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Voluntariness of consent in paediatric HIV clinical trials: a mixed-methods, cross-sectional study of participants in the CHAPAS-4 and ODYSSEY trials in Uganda

Shafic Makumbi ,[1,2] Francis Bajunirwe,[3] Deborah Ford,[4] Anna Turkova,[4] Annabelle South ,[4] Abbas Lugemwa,[1] Victor Musiime,[1,5] Diana Gibb,[4] Imelda K Tamwesigire[3]

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For numbered affiliations see end of article.

Correspondence to
Shafic Makumbi;
mshafic630@gmail.com

ABSTRACT

Objectives To examine the voluntariness of consent in paediatric HIV clinical trials and the associated factors.

Design Mixed-methods, cross-sectional study combining a quantitative survey conducted concurrently with indepth interviews.

Setting and participants From January 2021 to April 2021, we interviewed parents of children on first-line or second-line Anti-retroviral therapy (ART) in two ongoing paediatric HIV clinical trials [CHAPAS-4 (ISRCTN22964075) and ODYSSEY (ISRCTN91737921)] at the Joint Clinical Research Centre Mbarara, Uganda.

Outcome measures The outcome measures were the proportion of parents with voluntary consent, factors affecting voluntariness and the sources of external influence. Parents rated the voluntariness of their consent on a voluntariness ladder. Indepth interviews described participants' lived experiences and were aimed at adding context.

Results All 151 parents randomly sampled for the survey participated (84% female, median age 40 years). Most (67%) gave a fully voluntary decision, with a score of 10 on the voluntariness ladder, whereas 8% scored 9, 9% scored 8, 6% scored 7, 8% scored 6 and 2.7% scored 4. Trust in medical researchers (adjusted OR 9.90, 95% CI 1.01 to 97.20, p=0.049) and male sex of the parent (adjusted OR 3.66, 95% CI 1.00 to 13.38, p=0.05) were positively associated with voluntariness of consent. Prior research experience (adjusted OR 0.31, 95% CI 0.12 to 0.78, p=0.014) and consulting (adjusted OR 0.25. 95% CI 0.10 to 0.60, p=0.002) were negatively associated with voluntariness. Consultation and advice came from referring health workers (36%), spouses (29%), other family members (27%), friends (15%) and researchers (7%). The indepth interviews (n=14) identified the health condition of the child, advice from referring health workers and the opportunity to access better care as factors affecting the voluntariness of consent.

Conclusions This study demonstrated a high voluntariness of consent, which was enhanced among male parents and by parents' trust in medical researchers. Prior research experience of the child and advice from health workers and spouses were negatively associated with the voluntariness of parents' consent. Female parents and parents of children with prior research experience may benefit from additional interventions to support voluntary participation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The response rate was 100%.
⇒ The mixed-methods approach enhanced the interpretation of the results.
⇒ The assessments focused on participants' self-reports, which were vulnerable to social desirability bias.
⇒ Parents who declined consent to the original trials were not included in this study.

INTRODUCTION

Voluntary informed consent is a fundamental prerequisite for the ethical conduct of scientific research with human subjects. It refers to the ability to exercise free power of choice without the intervention of any element of force or other forms of constraints to enable one to make a meaningful decision.[1] Various strategies such as financial compensation and research conducted by clinicians offering routine medical care raise concerns about the voluntariness of consent.[2–5] Preliminary investigations on the voluntariness of consent among adults participating in research in both low-middle-income and high-income countries reported high voluntariness ratings on the voluntariness ladder. Appelbaum *et al*[6] reported as many as 85% of adult participants had a voluntary decision in studies conducted in high-income countries.[6] Mamotte and Wassenaar[7] reported that 89% of the adult

participants made a voluntary decision in an HIV clinical trial conducted in South Africa.

However, the findings appear different when consent is obtained from the parents as a proxy for their children to be involved in research.[8 9] For instance, Pace *et al*[9] reported 58% of mothers felt pressured by their child's illness and 15% reported being pressured by others to allow their children to be involved in a malaria clinical trial in Uganda.

