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Continuing review of ethics in clinical trials: a surveillance study in Iran

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Abstract

This study was conducted to examine adherence to ethical principles during research and the necessity to conduct systematic and continuing review of ongoing research in Iran.

All clinical trials approved by the Research Ethics Committee of Tehran University of Medical Sciences (TUMS) ongoing in 2007 (n = 21) were reviewed through receiving principal investigators' (PIs) reports, as well as reviewing patient consent forms. Two questionnaires were sent to PIs, one to collect information about the study and the other to evaluate PIs' perception and awareness about ethical codes of clinical trials. A representative of the TUMS research ethics committee was sent to the research site to fill a checklist by reviewing the obtained informed consent and fill the other checklist by interviewing a sample of participants regarding their perception of their volunteer participation in the clinical trial and receiving adequate information.

Only in 66.7% of the surveyed trials the objectives of the trial had been explained in the informed consent, and in 38.6% of the trials it was mentioned in informed consent that participation is voluntary. Among participants, 34.7% (n = 26) were not aware they were enrolled in a research project, 29.3% (n = 22) had not understood the information they had received, 74.7% (n = 56) did not know they could refuse to participate and still receive care from their physician, and 58.7% did not realize they were free to drop out of the study at any time.

The results point to the need for continuing review of clinical research, especially clinical trials, and the necessity for thorough assessment of patient consent forms during the process of approval in terms of their contents and their understandability.

Keywords: ***continuing review; clinical trial; research ethics; informed consent***

Introduction

Research Ethics Committees (RECs) were established in Iran more than 15 years ago. The national guideline of research ethics was released in 2000, and six specific guidelines were added in 2005 to place more focus on ethical considerations in research areas of clinical trials, genetics, vulnerable groups, organ and tissue transplantation, animals, and research on human embryo (1). The increasing number of medical researches and papers in Iran point to the important role of RECs in preserving the rights of participants. RECs in Iran are active in reviewing research proposals; however, it is not clear whether the review of proposals is enough to ensure protection of participants' rights.

One of the essential duties of RECs, as explicitly stated in the Declaration of Helsinki and the Iranian Ethics Guidelines, is ethical review of ongoing projects (2). This obligation, although necessary to ensure participants' rights and safety, is not fulfilled by any RECs due to the financial burden it causes for them. For this same reason, continuing review of ongoing research projects in other countries started with much delay compared to ethical review of proposals (3). According to the study by Thompson et al. in Scotland in 1980, only 6 of the 34 RECs (18%) had a formal process for continuing review of projects (4). In 1989, less than 50% of the RECs in Australia conducted continuing reviews; most of them were passive and relied on researchers' reports (5). In 1993, the National Council on Ethics in Human Research in Canada reported that 53% of committees requested annual reports from researchers and only 18% conducted continuing reviews (6). In a similar survey in 2007, the latter rate had reached 87.4%, although most continuing reviews were passive and mainly concerned clinical trials (7).

Tehran University of Medical Sciences first started continuing review of a number of projects approved by its REC during this study. Since clinical trials have more serious ethical considerations, all approved clinical trials conducted during 2007 were reviewed actively. Results can be a response for the needs assessment for conducting systematic continuing reviews of research projects by RECs in Iran.

Method

Research Tools

Questionnaire A. This questionnaire was completed by the PIs of clinical trials to collect information about the study. These included the start date, number of participants, occurrence of complications, changes in the study protocol, the intervention received by the control group, and the vulnerability of the participants.

Questionnaire B. In this questionnaire, investigators were asked 11 questions regarding their perception and awareness about ethical codes of clinical trials based on the National Guideline of Ethics in Clinical Trials. Responses to each question were "Yes", "No", or "Don't know".

Questionnaire C. This questionnaire was a checklist of informed consent requirements which was completed by the committee representative after viewing the informed consents obtained from study participants.

Questionnaire D. This questionnaire was completed by the REC representative through interviews with clinical trial participants. It contained 14 items concerning participants' information about the clinical trial in which they were participating, and their understanding of the information.

We did not evaluate the reliability of our data gathering method. In terms of validity, all questionnaires were reviewed by two research ethics experts.

Design

All ongoing clinical trials during October 2007 to March 2008 approved by the TUMS REC were enrolled in the study. The principal investigators (PIs) were informed about the study through a letter by the Secretary of the TUMS REC, and a representative was introduced to them for continuing review of their projects. Questionnaires "A" (study information and features) and "B" (investigators' awareness of codes of ethics for clinical trials) were sent enclosed with the letter, and investigators were asked to complete and return them. Follow-up reminder calls were made to investigators who did not respond. In the next stage, the REC representative visited the investigators and requested to see informed consent forms; questionnaire "C" was then completed based on the contents of informed consent forms. Investigators were required to provide the REC representative with the phone numbers and addresses of study participants. The representative randomly selected 10% of the study participants and received their contact information. The committee representative subsequently completed questionnaire "D" through phone interviews with participants by referring to their information about the study they were involved with.

