Am. J. Trop. Med. Hyg., 83(4), 2010, pp. 868–872
doi:10.4269/ajtmh.2010.10-0062

Comparing the Understanding of Subjects Receiving a Candidate Malaria Vaccine in the United States and Mali

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Abstract. Initial responses to questionnaires used to assess participants' understanding of informed consent for malaria vaccine trials conducted in the United States and Mali were tallied. Total scores were analyzed by age, sex, literacy (if known), and location. Ninety-two percent (92%) of answers by United States participants and 85% of answers by Malian participants were correct. Questions more likely to be answered incorrectly in Mali related to risk, and to the type of vaccine. For adult participants, independent predictors of higher scores were younger age and female sex in the United States, and male sex in Mali. Scores in the United States were higher than in Mali ($P = 0.005$). Despite this difference participants at both sites were well informed overall. Although interpretation must be qualified because questionnaires were not intended as research tools and were not standardized among sites, these results do not support concerns about systematic low understanding among research participants in developing versus developed countries.

INTRODUCTION

Individual informed consent is internationally recognized as an ethical requirement for research involving human participants.[1] Valid informed consent has four components: 1) the person giving consent must be competent, 2) relevant information must be disclosed, 3) the person must understand the information, and 4) the consent must be voluntarily given. Exactly how much must be understood is controversial.[2] However, most commentators consider that participants should at least understand the potential risks and benefits of the research, the ways in which participation will or will not differ from clinical care, and what will happen if participants want to withdraw.[1,3,4]

An increasing number of trials are now being conducted in developing countries.[5] Some reviewers are concerned that the participants in these trials are poor, often uneducated, and unfamiliar with the scientific basis of modern medicine.[6,7] Consequently, these research participants are thought less likely to understand the research and thus less likely to provide valid informed consent compared with participants from developed countries.

A number of studies have assessed trial participants' understanding of research and their perceptions of voluntariness. In both developed and developing countries, studies show wide variation in understanding on most required elements.[8] Scientific concepts like randomization are particularly difficult for participants from either location to understand. However, there is not clear evidence of substantial differences in understanding between participants from developed compared with developing countries,[9] although there are some indications that developing country participants are more likely to feel pressure to enroll.[10–12] These conclusions are tentative, because these studies look at participants in widely varying clinical trials. For instance, many of the studies of understanding in developed countries were Phase I oncology studies, which are not currently conducted in developing countries. Furthermore, the instruments used to assess the quality of understanding of research participants vary widely between studies, and few instruments have been validated.

This work reports consent data on participants in early phase trials of malaria vaccine candidates in the United States and in two villages in Mali, West Africa. As part of the informed consent process, questionnaires were administered to all participants or parent/guardians of pediatric participants who were screened for eligibility. The questionnaires were intended to confirm that potential participants understood the essential elements of the research before participation, and were not prospectively intended to collect data. However, to our knowledge, these data are the first to allow a direct comparison of the understanding of consent of similar clinical trials in the developed and developing world.

METHODS

Sites and participants. The Malaria Vaccine Development Branch, National Institute of Allergy and Infectious Diseases (MVDB/NIAID/NIH) develops recombinant protein malaria vaccines intended to reduce the severity and frequency of falciparum malaria. Two Phase 1 clinical trials were conducted in malaria naive adults at the Johns Hopkins University Center for Immunization Research (JHU/CIR) in Washington DC and one Phase 1 clinical trial was conducted in semi-immune adults in Donéguébougou, Mali.[13–15] A Phase 1,2 study was also conducted in 2–3 year old children in Donéguébougou and Bancoumana, Mali, with most of the participants recruited in Bancoumana, the larger village.[16,17] Three different vaccines were evaluated (AMA1-C1/Alhydrogel in Malian children, AMA1-C1/Alhydrogel+/–CPG 7909 in United States adults and Malian adults, and $MSP1_{42}$-C1/Alhydrogel+/–CPG 7909 in United States adults); all were recombinant protein vaccines targeting blood stage malaria. All trials were conducted under protocols reviewed by the Institutional Review Board of the

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NIAID, and by either the Western IRB (JHU/CIR) or the Ethics Committee of the Faculty of Medicine, Pharmacy, and Dentistry of the University of Bamako, Mali. All trials were conducted under Good Clinical Practice and International Conference on Harmonization guidelines.[4]

