FACTORS RELATED TO VOLUNTEER COMPREHENSION OF INFORMED CONSENT FOR A CLINICAL TRIAL

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Abstract. The informed consent process has become a universal requirement for research involving human subjects. Its goal is to inform volunteers regarding research in order to make decision to participate or not. This study aimed to measure volunteers' comprehension levels concerning the clinical trial and to find out factors associated with that comprehension levels. Eighty-one volunteers who enrolled in a malaria clinical trial were recruited into the study. A semi-structured questionnaire was used to collect the information. Non-participant observation was used to observe the process of informed consent. Volunteers were interviewed three days after being recruited into the trial. The results show the volunteers' comprehension was low. Only 44% of volunteers had an acceptable level of comprehension. It also revealed that 20 volunteers were not aware of being volunteers. Most volunteers knew about the benefits of participating in the trial and realized that they had the right to withdraw from the study, but not many knew about the risks of the trial. The results indicated the method of informing about the trial affected the volunteers' comprehension level. No relationship was found between comprehension level and volunteers' socio-demographic characteristics and their attitude toward the consent process. The findings from this study demonstrate volunteers who participated in the clinical trial were not truly informed. Further studies regarding enhancing volunteers' understanding of the trial are needed.

INTRODUCTION

Informed consent for research is a requirement for all studies involving human subjects (Johnson and Nelson, 2000; World Medical Association, 2000; CIOMS, 2002). Those requirements were made clear in the Declaration of Helsinki of the World Health Organization, which is widely regarded as providing the fundamental guiding principles of research involving human subjects (Angell, 2006). The concept of informed consent to research derives from ethical and legal theories which have been emphasized in The Nuremberg Code about the necessity of informed consent (Grady, 2002). The aims of the informed consent process are to ensure respect for the volunteer and to guarantee participant autonomy. Valid informed consent is a key to ethical research (Flory and Emanuel, 2004). For valid informed consent, the volunteer

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should have free choice and sufficient knowledge and comprehension of the subject to make an informed decision (Hewlett, 1996). It is not enough for volunteers to receive information, they should understand the trial they participate in. Comprehension is a necessary component of valid consent and essential for decision making. A volunteer's decision based on understanding will protect them from being taken advantage of by the researcher. Moreover, it ensures that volunteers who participate in the trial are free from coercion (Lynoe *et al*, 1991).

Although the use of an informed consent document has become common practice in medical research, some participants may not be truly informed (Mackin, 1999). Studies of the informed consent process show many research volunteers do not understand the study in which they were enrolled, nor their rights as participants, despite having signed a consent form (Mason and Allmark, 2000; Joffe *et al*, 2001; Schowen and Friele, 2001). If a volunteer does not fully understand the nature of the clinical trial, this may produce several undesirable outcomes, such as less satisfaction with their decisions to enroll in the trial, which may ultimately lead to regret about participation in the trial (Stryker *et al*, 2006). In addition, lack of understanding among a volunteer in research can lead to non-adherence and unethical studies. Several studies have found volunteer comprehension may be influenced by several factors, such as age and education (Featherstone and Donovan, 2002; Treschan *et al*, 2003). The process of informed consent may affect volunteer comprehension, but few studies have been done to confirm this aspect. Studies regarding volunteer comprehension have been given less attention, despite the fact that researchers have a responsibility to ensure the volunteer understands their participation in research (Davis *et al*, 1998b). Moreover, researchers in developing countries may pay more attention to the benefits of research and less attention to human rights and volunteer comprehension (McMillan and Conlon, 2004). Although there have been some studies regarding volunteer comprehension, most have been conducted in developed countries (Wirshing *et al*, 1998; Joffe *et al*, 2001; Wills and Holmes-Rovner, 2003). This study was designed to explore volunteer comprehension and find out the factors associated with comprehension. The goal was to measure comprehension of the volunteers according to the elements of informed consent. Factors related to the informed consent process were included to determine volunteer comprehension.