In paediatric HIV settings, the voluntariness of a parent's consent is a challenge. Factors such as the limitations related to shortages in drug availability and the concerns parents have over the health of their children make them especially vulnerable to the influence of others.[9–11] The absence of voluntariness in the consent decisions impairs the meaningfulness of parents' consent and may result in the loss of the community's trust in medical research, especially when participants experience the burden and risks of participating in the research.

Few studies have been conducted on the voluntariness of consent among parents. Available literature has focused on the assessment of knowledge of voluntary participation and the rights to withdraw consent, but whether consent was experienced as voluntary has hardly been studied.[11] Where studies assessed for the presence of pressures and influences, the nature, source and effect that such influences and pressures have on the voluntariness of parents' consent were not ascertained.[7] The purpose of this study was to examine the voluntariness of consent from the perspective of parents of children enrolled on paediatric HIV clinical trials and to describe the barriers and facilitators of voluntariness of consent in our setting. The study also examined the source of influence from others on the voluntariness of consent.

METHODS

Study design

We employed a cross-sectional, mixed-methods study design. The quantitative survey focused on formulating descriptions and uncovering relationship patterns, while the indepth interviews conducted concurrently aimed at adding context to enhance the interpretation of the quantitative findings. The data were collected concurrently and triangulated at interpretation.

Quantitative methods

Study population and setting

The study was conducted between January 2021 and April 2021 at the Joint Clinical Research Centre (JCRC) Mbarara Regional Centre of Excellence located in southwestern Uganda approximately 265 km from the capital (Kampala). The respondents were selected from parents of children already enrolled on the CHAPAS-4 (ISRCTN22964075) and ODYSSEY (ISRCTN91737921) clinical trials between January 2018 and March 2021.

The trials were randomised controlled clinical trials evaluating new paediatric medications against standard-of-care regimens to optimise HIV care for children on first-line and second-line Anti-retroviral therapy (ART).[12 13] The CHAPAS-4 trial recruited children aged 3–15 years weighing >14 kg at enrolment, with a total of 196 children enrolled at JCRC Mbarara between January 2018 and March 2021. The ODYSSEY trial recruited children aged 28 days to 18 years weighing >3 kg at randomisation and a total of 110 were enrolled between September 2016 and August 2019. The last phase of the ODYSSEY trial enrolled children in the WHO weight bands 3–<14 kg (enrolled from July 2018 to August 2019).

Sample size

The sample size for the study focused on estimating the proportion of participants who make a voluntary decision. Based on the findings of a study conducted among participants in an HIV clinical trial in South Africa,[7] we assumed a proportion of 0.89 (p). A sample of 151 participants (n) was required to estimate the proportion of the parents with a voluntary decision within ±5% error (d) and with 95% confidence (Z=1.96): $n=[p(1-p)Z^2]/d^2$.

Sampling

A sample of participants were selected by systematic random sampling using the fractional interval technique described in the literature.[14] Participants were numbered by order of their trial identification. A sampling interval was obtained by dividing the total number of participants by the required sample size (204/151=1.35). A random start was selected by considering a random integer 1. The sampling interval was repeatedly added to the random start to generate a series of selection numbers while retaining the decimal fraction until a selection number exceeded the last number of the sampling frame. Each selection number was truncated to a whole number by dropping its decimal portion. Numbers that were truncated beyond the end of the sampling frame were discarded and the remaining 151 numbers constituted the desired sample.

Data collection tools

Quantitative data were collected using an interviewer-administered tool (see online supplemental appendix 1). The tool was composed of the following sections: (1) demographics; (2) items assessing the factors affecting the voluntariness of consent adopted and modified from the survey of influences questionnaire[7]; and (3) voluntariness ladder, which is used to measure the voluntariness of parents' consent.[6 7]

Measurement of variables

Voluntariness of consent

Parents' voluntariness of consent was measured using the voluntariness ladder.[7 15 16] The voluntariness ladder is a scale of numbers ranging from 1 to 10, to which subjects were asked to rate the voluntariness of their consent decision. A score of 10 represented a decision fully voluntary, whereas scores from 1 to 9 represented a decision that was not fully voluntary. We dichotomised the score as either fully voluntary (10) or not fully voluntary (<10).