Questionnaires for all persons screened for participation were reviewed for this study. At JHU/CIR, age and sex were recorded as part of the baseline demographic information; all volunteers could sign their names and were considered to be literate. Written questionnaires were provided to volunteers and responses were reviewed with volunteers after answers were marked. In Mali, age and sex were available for the adults giving consent for their own participation, and the ability to sign one's name was used as a surrogate for literacy. Consent documents were translated into French in Mali, but consent procedures, including administration of the questionnaires, were conducted orally in the local language, which does not have a written form. Malian volunteers who were unable to sign fingerprinted the consent form with a witness co-signing. For parents and guardians who gave consent for their child's participation, age and sex of the consenting adult was not recorded and the only demographic information available was signature versus fingerprint. At both the Mali and United States sites consent procedures were conducted by clinical investigators.

SURVEY

A true/false questionnaire was administered by an investigator after the informed consent document had been reviewed. The questions are shown in Table 1. Questions that were answered incorrectly were used as teaching points, with the correct answer explained to the volunteer. All volunteers were expected to answer all questions correctly before additional screening procedures or enrollment. The questions focus on elements generally agreed to be necessary for valid consent, such as study procedures and design, possible risks, the absence of benefit, and participants' right to withdraw at any time.[1,18]

The questionnaires for the two United States trials contained 14 questions that were identical or very similar, and one question that was different. Data for these trials were pooled for all but the question that differed, which was discarded. The questionnaires used for the trials in Mali were almost identical to each other, except that in the child study the question regarding pregnancy was eliminated. Seven questions were judged to be the same or similar at the United States and Mali sites (indicated by asterisks in Table 1). Responses to these seven questions were used to analyze effects of age, sex, literacy, and location (United States versus Mali), as described below.

DATA ANALYSIS

The proportions of correct responses to each question were summarized using descriptive statistics. A cumulative logistic regression was performed on each of the three data sets (United States Adults, Mali Adults, and Mali Parent/Guardians) with overall score as the dependent variable. Independent variables included age group (18–25, 26–35, and over 35 years of age), sex, and literacy. The effects from the cumulative logistic regression were expressed as odds ratios (ORs). A similar analysis was used to compare scores between the United States and Mali adults using only the seven questions judged to be similar between the sites. (Data from the Mali Parent/Guardians was not used for this comparative analysis as only literacy was known for these subjects.) The *P* values were by Wald test, except for the overall location effect, which was by likelihood ratio test.[19] The SAS version 9.1 (SAS Institute, Cary, NC) was used for the analysis.

RESULTS

Participant demographics. A total of 960 participants from the United States and Mali completed consent questionnaires. The response rate for both studies was 100%, because completing the questionnaire was a necessary part of the consent process. There were 171 adults in the United States trials (JHU/CIR participants) with a median age of 30 (range 18–50). Fifty-six percent were male, 44% were female. There were 89 Malian adults with a median age of 27 (range 18–50). Seventy-three percent (73%) of Malian adults were male and 27% female. Only 9% of Malian adults signed the consent form; the other 91% used a fingerprint. All literate Malian adults (able to sign one's name) were male and < 25 years of age. There were 700 Malian parents or guardians of whom 84% used a fingerprint on the form. The literacy rate for parents/guardians varied between sites with 3% literate in Donéguébougou and 17% literate in Bancoumana.

Understanding. Initial responses to each question for the three trials are summarized in Table 1. In the trials conducted in the United States, 92% of initial answers for all questions were correct; Malian adults and parents/guardians answered correctly 85% of the time. On 5 of the 7 questions judged to be the same or similar among the studies (marked with an asterisk in Table 1) the proportion of participants answering correctly was similar between the United States and Mali. Regarding the question about being injected with live malaria parasites, only 47% of Malian adults and 64% of Malian parents/guardians recognized this as false. Similarly, 61% of Malian adults and 48% of Malian parents/guardians mistakenly said that the vaccine had been given to hundreds of people and was completely safe. However, there was a high frequency of errors in the final answers for this particular question in Mali. For the parents/guardians, 20% (143/700) of entries were either initially incorrect (true) and not corrected by the investigator, or were initially correct (false) but an incorrect answer was subsequently recorded as final. Errors were also discovered for some other questions in both this and the other Mali study, but with much lower frequency (6% or less). No errors in questionnaire administration were seen in the trials conducted in the United States.

