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How Well Informed of Participants in Clinical Trials: A Case Study of China

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Abstract

Background: With the development of globalization, the rising cost of clinical trials in Europe and the United States, and the huge drug consumption market in developing countries, multinational pharmaceutical giants have set their sights on emerging developing countries. As a leader in developing countries, China has unparalleled advantages, so more and more clinical trials are registered and carried out in China. **Objective:** The objective of the study is to understand the current practice of informed consent in clinical trials in public hospitals in Xuzhou. **Methods:** In this study, a 15-question questionnaire was distributed to 369 subjects in the affiliated hospital of Xuzhou medical university. Each question was graded on a 3-point scale (1 = no, 2 = unsure, 3 = yes). The sum of the scores for the 15 questions represented the level of awareness of clinical trials. **Results:** Valid questionnaires were received from 300 subjects. A considerable number of subjects still had insufficient understanding of clinical trials, especially concerning the nature of clinical trials, understanding of informed consent forms, contact with researchers, and ethics committee. (The "yes" rate was around or below 50%). Factors associated with responses to the survey include education, occupation, and source of medical expenses. **Conclusion:** Overall, this study showed that the implementation of informed consent in China remained room for improvement. Legislators, ethics officers, and researchers should work together to protect the interests of subjects.

Keywords

Clinical Trials, Informed Consent, Ethics-Research, China

1. Introduction

Clinical trials are playing an irreplaceable and important role in promoting the progress of medical science. China has become a vital country for conducting clinical trials considering its large population and increasing importance as a key player in global health [1] [2]. As a basic principle in modern medical ethics, informed consent is a process to ensure that participants fully understand the information relevant to the trial and then decide whether to accept or decline participation [3] [4] [5]. Informed consent is a prerequisite for enrolling human subjects in biomedical research [6] [7]. The World Medical Association (WMA)'s "Declaration of Helsinki" (DoH) [8] and the International Medical Science Organization Committee (CIOMS)'s "International Ethical Guidelines for Human Biomedical Research" [7] have provided ethical principles regarding human experimentation. China's "Good Clinical Practice" (GCP) [9] also stipulates that all research on human subjects must comply with the principles of DoH: respecting a participant's autonomy and protecting participants from harm [10].

Although the importance of the completeness of disclosure and the standardization of the procedure during the informed consent process is emphasized, informed consent is still a challenge to carry out in practice [11] [12]. Numerous studies have shown that a large number of participants cannot completely understand the content of informed consent forms because of too many obscure descriptions [13]-[18]. In addition, patient-centered barriers and researcher-centered barriers can hinder the informed consent process [19] [20]. These deficiencies lead to inadequate understanding of clinical trials and potentially threaten the safety of participants.

China remains the world's largest developing country. The economic and technological development is unbalanced between south and north, urban and rural areas [21]. Compared with southern Jiangsu, an economically advanced coastal province in China, the medical resources in the northern part are relatively poor. Xuzhou, as the "leader" of northern Jiangsu, its medical environment and implementation of informed consent show special reference to developing areas. Our study aimed to explore the protection of subjects' informed consent rights in drug clinical trials in Xuzhou and find the existing problems, so as to provide insights into the deficiencies and misunderstanding of the informed consent process and provide a sound basis for the standardization of the informed consent process in China.

2. Materials and Methods

2.1. Study Design

This study used a quantitative survey design. The survey study of patients was conducted between July and August of 2021. We selected the affiliated hospital of Xuzhou medical university as the field site in Xuzhou. This hospital was chosen because its medical capacity and services are considered to be the highest in

northern Jiangsu, and numerous patients from other parts of China, especially from adjacent less developed cities and provinces, seek medical care in this hospital. Participants must fulfil four criteria: 1) in-hospital patients after signing the informed consent forms; 2) aged over 18 years; 3) patients who voluntarily enrolled in this study; 4) conscious patients without psychiatric disorders. In total, 369 in-hospital patients have participated in the study. The questionnaires were sent to them to investigate their basic information and their understanding of informed consent for clinical trials.

