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Reasons for Non-Participation of Turkish Patients in International Clinical Trials

Türk Hastaların Uluslararası Klinik Araştırmalara Katılmayı Kabul Etmeme Nedenleri

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Abstract

Objective: Turkey is an emerging country in terms of clinical research with a large population of patients not previously exposed to clinical trials. Despite its increasing importance in the clinical research field, the recruitment process is very difficult for various reasons and may become a serious research limitation. A project was designed and implemented with a view to understanding the perceptions of Turkish participants to clinical trials.

Methods: Investigators were given a questionnaire booklet to complete with information about all patients that were potentially eligible for active involvement in international clinical trials. A total of 39 investigators from eight cities participated in the survey and they provided information on 410 patients who were candidates for ongoing international trials.

Results: A total of 306 out of 410 patients were eligible for the trials; the remaining 104 patients were ineligible based on inclusion and exclusion criteria, and physician estimation on patient's compliance. Of the 306 eligible patients, 80 refused to sign an informed consent form. The two most common reasons for refusing to participate in a clinical trial were the influence of patients' relatives (36.7%) and the risk of adverse events (27.8%). These were followed by the need for additional visits/tests (18.9%), the risk of being treated with inactive agents - i.e. placebo- (15.2%), and the probability of being randomized to unknown products (12.7%).

Conclusion: Patient barriers for enrollment include the 'guinea pig' perception held by patients and/or relatives, anxiety caused by uncertainty, additional demands of the trial, and concerns about information and consent. *(Marmara Medical Journal 2012;25:78-82)*

Key Words: Clinical research, Informed consent, Patient's perception, Recruitment and retention

Özet

Amaç: Türkiye, daha önce bir klinik çalışmaya katılmamış hasta sayısının yüksek oluşundan dolayı, klinik araştırma alanında dikkati üzerine çeken bir ülkedir. Klinik araştırma alanındaki artan önemine rağmen hasta alım süreci çeşitli sebeplerden ötürü çok güç olmakta ve bu durum araştırmaların ciddi ölçüde zorlanmasına neden olabilmektedir. Klinik çalışmalarda Türk katılımcıların algılarının anlaşılması açısından, bir proje tasarlanmış ve uygulamaya konulmuştur.

Yöntem: Araştırıcılara, aktif uluslararası klinik çalışmalara katılmaya potansiyel hastaların çalışmaya uygunluğu ve var ise reddetme nedenlerini prospektif olarak girecekleri bir anket kitapçığı verilmiştir. Sekiz şehirden toplam 39 araştırıcı bu ankete katılmıştır. Araştırıcılar sürmekte olan uluslararası çalışmalar için aday olan 410 hastanın bilgilerini vermişlerdir.

Bulgular: Toplam 410 hastadan 306'sı çalışmalar için uygun bulunmuştur; geriye kalan 104 hasta dahil etme ve dışlama kriterlerine veya çalışmaya olası uyum problemine dayalı olarak uygun bulunmamıştır. Uygun bulunan 306 hastanın 80'i bilgilendirilmiş gönüllü olur formu imzalamayı reddetmiştir. Bir klinik araştırmaya katılmayı reddetmenin en çok rastlanan iki nedeni hastanın yakınlarının etkisi (%36) ve advers olay riskidir (%27,8). Diğer nedenler ise ek vizitlere/testlere gerek duyulması (%18,9), aktif olmayan ajanlarla yani plasebo ile tedavi edilme riski (%15,2) ve bilinmeyen ürünlere randomize edilme riskidir (%12,7).

Sonuç: Hasta ve yakınlarındaki "kobay algısı", belirsizliğin verdiği sıkıntılar, çalışmanın ek külfetleri ve bilgilenme ve onam ile ilgili endişeler klinik araştırmalara hasta alımının önündeki engellerdir. *(Marmara Üniversitesi Tıp Fakültesi Dergisi 2012;25:78-82)*

Anahtar Kelimeler: Klinik araştırma, Bilgilendirilmiş onam, Hastaların görüşü, Hasta alımı ve tutumu

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Introduction

Clinical research is defined as any research involving human subjects which explores novel pharmaceutical approaches to the conditions of individuals suffering from debilitating and life-threatening diseases. However, most people are unaware of clinical trial processes and the role of research in the development of future drugs, devices and biologics for treatment.

Obtaining freely given informed consent for participation in research, involves important substantive ethical principles, including respect for persons, human dignity, and autonomy. Good Clinical Research Practice Guidelines[1] requires that all patients participating in clinical trials give written informed consent prior to participation in a clinical trial. To ensure that patients fully understand factors related to their care, researchers must explain to volunteers the details of the trial. The research team then provides an informed consent document, which includes key details about the study, such as its purpose, duration, required procedures, risks and potential benefits of investigational drugs (or treatments) and key contacts to get further information in case of need. The participant then decides whether or not to sign the document. Informed consent is not a contract; participants therefore have a legal right to refuse any clinical trial proposed and may withdraw from the trial at any time[1-3].

Informed refusal is a medico-legal concept whereby a person refuses an intervention based upon an understanding of the relevant facts and of the implications of not following a recommended diagnostic or therapeutic action. Informed refusal is linked to the informed consent process, as a patient has the right to consent, but also may choose to refuse[4].

Despite its increasing importance in the clinical research field, the recruitment process is very difficult for various reasons, and may become a serious research limitation. One of the main barriers for recruitment to a trial is patient refusal during the informed consent process. If the reasons for refusal are known, researchers can focus on improving research participants' understanding of the disclosed information. From a review of the literature, we found that this information related to reason of refusal was unavailable for the Turkish population even though there are large numbers of publications per therapeutic area (e.g anesthesiology, oncology, psychiatry, etc). The present survey was planned to overcome the current lack of information about Turkish patient attitudes towards clinical trial participation in order to improve patient recruitment strategies for future trials.

