ten questions, and if you failed five or four, you repeated, and if you failed two, you would not repeat… I got eight. (48-year old female, B003 trial participant)

It was also noted that the information provided may not have been difficult to comprehend. However, some participants had not taken their time to go through as had been directed by the trials staff resulting in a retake of the assessment as recounted by one female participant:

The document was not difficult. Only, when I took it, I just skimmed through it. That is why I failed the first time. However, when I went back I paid attention and I understood (23-year old female, S001 trial participant)

Overall, participants expressed satisfaction with the consenting process. From the information provided it was clear that they had to meet the given study inclusion criteria and wilfully provide written consent as summarised in the following quote:

It made me feel comfortable... I was not being forced to participate; it was you either know or you do not join the study (22-year old male, S001 trial participant)

Discussion

This paper explored the realities of implementing informed consent in HIV clinical research from the perceptive and experiences of KAVI-ICR research participants, in Nairobi, Kenya. We, therefore, discuss the various aspects of the consent process, while focussing on the information and sources, understanding, and implications on their decision-making to participate. What emerged at the fore was the potential role of friends and peer educators, including general community members, in the recruitment, enrolment, and retention of participants in clinical research studies. The information they provide invariably shapes individuals' perceptions of participation and their decision to participate or not in a given study. Of importance is the likelihood of this group misrepresenting research goals if unequipped with the correct and complete information. The influence of community members, including peer educators, in the recruitment and retention of participants in clinical research studies, has been documented in previous studies.(26,27) From an ethical standpoint, individuals' decisions should happen, following receipt of adequate information from trial staff as per the informed consent requirements.(4) However, for some participants decisions were made at the community level before engaging with the trial staff. These decisions were motivated by potential benefits such as free healthcare and monetary gain through transport reimbursement. Similar findings were reported in a Burkina Faso paediatric malaria trial where more than 70% of parents' decisions about their children's participation were taken at the community level based on information about participation benefits such as free health care to be received while participating.(28) Evidently, social inequalities due to unemployment, poor work opportunities, and limited access to healthcare can influence individuals' decisions before considering the associated risks and burdens of participation.(29)

Implementation of informed consent in poor resource settings remains challenged.(9,15) Low educational statues have been blamed for poor comprehension and grasp of scientific terminologies.(10,13,30) However, findings from this study demonstrate the viability of securing informed consent where the researcher and research subject interactions occur over a series of encounters, as opposed to a single encounter as proven

elsewhere(17,24,31)Additionally, these encounters had allowed for participants to seek clarity on areas of concern while enhancing understanding and recall of research information.(24,31,32) For some, this understanding and recall was demonstrated by their recount of the informed consent process through information seminars, assessment for understanding, and eventually written consent. Other studies have recommended the development and use of culturally acceptable tools(18,33) including community engagement, application of the tiered approach to information delivery.(34) Findings from this study showed the simplification and translation of research material into Kiswahili language to have offered the participants the much needed understanding for their decision-making.

Instances of incomplete understanding of certain facets of research information are not uncommon in clinical research studies where understanding is presumed following written consent.(15,35) Recent studies in Kenya and Uganda have shown people to offer their participation despite their incomplete understanding.(13,14,36) Aspects of incomplete understanding by participants included randomization(37) and vaccine-induced seropositivity, a state in which participants that have received an HIV trial vaccine test HIV- positive even when they are uninfected.(38) Although this phenomena is not uncommon, the caution by trial staff to participants to avoid taking routine HIV tests elsewhere had resulted in fears of a possible hidden agenda. Vaccine safety concerns, particularly on 'how and why' one could otherwise test positive if indeed not infected, have been expressed in other studies. (33,39,40) Also revealed in the study findings were apprehensions around the collection of human biological samples. Although blood specimens are routinely collected for screening diseases such as malaria, HIV and even for transmission to patients, there were doubts on why the trials needed it as some feared commercialization. Undoubtedly, questions raised by participants and rumours in their communities, point to persistent fears and mistrust in research occurring in other settings(41–44) that need to be addressed to improve research confidence and acceptability.

Additionally, study participants expressed inhibitions on mucosal sampling, particularly those collected from sites considered invasive. With the advent of mucosal immunological studies in the understanding of HIV transmissions,(45) there is increasing demand for various mucosal samples that include semen, saliva, vaginal, and anal secretions for laboratory analysis. Although recent feasibility studies have reported acceptability and tolerability for these samples, particularly those from the anal and genital sites,(46,47)our study findings revealed inhibitions towards semen sampling among some male participants despite having consented. Semen harvesting for fertility-assisted births at a fee is a phenomenon that is slowly growing and gaining acceptance in African settings.(48,49) Besides the fear of the samples being collected for sale, they expressed discomfort with masturbating to produce semen. This act was seen to contravene individuals' sexual practices and the sanctity of human sexuality.(50–52) The increasing demand for mucosal samples in HIV research, necessitates social science research to help unpack social–behavioural and cultural factors that may constrain participation in mucosal sampling studies particularly those thought to be invasive**.**

Findings from this study revealed inconsistency in individuals' reported understanding based on the quantitative and qualitative tools as has been reported elsewhere(15,53,54) suggesting the need for mixed methods approaches in evaluating the informed consent process.

Limitations of the study

Two major limitations were identified in this study, thus small sample size and recall bias. Given that the study population was drawn from phase 1 trials that by nature enrol small populations, the data lacked statistical power only allowing for simple descriptive statistical analysis. Additionally, participants' may have experienced selective recall given the time lapse between actual participation and interviewing for this study. For up-to date data, future trials may benefit from collecting social science data concurrently with clinical research implementation processes.

Conclusions

We conclude that beyond understanding, the information provided during recruitment and enrolment, participants' decisions are shaped by myriad factors that include personal motivations, community factors, as well as trust relations with trial staff. Furthermore, passing the assessment of understanding test and providing written informed consent may not be a conclusive measure for ascertaining the completeness of informed consent. Future studies can benefit from applying mixed methods approaches in assessing participants' understandings of research through the various stages of clinical research participation.

Authors' Contributions

EN: Study conceptualization and design, data collection and analysis, drafting manuscript and completion. RL, OA, JO: Study conceptualization and design, data interpretation, review of draft manuscript. All authors read and approved the final manuscript.

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Data Availability

The data for this article is stored in the KAVI-ICR archive. Access to anonymized data is possible upon request from the respective author.

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