2.2. Questionnaire Development

The understanding assessment part of the questionnaire was limited to 15 questions with a three-point response scale. The comprehension score was evaluated from level 1 to 3, with higher values indicating better understanding. A questionnaire scored 1 point if the participant chose "No", 2 points if the participant chose "Unsure", 3 points if the participant chose "Yes". The sum of the scores for the 15 questions represented the level of awareness of clinical trials. The reliability of the questionnaire was 0.718, which implied that the questionnaire was well designed.

In addition to the understanding questions, sociodemographic data (gender, age, education, occupation, source of medical expenses, source of participation in clinical trials) were also collected.

2.3. Data Collection

Data was collected using a questionnaire in Chinese, the language spoken by the study participants. The questionnaires were provided by researchers who have solid experience in conducting interviews during a face-to-face discussion with the study participants.

The risk of participating in this study was small and low levels of discomfort may occur due to the setting of the questions. Before participants filled in the questionnaire, the researchers briefly described the purpose and significance of the study and explained that the questionnaire is anonymous. Researchers who conducted clinical trials were unable to obtain positive or negative responses to the questionnaire, and participation in clinical trials was unaffected. During the process, participants were not in a hurry. When they had questions or didn't understand something, they were given an answer.

2.4. Data Analysis

Statistical analysis was performed with SPSS 25.0 software. We performed descriptive statistics, univariate analyses of variance (ANOVA), and multivariate analyses of variance (MANOVA). Statistical significance was set at 0.05.

3. Results

In order to eliminate possible interference factors, this survey selected all sub-

jects (a total of 369 participants) who participated in the third batch of clinical trials in the drug clinical trials institution of Xuzhou Medical University Affiliated Hospital. However, 69 surveys were discarded because responses to questions in the questionnaire were incomplete. Therefore, only 300 patients from the study were included in the analyses.

3.1. Sociodemographic Data of the Sample

Sociodemographic data of the sample are presented in Table 1. The proportion of male and female participants was 51.7% and 48.3% respectively. The results of this survey showed no significant gender bias. Most participants were aged between 56 and 70 (32.7%), were peasantry (28.3%), had less than 15 years of education (85.3% didn't attend college). More than half of the participants (53.7%) paid their medical bills mostly by themselves. 62.4% of the patients got access to participation in clinical trials from doctors.

3.2. Participants' Understanding of Clinical Trials

Responses to the 15 questions relating to the understanding of clinical trials are presented in Table 2. The validity of the questionnaire was 0.767, which could truly reflect the participants' understanding of clinical trials. Regarding the participants' understanding of the risks and benefits, less than 50% (49.7%) of participants agreed that clinical trials provide free treatment with both risk and benefit. Quite a lot of participants (45.6%) answered "not sure". Also, roughly a third of participants (33.7%) were unsure about whether there are related laws of scientific and ethical issues in clinical trials. Similar percentages were recorded for the questions evaluating the participant's subjective understanding of the informed consent form. The same number of participants answered "not sure" when asked about whether they could fully understand the informed consent form after the doctor's explanation and 20.7% answered "No". Regarding the purpose of research, 77.7% of participants agreed that clinical trials are meaningful for the medical development and treatment of future patients. Almost all patients (95.7%) knew that they would sign the informed consent forms before attending clinical trials. Additionally, nearly all of the respondents (99.0%) said that they were voluntary to participate in clinical trials. The percentage of participants who agreed that they were free to withdraw at any time during clinical trials is also above 90%. Roughly 90% (87.3%) agreed that doctors would keep their information confidential during clinical trials. However, regarding the contact with researchers in charge or with the ethics committee, the rates of "Yes" drop sharply and fluctuate around 50%. 64.3% were sure that they had the contact information of the doctor or nurse in charge of the trial. When it comes to the ethics committee, only 56.0% knew that they could appeal to the ethics committee if they get injured during the trial. Based on this, only 53.3% said that they were aware of the phone number of the ethics committee. Concerning details in the process of clinical trials, more than one-third of participants were not aware of or unsure about the meaning of "placebo" (10.3%, 23.3% respectively).