MATERIALS AND METHODS

Selection of clinical trials for the study

Using a snowball technique, 12 clinical trials of different departments from various medical institutions, including the National Cancer Institute of Thailand and Faculty of Medicine Siriraj Hospital, were approached and invited to participate in this study. All, except one, disagreed. Reasons for not agreeing included small sample size and inconvenience of time or place. Written consent was obtained from the accepting investigator team and official permission was given by the higher administrative unit of the project.

Subject

The subjects in this study were volunteers involved in a malaria clinical trial. There were 145 volunteers enrolled in a clinical trial between December 2004-December 2005. Under the inclusion criteria for this study, 81 volunteers (55.8% of the clinical trial volunteers) were included. The inclusion criteria for subjects in this study were: age 18 years or older, able to communicate in Thai, went to malaria clinics at Ratchaburi, Trat, Ranong and Kanchanaburi provinces and willing to participate in the study.

Description of the clinical trial

The clinical trial was undertaken to assess the efficacy of an antimalarial drug for uncomplicated faciparum malaria. It was carried out at the malaria clinics in eight provinces: Mae Hong Son, Tak, Kanchanaburi, Ratchaburi, Ranong, Ubon Ratchathani, Chanthaburi and Trat. A minimum of 50 patients per province were included for this trial yearly.

The inclusion criteria were age older than 10 years, infected only with *P. falciparum* with initial parasite densities between 1,000 and 100,000 asexual parasites/ml and an axillary temperature ≥37.5ºC. Patients who met all the inclusion criteria were informed about the objective, procedure and potential benefits and risks of treatment. The patients were then asked to participate in the trial. If the patients were willing to participate they received an information sheet and scheduled for a follow-up visit. The first day the volunteer was enrolled and received the first dose of medicine was designated day 0. The follow-up visits were scheduled on days 1, 2, 3, 7, 14, 21, 28, 35 and 42 (total of 9 visits). Blood samples and axillary temperature were taken at each of the follow-up visits. The volunteers received travel expenses to come to the malaria clinic.

Study instrument

A combination of methods were used to collect data: semi-structured questionnaire and non-participant observation. The semi-structured questionnaire was developed and pre-tested with 20 volunteers in another group of patients. Then the questionnaire was modified accordingly. The questionnaire covered four parts: socio-demographic characteristics, actual practices during the informed consent process, attitude toward participating in the clinical trial and informed consent process, and comprehension concerning the trial. The comprehension part covered basic elements of informed consent, such as propose of the study, study procedure, risks, benefits, confidentiality and withdrawal. The questions for measuring the volunteer's comprehension consisted of 19 items in multiple-choice format with some open-ended questions. Non-participant observation was used to observe the process of informed consent between the research assistants and volunteers.

Data collection

A total of 81 volunteers from four provinces were interviewed during their third visit to the malaria clinics for follow-up of the clinical trial. Data collection was carried out during December 2004-December 2005.

Data analysis

Coding and grouping. Attitude statements were structured in a 3-point Likert scale with responses being either agree, not sure and disagree. The attitude scores which were equal to or greater than the mean score were grouped as positive, and the rest were grouped as negative. For comprehension questions, correct and incorrect answers were given one and zero point, respectively. The total of comprehension score was 19 points. A score at least 70% of the total score (13.3 points) was used as a cut-off level. Volunteers with comprehension scores equal to or greater than 13.3 points were classified as having an acceptable level of comprehension, and volunteers with scores less than 13.3 points were grouped as having a below acceptable level of comprehension.

Statistical analysis. Descriptive statistics, including frequency, mean, standard deviation and percentage were used to describe the socio-demographic characteristics of the volunteers and the informed consent process. Bivariate associations with comprehension score were assessed with the Student's *t*-test and ANOVA.