The cut-off values were selected based on existing literature.[7 15 17]

External control

Controlling influences from others were assessed by asking parents to indicate the persons they talked to about their research participation (consultation) and whether they attempted to influence their decision. If they responded with a yes, they were asked to indicate the nature of that influence by selecting from a predetermined list of forms of influence. The frequencies of the different forms of influence were then analysed.

Situational influence

Influences from situations, such as the need for better care, trust in health workers, desire to advance medical knowledge and desire to help other children, were assessed using items adopted from the survey of influences questionnaire.[7] Parents were asked to rate on a Visual Analogue Scale the degree to which they agreed to five statements indicating that the situations influenced their decision to participate in the study. A dichotomous scale to which items were categorised as either agreed or did not agree was created to facilitate analysis. Social demographics and other characteristics of the parent and the child, such as age, gender, education level, household income, prior research experience and time since enrolment into the parent trial, were assessed using semistructured questions. Parents were also asked to rate the overall health status of the child at enrolment into the parent study on a scale of 1–10, where 1 indicated extremely poor health and 10 indicated extremely healthy.[18]

Sources of influence

The sources of the influence were analysed using the frequency at which the influence was reported as coming from each category of the persons consulted.

Data analysis

Data were presented using descriptive statistics. χ^2 and logistic regression analyses were performed to examine the association of situational constraints and the characteristics of the child and the parent with the voluntariness of consent. Multivariable analysis included all factors with a p value less than 0.05 in the bivariate analysis. The findings were reported using adjusted ORs (aOR) and their 95% CIs. The source of influence was analysed using descriptive statistics of reports of the influence in each category of the persons contacted.

Qualitative data collection

The indepth interviews were explanatory and based on the phenomenological approach.

Sample size

The indepth interviews included 14 respondents. Respondents to the interviews were selected until thematic saturation was achieved, that is, when no new themes were generated on analysis of additional transcripts. This occurred after analysis of 14 interviews.

Sampling

Participants for indepth interviews were selected purposively from the respondents to the quantitative interviews based on equal representation of age, sex and parent study.

Data collection tools

The qualitative data were collected by indepth interviews using an interview guide that followed a life history approach and allowed participants to trace the steps involved in their consent (see online supplemental appendix 2). The indepth interviews were conducted by two female trained research assistants aged 22 and 24 years. The research assistants were neither known to the participants nor involved in their care. The interviews were recorded using an audio recorder. Each interview was conducted by one research assistant who took field notes to capture any information missed by the audio recording. The investigators of the current study were also involved in both trials and known to the respondents and therefore did not participate in the indepth interviews to avoid biasing participants' responses.

Potential participants were approached either before or after trial follow-up visit procedures. The interviews were conducted face-to-face at the research clinic. Informed consent was obtained prior to the interviews. Participants were informed of the risks and benefits of the indepth interviews and that their interviews were to be audio-recorded. All participants who were approached for the indepth interviews agreed to participate and were interviewed.

The audio files were transcribed verbatim. The first author reviewed the transcripts against the original audio file. The transcripts were assigned to a translator for translation from the local languages to English. A second person who is conversant with the local languages reviewed the translated transcripts and confirmed that the translations were an accurate interpretation of the local languages. No transcripts were returned to participants for comments or correction.

Data analysis

Data from indepth interviews were analysed thematically in NVIVO V.12 using both deductive (based on Appelbaum *et al*[6] and Nelson *et al*'s[19] empirical conceptualisation of voluntariness) and inductive (to examine new findings from the quantitative data) approaches. A list of themes was generated based on prior conceptual models of voluntariness.[6 7 19] Each translated script (English version) was coded by two independent coders who had not participated in the interviews. The coders independently reviewed the English version scripts sentence by sentence and one paragraph at a time to identify codes. The codes were compared one with the other along subsequent interviews and common themes