What's more, 7.3% were not aware of the fact that they would be randomly assigned to a control group or treatment group and 21.0% were not sure.

Table 1. Sociodemographic data of the sample.

Variable	Number
Gender	
Male	155 (51.7%)
Female	145 (48.3%)
Age	
25 and below	25 (8.3%)
26 - 40	81 (27.0%)
41 - 55	78 (26.0%)
56 - 70	98 (32.7%)
70 and above	18 (6.0%)
Education	
Junior high and below	132 (44.0%)
Senior high	124 (41.3%)
College graduate	35 (11.7%)
Postgraduate and above	9 (3.0%)
Occupation	
Worker	49 (16.3%)
Peasantry	85 (28.3%)
Educator/healthcare worker	24 (8.0%)
Employee in state-owned enterprises	24 (8.0%)
Freelancer	54 (18.0%)
Retired	19 (6.3%)
Service employee	11 (3.7%)
Student	11 (3.7%)
Others	23 (7.7%)
Source of medical expenses	
Mostly paid by the company or insurance	122 (40.7%)
Mostly paid by myself	161 (53.7%)
Borrowed	12 (4.0%)
No source of income	5 (1.6%)
Source of participation in clinical trials	
Doctors	187 (62.4%)
Family and friends	39 (13.0%)
Social media	10 (3.3%)
Others	64 (21.3%)

Table 2. Participants' understanding of clinical trials.

Question	No	Unsure	Yes
Clinical trials provide free treatment with both risk and benefit.	14 (4.7%)	137 (45.6%)	149 (49.7%)
Clinical trials are meaningful for medical development and treatment of future patients.	16 (5.3%)	51 (17.0%)	233 (77.7%)
I will sign the informed consent forms before attending clinical trials.	3 (1.0%)	10 (3.3%)	287 (95.7%)
I am voluntary to participate in clinical trials.	0 (0.0%)	3 (1.0%)	297 (99.0%)
Doctors will keep my information confidential during clinical trials.	2 (0.7%)	36 (12.0%)	262 (87.3%)
I am free to withdraw at any time during clinical trials.	10 (3.3%)	17 (5.7%)	273 (91.0%)
I will get compensation of damage as a result of clinical trials.	3 (1.0%)	44 (14.7%)	253 (84.3%)
There are related laws of scientific and ethical issues in clinical trials.	23 (7.7%)	101 (33.7%)	176 (58.7%)
I think the informed consent form is sufficiently detailed.	44 (14.7%)	33 (11.0%)	223 (74.3%)
After the doctor's explanation, I can fully understand the informed consent form.	62 (20.7%)	101 (33.7%)	137 (45.7%)
I have the contact information of the doctor or nurse in charge of the trial.	50 (16.7%)	57 (19.0%)	193 (64.3%)
I can appeal to the ethics committee if i get injured during the trial.	44 (14.7%)	88 (29.3%)	168 (56.0%)
I am aware of the phone number of the ethics committee.	113 (37.7%)	27 (9.0%)	160 (53.3%)
I am aware of the meaning of "placebo".	31 (10.3%)	70 (23.3%)	199 (66.3%)
I am aware of the fact that i will be randomly assigned to control group or treatment group.	22 (7.3%)	63 (21.0%)	215 (71.7%)

3.3. Factors Associated with Responses to the Survey

Univariate analyses showed that education ($P = 0.009$), occupation ($P = 0.001$), source of medical expenses ($P < 0.001$) were significantly correlated with the level of patients' understanding (Table 3). To be specific, college graduates had the highest understanding of clinical trials. Meanwhile, junior high school graduates and elementary school graduates had the lowest understanding of clinical trials. In terms of occupation, educators, healthcare workers or employee in state-owned enterprises showed the highest level of understanding of clinical trials. Otherwise, workers and peasantry had the greatest difficulty in truly understanding drug clinical trials. Another influencing factor was the source of medical expenses. Statistics showed that participants who paid medical expenses by insurance had a better understanding than those who paid by themselves or borrowed money. Other factors such as age, gender, source of participation in clinical trials were not found to be related to patients' understanding of clinical trials ($P > 0.05$).