Eighty percent of Malian adults and 90% of parents/guardians answered a question about randomization correctly; 96% and 93%, respectively, understood that they could withdraw their consent, compared with 98% of United States participants. In the United States studies, 40% answered all questions correctly on the first attempt, while in the Mali studies 22% of adults and 29% of parents/guardians did so.

Predictors of understanding. Demographic variables (age, sex, literacy) were available for United States adults and for Malian adults consenting for their own participation. In the United States studies, younger age was associated with higher scores (OR for the two younger groups relative to the oldest group 2.1 and 2.5, respectively; $P = 0.02$) and female sex was marginally associated with higher scores (OR female/male = 1.7; $P = 0.06$). In Malian adults, the effects for age and literacy

TABLE 1
Frequency of correct answers by question

Question (correct answer)	% Correct
United States adult participants (N = 171)	
1*. As part of this study, you will be injected with a live malaria parasite (false)	94
2. This vaccine will protect you from getting malaria (false)	89
3*. There is a chance you could have local reactions (pain, redness, swelling, itching) at the site of the injection (true)	99
4*. Women enrolled in this study must not be pregnant or nursing (true)	96
5*. If you change your mind about being in the study after you are vaccinated, you can withdraw your consent (true)	98
6*. This vaccine has been given to hundreds of people already, so we know it is completely safe (false)	85
7. You will receive an injection of the same vaccine once monthly for (3 or 2) months (true)	84
8*. If you feel sick during the study, you should keep it to yourself (false)	99
9*. If you join this study, you will need to be followed for a total of (8 or 6) months (true)	81
10. Before joining the study you will be tested for HIV, Hepatitis B, and Hepatitis C (true)	99
11. You will fill out a diary card for 6 days after each vaccination (true)	90
12. It is ok to enroll in other investigation agent studies while you are still in this study (false)	98
13. It is important for you to stay in the clinic for (60 or 30) minutes after each injection (true)	93
14. You cannot get malaria from this vaccine (true)	88
Mali adult participants (N = 89)	
1*. As part of the study, you will be injected with a live malaria parasite (false)	47
2*. There is a chance you could get sick from this vaccine (true)	88
3*. Women enrolled in this study should not become pregnant up until 1 month after the last shot (true)	98
4*. If you change your mind about being in the study after you are vaccinated, you can withdraw your consent (true)	96
5*. This vaccine has been given to hundreds of people already, so we know it is completely safe (false)	61
6. You will have your blood drawn as part of this study (true)	100
7. You will get two vaccinations in this study (true)	92
8*. If you feel sick during the study, you shouldn't tell anyone (false)	89
9*. If you join the study, you will need to be followed in our clinic for 7 months (true)	99
10. Everybody in this study will get the same kind of vaccine (false)	80
Mali parents/guardians of child participants (N = 700)	
1*. As part of the study, your child will be injected with a live malaria parasite (false)	64
2*. There is a chance your child could get sick from this vaccine (true)	83
3*. If you change your mind about your child being in the study after your child is vaccinated, you can withdraw your consent for your child (true)	93
4*. This vaccine has been given to hundreds of people already, so we know it is completely safe (false)	48
5. Your child will have blood drawn as part of this study (true)	99
6. Your child will get two vaccinations in this study (true)	96
7*. If your child feels sick during the study, you shouldn't tell anyone (false)	94
8*. If your child joins the study, your child will need to be followed in our clinic for 12 months (true)	99
9. Everybody in this study will get the same kind of vaccine (false)	90

Questions marked with an asterisk (*) were judged to be the same or similar among the studies.

were not significant (P = 0.45 and P = 0.39, respectively), although the number of literate volunteers was very small, thus limiting power. The only significant independent predictor of higher scores in Malian adults was male sex (OR male/female = 3.2; P = 0.02); as opposed to the United States adults, where female sex was associated with higher scores. For the Malian parents/guardians, literacy was significantly associated with higher scores (OR = 2.8; $P < 0.0001$); no other variables were available.

In the analysis of the seven questions common to both sites, literacy was non-significant (P = 0.70) and age was marginally significant (OR for younger groups 1.5 and 2.1; P = 0.09). The location effect was significant, with higher scores in the United States compared with Mali adults (P = 0.005).