Table 1 Characteristics of the parents and children

Characteristics	Frequency (%)
Parents' prior research experience	
Yes	32 (21.2)
No	119 (78.8)
Period between the current study and enrolment into the parent trials, median (range)	16 (1–36)
Gender of the parent	
Female	127 (84.1)
Male	24 (15.9)
Age of the parent, median (range)	40 (18–69)
Education level of the parent	
Tertiary level	1 (0.7)
Secondary level	38 (25.2)
Primary level	86 (56.9)
None	26 (17.2)
Monthly income of the main earner (Ugandan shilling)	
Less than 200 000	79 (52.3)
200 000–499 999	34 (22.5)
500 000 and above	38 (25.2)
Relationship to child	
Biological parent	89 (58.9)
Grandparents	32 (21.2)
Others	30 (19.9)
Child had prior experience with research	
Yes	28 (18.5)
No	123 (81.5)
Gender of the child	
Male	75 (49.7)
Female	76 (50.3)
Age of child in years, median (range)	9.02 (1–16)
Overall health status score on a scale of 1–10, median (IQR)	3 (1–4)

were identified and new themes were suggested. The two coders later met to discuss and refine the code list. Variations in coding were resolved by group consensus.

Patient and public involvement

None.

RESULTS

Enrolment

All 151 respondents approached were enrolled in this study and all completed the questionnaire.

Table 2 Raw scores on the voluntariness ladder

Score	Frequency (%)
10	101 (66.9)
9	12 (8.0)
8	13 (8.6)
7	9 (6.0)
6	12 (8.0)
5	0
4	4 (2.6)
3	0
2	0
1	0

Parents' characteristics

As shown in table 1, majority of the respondents were female, aged 18–69 years. Education level was low, with the majority reporting only primary level education and few reporting secondary or tertiary education. The majority were low-income earners, and biological parents (59%) reported no prior experience with research (79%). The respondents were approached at a median duration of 16 months into the parent study.

Characteristics of the children

The characteristics of the children are summarised in table 1. Fifty per cent (75) were female. The median age at enrolment into the parent study was 9.02 years (range 1–16 years). Most children were rated by their parents/guardians as having poor health, with a median of 3 (on a scale of 1–10, where 1=extremely poor health and 10=extremely good health). Only 28 (19%) children had experience with research before enrolment into the parent study.

Voluntariness of consent

A majority (67%) of the respondents had a fully voluntary decision with a score of 10. The raw scores on voluntariness are summarised in table 2. Only four had a voluntariness score in the lower half of the ladder.

Factors influencing the voluntariness of parents' consent

As indicated in table 3, on multivariate analysis, the child's prior research experience (aOR=0.31 (0.12–0.78), p=0.014) and the male gender of the parent (aOR=3.66 (1.00–13.38), p=0.05) were significantly associated with voluntary consent. The health status of the child was not significantly associated with the voluntariness of consent (crude OR (cOR)=0.997 (CI 0.87 to 1.19), p=0.978).

External controlling influence

Consulting others was significantly associated with the voluntariness of consent (aOR=0.25 (0.10–0.58), p=0.001). Of the 99 respondents who consulted, 98 (99.0%) reported that the person they consulted

Table 3 Analysis of the factors influencing the voluntariness of consent

Bivariate analysis				
	Voluntary	**Non-fully voluntary**	**Crude OR**	**P value**
Parents' prior research experience				
Yes	21 (20.8)	11 (22.0)	0.93 (0.41–2.12)	0.864
No	80 (79.2)	39 (78.0)	1	
Child's prior research experience				
Yes	13 (12.9)	15 (30.0)	0.34 (0.15–0.80)	0.011
No	88 (87.1)	35 (70.0)	1	
Gender of the parent				
Male	21 (20.8)	3 (6.0)	4.1 (1.16–14.53)	0.019
Female	80 (79.2)	47 (94.0)	1	
Health status of the child			1.0 (0.87–1.19)	0.978
Relationship				
Biological parents	57 (56.4)	32 (64.0)	1	
Grandparents	20 (19.8)	12 (24.0)	0.94 (0.40–2.16)	
Guardian and others	24 (23.8)	6 (12.0)	2.25 (0.83–6.07)	0.231
Possibility of better care				
Agree	99 (98.0)	49 (98.0)	1.01 (0.89–11.41)	1
Did not agree	2 (2.0)	1 (2.0)		
Opportunity for free medication				
Agree	91 (90.1)	42 (84.0)	1.73 (0.64–4.71)	0.276
Did not agree	10 (9.9)	8 (16.0)	1	
Trust in medical researchers				
Agree	100 (99.0)	45 (90.0)	11.11 (1.26–97.87)	0.015
Did not agree	1 (1.0)	5 (10.0)	1	
Desire to help other children				
Agree	86 (85.1)	37 (74.0)	2.01 (0.88–4.65)	0.097
Did not agree	15 (14.9)	13 (26.0)	1	
Desire to advance medical knowledge				
Agree	73 (72.2)	31 (62.0)	1.60 (0.78–3.28)	0.199
Did not agree	28 (27.7)	19 (38.0)	1	
Trial				
ODYSSEY	8 (7.92)	5 (10.0)	1	
CHAPAS-4	93 (92.06)	45 (90.0)	1.29 (0.40–4.17)	0.76
Consulting				
Yes	57 (56.44)	42 (84.00)	0.25 (0.11–0.58)	0.0005
No	44 (43.56)	8 (16.00)	1	
Multivariable analysis				
Variable	**Adjusted OR**		**P value**	
Gender of the parent				
Male	3.66 (1.00–13.38)		0.05	
Female	1			
Trust in medical researchers				
Agree	9.90 (1.01–97.20)		0.049	
Did not agree	1			
Child's prior research experience				