Multivariate analyses showed that the source of medical expenses had the greatest impact on the understanding of clinical trials and was the only independent factor affecting the level of informed consent (Table 4). Participants who paid medical expenses by insurance had a better understanding of clinical trials.

Table 3. Univariate analyses of subjects' understanding of clinical trials.

Variable	Number	X2/t	P
Gender			
Male	155	1.627	0.105
Female	145		
Age			
25 and below	25		
26 - 40	81	0.199	0.939
41 - 55	78		
56 - 70	98		
70 and above	18		
Education			
Junior high and below	132		
Senior high	124	3.943	0.009
College graduate	35		
Postgraduate and above	9		
Occupation			
Worker	49		
Peasantry	85		
Educator/healthcare worker	24		
Employee in state-owned enterprises	24	3.552	0.001
Freelancer	54		
Retired	19		
Service employee	11		
Student	11		
Others	23		
Source of medical expenses			
Mostly paid by the company or insurance	122		
Mostly paid by myself	161	6.431	P < 0.001
Borrowed	12		
No source of income	5		
Source of participation in clinical trials			
Doctors	187		
Family and friends	39	0.91	0.436
Social media	10		
Others	64		

Table 4. Multivariate analyses of variables associated with understanding of clinical trials.

Variable	Unstandardized Coefficients		Standardized Coefficients	t	P
	β	Std.Error	β		
Sex	−0.763	0.468	−0.092	−1.631	0.104
Age	0.115	0.277	0.03	0.414	0.679
Education	0.766	0.393	0.143	1.947	0.052
Occupation	−0.021	0.107	−0.012	−0.2	0.842
Source of medical expenses	−1.206	0.401	−0.184	−3.011	0.003
Source of participation clinical trials	−0.245	0.201	−0.072	−1.219	0.224

4. Discussion

Informed consent is vital in protecting participants' rights in human research. However, it is a challenge to ensure subjects are adequately informed and fully understand the research, and able to make a voluntary decision in taking part or declining participation [22]. There is still a big gap between the findings of this study and those of previous foreign studies [23] [24] [25]. In our study, only three questions reached an approval rate of 90%. The approval rate of the two questions was even no more than half. The disapproval or uncertainty rate of the nine questions reached 20%.

To determine factors associated with responses to the survey, we focused on four variables deemed central to patients' understanding of clinical research: age, education, occupation, and source of medical expenses. Univariate analyses showed that education, occupation, and source of medical expenses were associated with responses to the items selected. In terms of education, participants who only attended junior high school or below showed a poorer understanding of clinical trials than those who attended senior high or college. More educated participants were more likely to understand the purpose of research, the methods, the content of the informed consent form, the contact information of the researchers in charge, risks and benefits, and other clinical trial information. It can be presumed that participants with superior education are more willing to contribute to the promotion of medical science. Regarding occupation, educators, healthcare workers, or employees in state-owned enterprises showed the highest level of understanding of clinical trials. Otherwise, workers and the peasantry showed a poor level. Educators, healthcare workers, or employees in state-owned enterprises are more likely to receive higher education, understand and accept advanced things. They have more information, a broader vision, and a mind. While education and occupation are important, multivariate analyses indicate that source of medical expenses has a greater influence on patients' perceptions about clinical research. Participants who paid medical expenses by insurance had a better understanding than those who paid by themselves or bor-

rowed money. With less pressure to pay for their own medical treatment, participants feel more comfortable trying advanced clinical trials. Even if clinical trials fail, reverting to present treatments will not add to the financial burden. These findings provide insight regarding strategies to improve the recruitment of patients from diverse socioeconomic backgrounds. More importantly, it reflects the necessity of improving China's medical insurance system.