Human subject protections

Permission to carry out this study was

obtained from both the principal investigator and the Director of the Bureau of Vector Borne Disease, Department of Disease Control, Ministry of Public Health, Thailand. The study was approved by the Committee on Human Rights Related to Human Experimentation, Mahidol University, Bangkok and The Ethical Review Committee for Research in Human Subjects, Ministry of Public Health, Thailand. Before enrolling in the study, volunteers were informed of the purpose of the study, procedures, benefits and possible risks that may be involved. Volunteers were also informed that all information obtained in this study would remain confidential and they had the right to refuse to participate in the study and could end the interview any time. Informed consent was taken from all volunteers prior to their participation. To protect the confidentiality of the volunteers, the results were given to the principal investigator as a group, not per individual volunteer.

RESULTS

Volunteer characteristics

The characteristics of the volunteers in this study are summarized in Table 1. Forty-four percent of the volunteers came from Ratchaburi Province. Most of them (74.1%) were male. Fifty-two percent of volunteers was married, 42% were single. The age range was between 18 and 58 years, with a mean of 32 years. Half the volunteers had completed primary school, 34.5% were illiterate. Most of them (69.1%) had a low income (3,000 baht or less); only 13.6% had an income more than 5,000 baht per month. More than 60% of them were laborers, and about 11% were in non-income generating groups, such as housewives, students and monks.

Attitude toward informed consent and participating in a clinical trial

With regards to the attitude toward informed consent, most volunteers (73.8%) had a positive attitude, while 26.2% had a negative attitude. About sixty percent of volunteers had a positive attitude toward participating in the clinical trial and 39.3% of volunteers had a negative attitude (Table 2).

Informed consent process

The informed consent process, including the method of receiving information, length of time spent to obtain informed consent and

Table 1
Volunteer demographic information.

	Volunteer (n=81)
No. of volunteers per province	
Ratchaburi	36 (44.4%)
Trat	24 (29.6%)
Kanchanaburi	17 (21.0%)
Ranong	4 (5.0%)
Ages (years)	
≤ 20	13 (16.1%)
21-30	30 (37.0%)
31-40	15 (18.5%)
41-50	16 (19.8%)
≥ 51	7 (8.6%)
Mean age±SD	32±10.9
Gender	
Male	60 (74.1%)
Female	21 (25.9%)
Marital status	
Married	42 (51.9%)
Single	34 (42.0%)
Widowed/separated	5 (6.1%)
Education	
No schooling	28 (34.5%)
Primary school	42 (51.9%)
Secondary school	11 (13.6%)
Monthly income (baht)	
≤3,000	56 (69.1%)
3,001-5000	14 (17.3%)
>5000	11 (13.6%)
Occupation	
Laborer	50 (61.7%)
Farmer/Gardener	15 (18.5%)
National park staff/Soldier	4 (4.9%)
Merchant	3 (3.7%)
Non-income generating	9 (11.2%)

Table 2
Attitude regarding informed consent process and participating in clinical trial.

Attitude	Informed consent process No. (%)	Participating in the clinical trial No. (%)
Negative	21 (26.2)	32 (39.3)
Positive	60 (73.8)	49 (60.7)

opportunity to ask questions after informed consent, were covered. Twenty volunteers did not know they were volunteers in a clinical trial, and said they did not receive any information about the trial. Therefore, only 61 volunteers were asked about the informed consent process. About 77 % of volunteers who received information about the trial received only verbal information. The rest (22.9%) received information both verbally and in writing. The average time for the informed consent process was 11 minutes ranging from 3-30 minutes. Most of volunteers (83.6%) were given informed consent within 15 minutes. After being informed, only 16.4% of volunteers asked questions, the rest (83.6%) did not (Table 3).