Continued

Table 3 Continued

Bivariate analysis				
	Voluntary	Non-fully voluntary	Crude OR	P value
Yes	0.31 (0.12–0.78)		0.014	
No	1			
Consulted others				
Yes	0.25 (0.10–0.60)		0.002	
No	1			

attempted to influence them into participating in the study.

Forms of influence

Three forms of influence were identified in the survey as shown in table 4. The most reported influence was in the form of advice, as reported by 64.2% (97) of the respondents.

As shown in table 4, only one respondent reported influence in the form of pressure from their spouse, and another respondent reported influence in the form of threat from a friend.

Influences from situational factors

As shown in table 4, only trust in medical researchers was significantly associated with the voluntariness of consent (cOR=11.11 (CI 1.26 to 97.88), p=0.015). Only six participants did not trust the researchers, and five of whom did not make a voluntary decision.

The possibility of better care was not significantly associated with the voluntariness of consent on bivariate analysis (cOR=1.01 (0.89–11.4), p=1.0).

Source of influence

The sources of external influence in the form of pressure, threats, advice and force are summarised in table 4. Most of the respondents (65.6%) reported that they consulted another person before deciding to participate in the study. The main influence reported was in the form of advice. The advice was mainly reported as coming from the healthcare doctors (36.4%) and spouses (29.1%). Influence in the form of pressure was only reported by one respondent as coming from a spouse, whereas another respondent reported influence in the form of threat from a friend.

Indepth interviews findings

Fourteen parents participated in the indepth interviews. Of these, majority were female(8), with a median age of 43 years (range: 26–68). In terms of relations to the child, interview participants were mothers (8), uncles (2), fathers (2), grandfather (1) and guardian (1). Majority had primary level education (8), while others had ordinary level (2) and advanced level (4).

The indepth interviews identified three themes related to the voluntariness of consent: health condition of the child, influence from others and the opportunity for better care (see online supplemental appendix 3). Under each theme, subthemes were also identified as described in the following:

Theme 1: health condition of the child

The health condition of the child at enrolment into the study frequently came up during the indepth interviews.

Expectation of improvement in the health condition of the child

Most indepth interview participants reported that the condition of their child left them with no option but to participate in the trial with the expectation that the child's condition would get better within the trial. Some even saw a possibility of a cure for the child's HIV.

> I wanted the health of my child and I was seeing that my child's condition was only getting worse…. I even repeat it about my child, the condition I brought him in hit me hard yet he was in good condition at first. But his condition reached a time and failed. I got scared so much to my heart and then I had to put emphasis on that trial so that I could save my child. —VC053

Table 4 Source of influence

Nature of influence	Source of influence, n (%)						
	Participants' doctor	Spouses	Study doctor	Friend	Family member	Community member	Another member of the study team
Advice	55 (36.4)	44 (29.1)	8 (5.3)	23 (15.2)	40 (26.5)	7 (4.6)	10 (6.6)
Pressure	0	1 (0.0)	0	0	0	0	0
Force	0	0	0	0	0	0	0
Threat	0	0	0	1 (0.0)	0	0	0

Fear of negative consequences to the child's health

Some interviewees expressed fear of what would happen to their child if they did not choose to participate in the trial. The fear of negative consequences associated with non-participation in the trial made it impossible for them to say no to participation in the trial.