In China, current laws on clinical trials include the relevant provisions of "Law on Licensed Doctors of the People's Republic of China" and "Drug Administration Law of the People's Republic of China". Administrative regulations include "Measures for Ethical Reviews of Biomedical Research Involving Humans". Generally speaking, the legislative level is relatively low and the content is inadequate, especially the provision of informed consent. In practice, not all clinical trial participants truly understand the informed consent process. Apart from participants' own issues like educational issues, researchers may be to blame. In many cases, informed consent has become expedient for researchers to shirk their responsibility. At the same time, in China's profound cultural heritage, some traditional beliefs in Confucianism are contrary to the requirement of subjects' autonomy in informed consent [26] [27], which subtly increases the difficulty of subjects' autonomy. In China, doctors and subjects in clinical trials are more like parents and children (researchers recruit subjects and standardize all the procedures in the trials), rather than participants who actively hope to participate in clinical trials, and fully fulfill their rights and obligations informed by researchers.

To promote the practice of informed consent in China's health care system, we provide several possible solutions.

First of all, improve details and hierarchy of laws. At present, there is no targeted basic law, most are regulations and departmental rules whose legal effect is still insufficient. Moreover, the existing regulations on informed consent are still incomplete. For instance, the signing authority of the subject and his/her guardian is not clear. Although the role of "legal representative" in clinical trials was abolished in the 2020 version of GCP, it is likely that the guardian will replace the subject himself to decide whether to participate in a clinical trial, especially in the cases that subjects are children or people who have limited capacity to make decisions. Therefore, for children and people with limited capacity, the protection of their informed consent rights needs to be further increased.

Second, strengthen the supervision and examination of informed consent. The core purpose of an ethics committee is to protect the interests of subjects. One of the responsibilities of the ethics committee is to supervise and examine approved studies and to promptly address complaints and adverse events during the process of clinical trials. In order to ensure the practical implementation of informed consent, the ethics committee should not only strictly examine the informed consent form, but also continuously strengthen the protection of informed consent in the process of trials. The ethics committee can regularly send

personnel to supervise the process of clinical trials. They can inquire about the implementation of informed consent, and randomly examine whether the researchers have fulfilled the obligation of informed during the trials.

Third, strengthen training for researchers. At present, a number of Chinese researchers have insufficient cognition of clinical trials, which leads to the violation of protocols. Effective clinical trials training can improve researchers' awareness. The sponsor and the principal researcher should provide systematic and comprehensive training to all the researchers on possible problems and considerations in the process of trials before implementation. Furthermore, humanistic training in areas, such as communication skills, medical ethics, and professionalism, should be given more weight in the medical school curriculum and licensing process by medical policy-makers [28].

Finally, improve subjects' autonomy in participating in clinical trials. In many cases, although participants in clinical trials sign informed consent forms, they are not fully aware of their rights and duties. Chinese subjects' understanding of their autonomy is still in its infancy. Because of the lack of awareness, participants are prone to over-safeguard or be in a weak position, which requires ethics officers to tell the subjects proper measures. In addition, in order to enhance the self-consciousness of potential subjects, we suggest that ethics officers regularly go to communities to carry out relevant universal education.

Several limitations of this study must be considered. First, our sample was relatively small and all the participants were obtained from one single clinical trials institution. Although this institution is the biggest and the most authoritative one in Xuzhou, it is difficult to ensure complete consistency among patients in all developing areas. Further study should be carried out to assess the understanding of informed consent of patients from multiple clinical trials institutions. Second, our study lacked the information of those patients who refused to participate or failed to be included in the valid number. Third, the assessment may not accurately reflect the perspectives of our subjects.

5. Conclusion

This small-scale study gained an insight into patients' understanding of clinical trials by assessing their responses to a questionnaire. The results showed that factors influencing participants' understanding of the clinical trial were the level of education, occupation, and source of medical expenses. The findings also revealed weak points of the current informed consent process and a need to improve it. We suggested that legislators, ethics officers, and researchers should work together and put more effort to help participants achieve a better understanding of informed consent. Only with joint forces will they ensure that participants' decision-making is meaningful and that their interests are protected.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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