Comprehension

The comprehension score of the 61 volunteers varied from 5 to 18, with a mean score equal 11.5, 66.6% of the total score. With a cut-off point of 70% of the total score used for categorizing volunteers, 44% of volunteers had acceptable levels of comprehension, the rest (56%) had scores below the acceptable level. Most (78.7%) could recall benefits of participating in the trial, and half (50.8%) knew the purpose of the trial they participated in. About 69% knew the trial procedure and about 75% knew the duration of the clinical trial. Only 6% of the volunteers could recall being informed regarding the risks and discomfort during the informed consent process (Fig 1). Nearly 60% believed the information regarding the volunteer in the trial would be kept confidentially. About 30% of volunteers believed they could not withdraw from the trial, half (53.1%) knew they were able to withdraw from the trial at anytime. The remainder (17.3%) said they could withdraw if they had a reason (Table 4).

There was no significant difference between the comprehension score and sociodemographic characteristics and study sites.

Table 3
Frequency of volunteers by informed consent process (N=61).

Informed consent process	Frequency No. (%)
Method of giving information	
Verbal	47 (77.1%)
Verbal and written	14 (22.9%)
Time for explanation	
≤ 15 minutes	51 (83.6%)
> 15 minutes	10 (16.4%)
Asking questions	
Yes	10 (16.4%)
No	51 (83.6%)

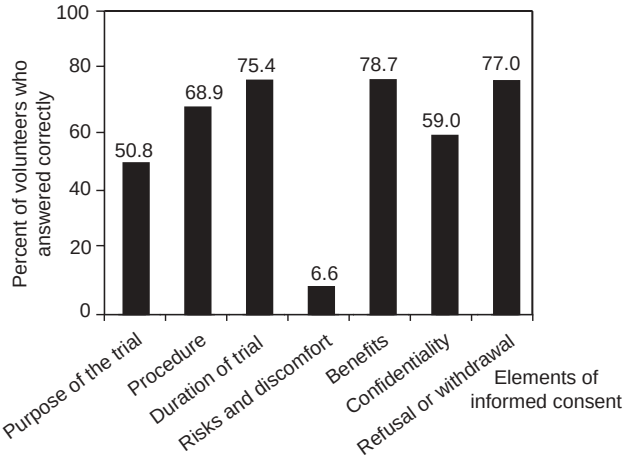

Fig 1–Comprehension of volunteers concerning elements of informed consent.

Comprehension scores among volunteers with positive and negative attitude were not different (Table 5).

Comprehension scores were significantly different between volunteers who received verbal information only and those who received both verbal and written information. Comprehension scores among volunteers who received both types of information were higher than those who received verbal information only.

Comprehension scores of volunteers who asked questions were slightly higher than those of volunteers who did not ask question, but with no significant difference. No significant difference appeared between the time of the informed consent process and the comprehension scores (Table 6).

Although this study did not directly affect the original trial, it made the volunteers realize that they were volunteers in a clinical trial. This realization did not cause volunteers to withdraw from the trial.

Table 4
Volunteer comprehension concerning freedom to withdraw.

Item	Frequency No. (%)
Withdraw at any time	43 (53.1%)
Not allowed to withdraw	24 (29.6%)
Withdraw with good reason	14 (17.3%)

Table 5
Comprehension scores by attitude toward informed consent process and attitude toward participating in clinical trial.

	Comprehension score	Std. deviation	p-value
Attitude toward informed consent process			
Positive	11.6	3.3	0.78
Negative	11.3	4.0	
Attitude toward participating in clinical trial			
Positive	11.1	2.8	0.19
Negative	12.3	3.8	

DISCUSSION

To our knowledge, this is one of the first studies to explore volunteer comprehension and factors associated with comprehension in a clinical trial in Thailand. Comprehension of volunteers in this study was lower than expected when 70% of the total score was used as a cut-off point. Volunteer comprehension in this study was lower than in a study by Scanlan *et al* (2003) who used a multiple-choice questionnaire to test patient compre-

Table 6
Comprehension scores regarding informed consent process.