DISCUSSION

The questionnaires used in these clinical trials were intended for teaching participants rather than for collecting data, and these data therefore have several limitations, as discussed later. However, the data presented here allow the first direct comparison of the quality of understanding of participants in similar clinical trials in developed and developing countries, and allow exploration of the predictors of understanding at sites in both the United States and Mali. Although there was a higher level of understanding in the United States volunteers compared with those in Mali, the overall level of understanding of participants in Mali was almost as good as that of participants in the United States who had presumably far higher levels of education, with the exception of two questions. These data do not support concerns about a systematic lack of understanding among research participants in developing as compared with developed countries.

Overall, in this study 80% or more of initial answers were correct in all three groups. This compares favorably with previous studies of understanding in both developed and developing countries, although a lack of standardized instruments makes precise comparison with the other studies impossible. For example, another study of understanding among participants in a different malaria vaccine trial in Mali resulted in correct answers to multiple choice questions by between 7% and 73% of participants.[20] A study of parents of child participants in a South African tuberculosis vaccine trial whose authors judged its results "encouraging" showed correct recall between 37% and 85% of the time.[21] Likewise, a cross-sectional survey of participants in 73 different Phase 1, 2, and 3 oncology trials in the United States revealed widespread confusion about the purpose, procedures, and risks of trial participation.[22]

United States participants had a much better understanding on two questions—concerning experimental procedures and risks—and a small but significant improved understanding overall. Results may have been biased by the high rate of

errors detected in questionnaire administration in Mali for one question regarding risk. However, this question ("This vaccine has been given to hundreds of people already, so we know it is completely safe") was also one of the questions less likely to be answered correctly in the United States. This question may have been especially problematic, because it contains two concepts: "This vaccine has been given to hundreds of people already," and "we know it is completely safe." Risk was the concept least well understood in the previous study of understanding in Mali and was also poorly understood by oncology patients in the United States.[20,22]

More than 90% of participants at all sites correctly answered the question regarding withdrawal of consent. This contrasts with other studies indicating that participants in the developing world are more likely to feel pressured into enrolling into research,[12,23] and often have a poor understanding of their right to withdraw.[10,20,24]

Over 80% of Malian participants correctly answered the question about randomization ("Everybody in this study will get the same kind of vaccine," correct answer false). Although the United States vaccine trials in this assessment of consent were also randomized, this question was not included in the United States questionnaires. In previous studies in both developed and developing countries it is frequently the case that 50% or fewer participants understand that they will be randomized.[13,25,26]

In the Mali child study, scores for parents/guardians were higher for those who were literate; however, no data were available for age and sex so whether this is a true effect of literacy or rather because of age or sex, which are confounded with literacy in Mali (younger males being more likely to be literate), is not known. Notably, though illiteracy is associated with lower understanding, the high scores for Malian participants, who were mostly illiterate, suggest that illiteracy need not be a barrier to valid consent. In both countries younger volunteers were more likely to achieve higher scores. This is consistent with previous research indicating that increased age may be a predictor of lower understanding.[27,28]

The study has several limitations. The questionnaires were intended for teaching participants, rather than for collecting data. Some of the differences observed may have resulted from different modes of conveying the information: potential participants in the United States received written questionnaires, whereas most participants in Mali consented orally. Results from one developed and one developing country may not generalize to other contexts. Moreover, the comparative analysis rests on just seven questions concerning understanding that were the same or very similar between the sites. A study specifically designed to compare understanding among trial participants at different sites, and one that covered all aspects of the requirements for informed consent, would be needed to draw more comprehensive conclusions. However, the opportunities to gather such data are rare, and this study is a unique "snapshot" of understanding of consent in a set of clinical trials conducted in widely varying settings yet still using similar investigational products and similar protocols. Continued efforts to enhance understanding at both sites are ongoing, and questionnaires have been revised for greater clarity. Women in Mali, men in the United States, and older volunteers at both sites may particularly benefit from more intensive efforts to increase understanding.

Received January 28, 2010. Accepted for publication May 14, 2010.

Acknowledgments: We are grateful for the assistance of Mark Pierce, the former head of the clinical group at the Malaria Vaccine Development Branch of NIAID. We also thank the Institutional Review Board members in the United States and Mali, Etsegenet Meshesha, Regina White, Mohamed Balla Niambele, Wenjuan Gu, study guides and witnesses at the sites in Mali, and study volunteers at all sites.

Financial support: This research was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID).

Disclaimer: The authors declare that they have no conflicts of interest.

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