> we both didn't understand it at first… when they told us that in the study there are drugs that will be tested on children with HIV to see if the drugs work… it was hard for me and for us to comprehend. But later I decided to participate, and when the drugs were given, I realized that the child was getting better from one stage to another…. I also have relief that I thought I was going to suffer with her but now I see she is a normal child and the frequency of falling sick reduced since she was enrolled on the study. —VC079

Theme 2: influence of others

None of the participants reported pressure or threats. The majority of the participants reported that they were given some form of advice in favour of participation by the people they consulted.

Advice of others increased confidence and satisfaction with the consent decision

Some interview participants indicated that their confidence and happiness with the decision to participate increased following the advice of others. These participants also indicated that they lost all their fears after consulting others about participating in the trial.

> Yes… when I saw that her father has liked it (parent study) and again has advised me… I lost the fear in me and I started coming to this side (referral site) without any doubt. I am in it willingly nothing has bothered me. —VC149

The reports of advice were explored further to put into context the nature of the advice.

Change in perception of the decision after the advice of others

About half of the indepth interview participants reported that they had concerns and fears about making the decision but all that changed once they were advised by the people they consulted to join the study.

> when I told him (husband), he said "my dear you have to do what health workers (researchers) want… those people have more experience than us the local people (ordinary)…" … then I said I want this child alive and healthy so I have to agree to whatever the healthy workers have told us. From that instance on, we joined the study and haven't regretted it a bit and we have never had second thoughts about it…. —VC079

Influence of the referring healthcare workers' advice

Some participants reported that they participated in the trial because, based on what they were told by their healthcare providers, that was the only option available.

> I accepted because they (referring Health workers) told me that my child has to get the medicine that will make him better from the other side (research Centre) and so I had to accept and ok I also accepted willingly. —VC53

Theme 3: opportunity for better healthcare

Interviewees reported that their voluntariness to participate in the trial was out of the need and expectation that participating in the trial was an opportunity to access better care. We identified three subthemes under the theme of better care as described in the following:

More advanced tests and examinations than the standard of care

Some participants reported that their willingness to participate in the trial was motivated by the opportunity to have more tests and examinations than that which they have access to in the standard of care. The examination procedures and tests included assessment of bone density using calcaneal scans, body composition analysis, anthropometric measurements including skin fold thickness, pharmacokinetics and urine biochemistry, among others, many of which were done regularly in the trials and never experienced before by the respondents.

> When we reached here… I saw that my child was going to be tested on everything which was not the case on the other side (Health Centre IV)…. On the other side she was only getting drugs but not tests like liver tests, bone and all other things and tests that were done this side all along the other side they had never been done and it was good on my side and I wanted to be part of it…. —VC149

Better medicines

Some reported to have voluntarily participated in the trial out of the hope that they would be able to access better drugs than what is available in the standard of care.

> because the other side he was getting medicine, it was not working well, and they told us that they brought an organization that has new medicine that was more powerful (better) than the other one…. —VC063

More specialised services

The trial was conducted at a regional referral hospital, and to some interviewees this was an undeniable opportunity to access more specialised healthcare services compared with services offered at Health Centre IV and this influenced the voluntariness of their consent to participate in the trial.

> at least where we were (Health Centre IV), the services were there, and we were receiving them. But I

saw that when you come from Health Centre IV and you come to the regional referral, services might be better compared…. (to the Health Centre IV services)… because even the services that they give from Health Centre IV come from here (from Regional Referral hospital) be it drugs and the rest. —VC132

DISCUSSION

Voluntariness of consent is the research participant's willingness to participate in research. This study presents a unique insight into the voluntariness of a parent's consent, and the barriers and facilitators of voluntariness from the perspective of the parents. Findings from this study demonstrated a relatively high voluntariness of parents' consent, which was more in people who trust medical researchers and among male respondents. Conversely, prior research experience of the child and advice from others had a negative influence on the voluntariness of consent.