Informed consent process	Comprehension score	Standard deviation	p-value
Method of giving information			
Verbal	11.0	3.4	0.03
Verbal and written	13.3	2.9	
Time for explanation			
≤ 15 minutes	11.6	3.5	0.83
> 15 minutes	11.3	3.4	
Asking questions			
Yes	12.6	3.3	0.30
No	11.2	3.5	

hension, and noted a comprehension mean of 73%. In our study, more than half the volunteers (56%) were below acceptable level of comprehension.

Regarding the method to inform the volunteer, the results show that volunteers who received both verbal and written information had comprehension scores greater than volunteers who receiving verbal information alone. This finding is consistent with studies regarding verbal and written information and volunteer comprehension (Tindall *et al*, 1994; Mayeaux *et al*, 1996; Davis *et al*, 1998a).

Similar to a study by Yuval *et al* (2001), this study found the duration of the information process did not have any effect on the comprehension level. The range of time for the informed consent process in the study was large (3-30 minutes). This result indicates the amount of time used in the informed consent process may vary among research assistants and volunteers. Sometimes research assistants did not have much time to inform the volunteer because other patients were waiting for the service. Some volunteers needed longer time to inform because of hearing problems.

After informed consent, volunteers had the opportunity to ask questions, however, few volunteers asked questions. In the Thai culture, patients do not ask for clarification because they are afraid of the medical provider. In addition, asking questions may make them look stupid (Rothmier *et al*, 2003). Although there is no significant association between asking questions and comprehension of volunteers, comprehension scores among volunteers who asked questions were slightly higher than those who did not.

No significant difference was found between comprehension level and socio-demographic characteristics, knowledge and attitudes towards the consent process. This finding supported McGaughey's study (McGaughey, 2004), which reported that age and education did not influence comprehension. However, a study by Treachan *et al* (2003) showed age and education level influence patient understanding of the trial.

Similar to Tattersal's study (2001), this study revealed that some subjects did not know they were volunteers in a trial. Three possible reasons could explain this: first, when the patient came to the malaria clinic and signed consent, they were sick with malaria, so they may not remember being informed. This finding is similar to a study by Schaeffer *et al* (1996) which revealed the severity of the disease affected the volunteers' comprehension. Second, research assistants who asked for consent from the volunteers did not clearly explain the information to the volunteer. Third, volunteers may not have been able to differentiate between being a volunteer in a trial and being a patient for regular treatment. Some believed this trial was a part of regular treatment.

Few volunteers were concerned about risks and discomfort because they took the pain required for the blood sample to be taken for granted. The majority of volunteers could respond correctly to the issue of benefit of participation, since this benefit was an important reason that motivated them to participate in the clinical trial. However, 30% were unaware of their right to withdraw. This could lead to unethical conduct.

Since the study was only conducted in one clinical trial, it cannot be generalized to all trials in the country. However, it demonstrates the informed consent process, a requirement for research, was not adequate. Some volunteers were not aware of being volunteers, while others had low levels of comprehension. This information might be used by ethical review committees to inform investigators to take the informed consent process more seriously. The positive aspects of the

informed consent process, such as helping the volunteer to cooperate better, should be informed as well. In addition, the ethical review committee may offer training to the investigators on how to carry out an effective informed consent process. This should maintain a good relationship between the trial investigators and the ethical review committee.

In conclusion, despite a long standing mandate for clinical researchers to obtain informed consent from volunteers, this study demonstrated that volunteers were not truly informed. Lack of comprehension among volunteers in clinical trials still happens. The method of informing the volunteer had an effect on volunteer comprehension. A combination of verbal and written information affects comprehension of the volunteers. The results of this study can be used to develop interventions to facilitate the appropriate recruitment of volunteers to participate in studies. There are other factors which can influence comprehension which this study did not evaluate such as severity of illness, payment and staff interaction. Further studies of these factors are needed.

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