Results

There was no response to the REC secretary letter in two cases of twenty-five ongoing clinical trials (response rate: 92%), and in two cases, the study was cancelled because no funding was received. Eventually, analysis was done with data

from 21 clinical trials summarized in Table 1. These 21 projects were being executed by 14 PIs.

Table 1. Attributes of the reviewed clinical trials

Variables		Percent	Number
Control group intervention	Standard treatment	35.0	7
	Standard + Placebo	50.0	10
	Placebo	5.0	1
	No treatment	5.0	1
	Non-standard inter-vention	5.0	1
Participants	Vulnerable groups	57.1	12
	Children	9.5	2
	Pregnant ladies	4.8	1
	Unconscious people	4.8	1
	Mentally disabled	23.8	5
Side effects leading to sample exclusion	Yes	19.0	4
	No	81.0	17
Protocol modification during execution	Yes	14.3	3
	No	85.7	18
Informed consent form	Lacking	15.8	3
	Exists	84.2	16

Informed consents of 18 studies were reviewed. In 3 trials, release of liability was obtained and information about the given study was not mentioned. Table 2 shows the inclusion of necessary items in the reviewed informed consents.

On average, 57.3 people were enrolled in each study. Ten percent of the participants (a total of 75 people from 15 trials whose phone numbers were provided for the REC representative) were interviewed. Twenty-five people (34.7%) had not signed their informed consents; in all these cases, studies were conducted on people with mental disabilities and children, and interviews were done with the person who had signed the consent form. Table 3 shows the patients' awareness of the clinical trial in which they were enrolled.

Table 2. Adherence to the ethical guideline in informed consent forms of clinical trials

	Items	**Yes No (%)**	**No No (%)**
1	Consent form is in simple language and free of jargons	12 (66.7)	6 (33.3)
2	Consent form explicitly states the project is a research	13 (72.2)	5 (27.8)
3	Research objectives are explained	12 (66.7)	6 (33.3)
4	Random assignment of participants to the treatment or control group is stated	2 (11.1)	15 (83.3)
5	Potential risks are explained	7 (38.9)	11 (61.1)
6	Potential benefits are explained	3 (16.7)	15 (83.3)
7	Other available treatment options, and their risks and benefits are stated	1 (5.6)	15 (83.3)
8	The compensation process, in case of harm, is explained	3 (16.7)	15 (83.3)
9	There is emphasis that participation is voluntary	7 (38.9)	11 (61.1)
10	The option to withdraw after giving consent, without punishment, is explicitly mentioned	10 (55.6)	8 (44.4)
11	Confidentiality and its process are explained in the form	9 (50.0)	9 (50.0)
12	The person(s) whom participants can contact for receiving more information is introduced	8 (44.4)	10 (55.6)
13	Circumstances that terminate participation are explained	2 (11.1)	16 (88.9)
14	Approximate participation time is mentioned	5 (27.8)	13 (72.2)

Table 3. Patients' awareness about the clinical trial in which they were participating

	Question	Yes No (%)	No No (%)	I don't know No (%)
1	Did you know you were part of a clinical trial?	46 (63.3)	26 (34.7)	3 (4.0)
2	Were you given written information about the research project or a copy of the informed consent form?	52 (71.2)	21 (28.8)	0 (0)
3	Did you receive verbal information about the research project?	59 (78.7)	16 (21.3)	0 (0)
4	Did you understand the information well?	52 (69.3)	22 (29.3)	1 (1.3)
5	Did you have the chance to ask your questions about the project?	54 (72.0)	19 (25/.3)	2 (2.7)
6	Were you given enough time to consider and decide about participating?	51 (68.0)	21 (28.0)	3 (4.0)
7	Were you told you could withdraw without any disruption in your care?	31 (41.3)	44 (58.7)	0 (0)
8	Were you informed what to do in case of side effects or concern?	27 (36.0)	47 (62.7)	1 (1.3)
9	Was it your perception that you were free not to take part in this project if you did not want to and your physician would give you the due treatment?	18 (24.0)	56 (74.7)	1 (1.3)

All PIs (14 people) completed the questionnaire concerning their information about ethical considerations of clinical trials; their median score was 4 out of 8 (Table 4). Seven (50%) were not aware of the specific ethical guideline on clinical trials. All investigators believed continuing review of ongoing clinical trials was necessary to maintain research standards.