Most respondents to this study reported having made a voluntary decision to allow their children to participate in research, with scores on the higher end of the voluntariness ladder. This finding is consistent with previous studies which reported high voluntariness of consent in adult populations in both high-income and low-middle-income countries.[7 15 17] In a study by Appelbaum *et al*,[15] 73% of the adult respondents involved in substance abuse, cancer, HIV, depression and cardiology trials in the USA rated their consent as fully voluntary. A study by Mutenherwa[17] was conducted among individuals involved in a randomised clinical trial of a new diagnostic instrument for tuberculosis in Zimbabwe and reported as high as 98% (scored 8–10 on the voluntariness ladder). In another study conducted among women involved in trials evaluating the prophylactic or therapeutic effect of tenofovir gel in South Africa, 89% had a voluntary decision, with scores of 10 on the voluntariness ladder.[7] In our study, 67% of the respondents rated their consent as fully voluntary. The variation in voluntariness of consent between our study and previous studies may be explained by the nature of proxy consent obtained from the parents of children living with HIV in relatively poor health conditions. Advice from the referring healthcare workers and spouses was associated with non-voluntary decisions. Despite this association, some participants expressed that their confidence and happiness with the decision increased after they consulted others. The increase in confidence of such parents' decisions may be expected to occur (1) if family members have their backing, (2) if others believe that it is the right choice, (3) if others take part in the shared decision-making process and (4) if the advice comes from someone trusted and respected.

Even though advice may not be intended to alter the parent's self-directed course of action, it could be interpreted by participants in a way that would render the decisions not their own.[4 20 21] There are two scenarios under which advice may constrain voluntariness of consent: (1) a research subject's self-directed course of action may change due to the merit of reasons proposed by another person, or when a person intentionally and successfully draws the attention of a subject to reasons why they should accept a perspective that is desired by the other person; and (2) a subject's perception of the situation is altered with the intention to motivate him/her to act in a particular way.[4 19] For both trials, healthcare workers who were from various health centres and independent of the trial teams referred eligible participants to the research centre where they were considered for participation in the trials. In the current study, the findings from both the survey and the indepth interviews suggest that the health worker's advice negatively affected the voluntariness of consent. With advice from referring health workers, parents interpreted that participating in the trial was the only way for their child's condition to improve. The referring health worker's advice therefore presents a significant impediment to the voluntariness of consent. Nelson *et al*[19] and Dekking *et al*[4] described this phenomenon as manipulation of information and options. They argued that the way health workers present or frame information about trials may alter perceptions of the situation and motivate them to make particular decisions, and therefore constraining the voluntariness of their decisions. In the case where the referring healthcare workers are independent of the research team, the researcher-delivered informed consent process exists as a safeguard and researchers have a responsibility to ensure that participants fully understand their options correctly and are free to choose either to participate or not to participate.[3 20 22] The current study did not explore whether the influence of the referring health workers was addressed during the consent process.

There were hardly any reports of threats and pressure from others, and this is consistent with findings from research by Mamotte and Wassenaar[7] and is contrary to the findings of a study by Pace *et al*.[9] Pace *et al*[9] reported pressure from others in 15% of the respondents of the malaria trial. This study did not find evidence of pressure from others.

Literature suggests that trust in medical researchers potentially impairs the voluntariness of consent especially when it undermines the participant's assessment of the risks of trials and comprehension of consent information.[23] In the current study, trust in medical researchers promoted the voluntariness of consent. This finding supports literature that suggests that trust in medical researchers facilitates voluntary research participation.[7 24]

The current study suggests that prior research experience of the child is negatively associated with voluntariness of consent of the parent. This finding may be attributed to differences in the perception of risks/benefits to the child. Parents of children with no prior research may be more likely to overestimate the benefits and underestimate the risks compared with parents with prior research exposure. However, this association is subject to research.

In the current study, male parents were more likely to make a voluntary decision compared with their female counterparts. In addition, the influence of the spouse was the second most common source of external controlling influence on the voluntariness of consent. Because our study population was predominantly female, the influence was likely coming from their male spouses. Male spouses may influence the decisions of their female partners. This opinion is supported by the indepth interview discussions in which the opinions of female respondents changed on their partners' expression of approval towards participation in the trials.

The findings from our study also suggest that the condition of the child may be associated with the voluntariness of parents' consent to participate in the paediatric trials. Some parents felt excessively pressured by the health condition of their children to participate in the trials. This finding is consistent with a previous study by Pace *et al*,[9] in which pressure from the child's condition was reported by 50% of the respondents. The respondents to this study by Pace *et al*[9] were mothers of children enrolled into paediatric malaria trials. In addition, the finding supports Nelson *et al*'s[19] suggestion that controlling influence may also come from internal influences especially when there is a perception of a coercion-like force that does not originate from any outside agent. In the current study, some respondents perceived that harm or punishment in the form of worsening of the child's condition would result from non-participation in the trial.

The analysis of the indepth interviews highlights two key concepts: therapeutic misestimation or misconception and the provision of ancillary care, and their contribution to the voluntariness of consent. Responses to the indepth interviews suggest that parents made decisions under conditions of therapeutic misestimation and with the expectation of deriving benefits from the provision of ancillary care within the trial. The concept of therapeutic misestimation is often confused with therapeutic misconception. Therapeutic misconception is the persistent misplaced belief that treatment decisions while in a trial will be made based on one's individual health conditions and needs rather than to answer research questions as prescribed by the protocols.[25] Therapeutic misestimation, on the other hand, is the unrealistic expectation of personal benefit from the research procedures and tests, and personalised care and treatments.[25] The responses to the indepth interviews suggest that respondents weighed the benefit to the child's health that would result from exposure to the trial medications and tests, access to senior doctors and ancillary care against the benefit that they would derive from continuing care at their lower level health centres. Scholars have argued that the mere expression of expectations related to therapeutic misestimation and/or misconception does not constrain the voluntariness of consent or undermine a subject's autonomy.[26 27] This is because such expectations may represent participants' legitimate understanding of the potential benefits from a trial, as may be the case with the expectation of ancillary care. Incomplete comprehension may be just enough for subjects to engage in substantial autonomous decision-making, that is, poor comprehension does not always translate into lack of voluntariness of consent.[28 29]

Ancillary care in the context of clinical trials refers to the medical or healthcare services provided to research participants that are not directly related to the primary purpose of the study but may be necessary for the participants' well-being or safety. For the current trials, ancillary care included routine safety laboratory investigations such as full blood counts, liver function tests, and investigation and treatment of other illnesses like malaria and upper respiratory tract infections, among others, which are not related to the study objectives.

Strengths and limitations

Our study had a very high response rate; 100% of the parents approached agreed to participate, thus adding to the reliability and confidence in our results. The mixed-methods approach used in this study allowed us the opportunity to explain quantitative findings based on indepth interviews. However, with such an approach, some unexpected quantitative findings were not explored in the indepth interviews, which would not have been the case with a more sequential triangulation design. We assessed the voluntariness of consent based on participants' self-reported ratings, which may have implications of social desirability bias. The study included only parents who gave consent for their children to participate in the original trials and excluded the perspectives of those parents who declined consent to the trials. The indepth interviews were conducted with less than 10% of the survey respondents and therefore the indepth interview results may not be a good representation of all the survey respondents.

CONCLUSIONS

This study demonstrated a relatively high voluntariness of consent, which was enhanced in those with trust in medical researchers and male parents. Female parents and parents of children with prior research experience may benefit from additional interventions to support voluntary consent decisions. We recommend that future research on the voluntariness of consent should explore the relationship that prior research exposure of the child, parents' perception of risks and benefit associated with the participation of their children in research and gender of the child have on the voluntariness of parents' consent.

Author affiliations
[1]Joint Clinical Research Centre, Mbarara, Uganda
[2]Mbarara University of Science and Technology, Mbarara, Uganda
[3]Department of Community Health, Mbarara University of Science and Technology, Mbarara, Uganda
[4]Medical Research Council Clinical Trials Unit, University College London, London, UK
[5]Makerere University, Kampala, Uganda

Twitter Francis Bajunirwe @FrancisBaj

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ORCID iDs
Shafic Makumbi http://orcid.org/0009-0009-2284-9017
Annabelle South http://orcid.org/0000-0001-8912-2001

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