Table 4. Principal investigators' perception and awareness of reviewed clinical trials

	Questions	Yes No (%)	No No (%)	I don't know No (%)
1	Is the investigator obliged to report any serious side effect to the ethics committee?	13 (92.9)	0 (0)	1 (7.1)
2	Should all clinical trials be reviewed for ethical issues every 6 months?	5 (35.7)	2 (14.3)	7 (05)
3	Does the ethics committee have the right to examine scientific qualifications of investigators?	5 (41.7)	4 (33.3)	3 (25)
4	Is it ethically permissible to do clinical trials in emergency situations when obtaining informed consent from the patient or guardian is not possible?	0 (0)	11 (78.6)	3 (21.4)
5	It is ethically permissible to obtain release of liability from participants of a clinical trial?	3 (25)	3 (25)	6 (50)
6	Does the research ethics committee have the right to access recorded research data directly?	7 (53.8)	2 (15.4)	4 (30.8)
7	Is the physician ethically allowed to adjoin clinical trials with medical treatments?	8 (66.7)	2 (16.7)	2 (16.7)
8	Did you know the research ethics committee should monitor research projects, especially clinical trials?	8 (57.1)	6 (42.9)	0 (0)

Discussion

Results of our study indicate that there are many shortcomings in observing ethics in research. Although research proposals were reviewed in terms of ethical considerations, 14% of the trials had not obtained written informed consents for participating in the project. An almost equal number of them had obtained signatures on release of liability forms rather than informed consent forms. In addition, protocol modification and serious side effects were not reported to the REC, and thus, it appears that a simple ethical review of proposals does not ascertain adherence to codes of ethics in research and it is necessary to have continuing review during execution to monitor such adherence in practice.

Our results revealed how little the investigators were aware of ethics codes in research; half of them did not know there was a special guideline on ethical considerations in clinical trials. Short or virtual refresher courses are needed for investigators to teach them the codes of ethics and better familiarize them with ethical principles especially in designing clinical trials.

In our study, one-third of the participants were not even aware they were taking part in a clinical trial. More than two-thirds were not aware they could refuse to participate and more than half did not know they were free to withdraw from the trial at any time. Part of this lack of awareness was due to failure to provide sufficient information in the informed consent forms and we found serious shortcomings in the reviewed informed consent forms. The lack of awareness can also be attributed to the readability of the forms to some extent. Many studies have demonstrated how unreadable and incomprehensible informed consent forms can be compared to public material (8-10). We did not examine readability of the consent forms, but the mismatch between the amount of given information and the level of understanding them (Tables 2 and 3) suggests the difficulty of the contents of the informed consents as one-third of the patients

stated they had not understood the information contained in the consent forms.

Another noteworthy finding was the failure to provide information regarding possible risks. In two-thirds of the trials, potential complications of participating in the study were not mentioned in the informed consent forms, and half of them had not designated someone who could be contacted in case of concerns or problems. Our interviews with patients showed that two-thirds did not know what to do in case of side effects. This observation, in addition to their failure to report serious side effects to the ethics committee, questions the safety of approved studies to a great extent.

In terms of trials' adherence to ethical codes, our findings were more comparable to older studies. In the study by Olver et al. in 1995, 60% of the patients had understood the contents of the informed consent form (11). In a study reported from Sweden in 1991, about 40% of the patients were not aware of their right to withdraw from the study and 16% did not know they were part of a research project (12). However, more recent studies have shown a better situation compared to our study. In a 1997 study, Smith et al. found that at least one consent form was incomplete in one fourth of studies (13). According to Mc Cuskers et al., only about 4% of consent forms differed from the original informed consent forms (14). One of the most recent studies, which was conducted in 2002 in the UK, reported that 99% of the patients understood all or most of the information and 95% had the opportunity to ask the investigators their questions (15). In our study, these figures were 79% and 72%, respectively. The rate of observing ethics in research may be lower in Iran compared to the UK and the US, but comparing our results with those of a study conducted 15 years ago at Tehran University of Medical Sciences shows a remarkable increase in this regard. According to Larijani and Rashidian, participants were aware of being in a trial in only 11.8% of studies, and informed consents were not obtained from 92.2% of participants; it should be mentioned, however, that one fourth of the studies were conducted on children. In 80% of the studies, the patient was charged for the treatment expenses, and if a placebo was used, participants were not aware that they were assigned randomly to one group or another (16).

Our study had limitations that should be noted. One limitation was that we did not match the reviewed informed consents with those presented in the proposal at the time of approval. Also, our study was restricted to clinical trials, which usually have more serious ethical considerations; we did not include all research projects with human samples and thus, results cannot be generalized to all research conducted at the university.

Our study is the first ethical review of ongoing clinical trials in Iran where all principal investigators believe continuing review of ongoing trials is necessary to maintain ethical standards in research. Teaching ethical codes along with performing continuing review of research projects can increase investigators' adherence to such codes and minimize changes that can reduce the safety of projects. Nonetheless, it must be noted that continuing review programs require considerable budget and staff, and their sustainability calls for a cost-effectiveness assessment of the review. Based on the result of this study the TUMS REC pioneered to plan for continuing ethical review in Iran.

This study demonstrated the essential role of continuing review of research projects, especially clinical trials, and the necessity to pay more attention to the contents of informed consent forms and assessment of their comprehensibility.

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Competing Interests

All authors declare having no conflict of interest.

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