Methods

A project entitled Clinical Research Patient Recruitment and Retention Project (ClinRec) was launched by the Sanofi-aventis Turkey Clinical Research Unit in 2006. The project was created with a view to understanding the perceptions of Turkish participants in international clinical trials and to overcome recruitment and retention barriers in international interventional clinical trials.

As the first step of the project, a survey of investigators, who were actively participating to an international Sanofi-aventis trial, was conducted between June and December 2007 to evaluate the reasons for patient non-participation in clinical trials. Investigators were given a questionnaire booklet prepared by Sanofi-aventis Turkey clinical research team and asked to complete it with information on all patients who were potentially eligible for participation in active multinational, multi-centric, interventional, phase II and III clinical trials, regardless of sponsor. Due to the confidentiality of the trails, the questionnaire did not solicit information regarding therapeutic area (e.g cancer type for oncology trials), phases, investigational drugs or biologics, registered or unregistered investigational products, long or short-term trials, objectives, duration of enrollment, or a targeted population.

This survey collected the reasons for refusing to sign an informed consent from investigators in two steps: whether or not the patient was eligible for the trial and if patient was eligible, whether or not the patient had signed the informed consent. If the answer to signing informed consent was "No", then the reason(s) for refusing consent was/were asked to be ticked by investigators (Table I).

Table I. Questionnaire content

No. Gender* Date of Birth	Eligibility for Trial (If patient not eligible, please tick reason)	Has patient signed Informed Consent? (If not, please tick reason)
	☐ Yes If "Yes", go straight to next column →	☐ Yes
	☐ No If "No", tick at least one reason below:	☐ No If "No", tick at least one reason below:
	☐ Inclusion criteria ☐ Exclusion criteria ☐ Treatment/follow-up compliance issues ☐ Other	☐ Informed Consent Form too long ☐ Factors concerning patient's family ☐ Risk of taking inactive agents ☐ Risk of being randomized on investigational arm ☐ Additional tests and visits required by clinical trials ☐ Trial specific additional visits ☐ Possible side effects ☐ Already covered by social security ☐ No specific reason (before ticking here, underlying reason should be questioned in detail) ☐ Other

*Gender: "E" for Males and "K" for Females

Table II. Location of sites

Location	No. of sites
Istanbul	14
Ankara	11
Izmir	6
Edirne	3
Kocaeli	1
Adana	1
Erzurum	1
Gaziantep	1

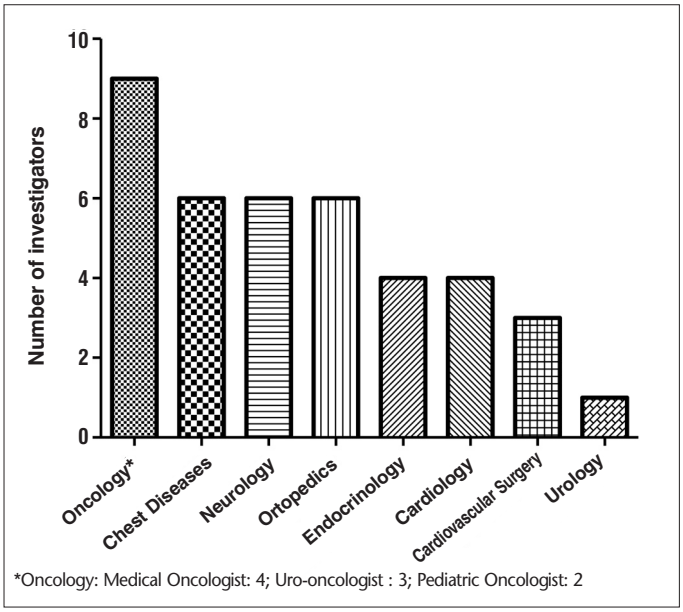

Figure 1. Number of Investigators per Therapeutic Area

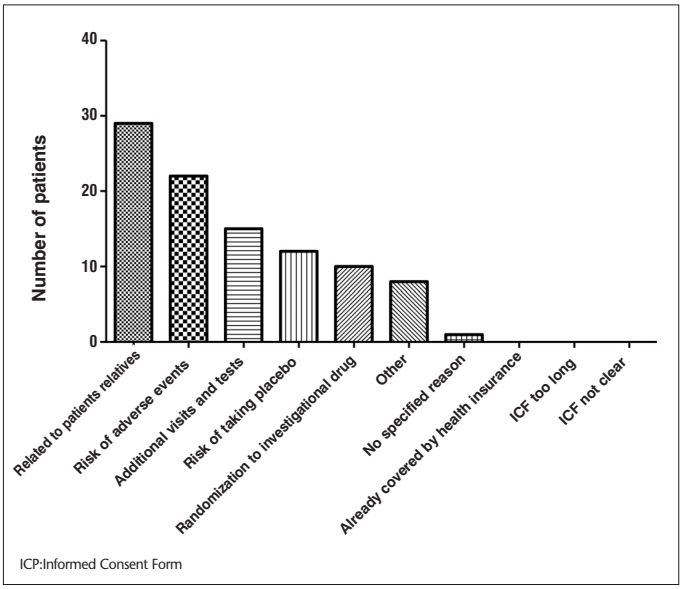

Figure 2. Distribution of reasons for not signing Informed Consent Form (more than one reason could be selected)

Investigators filled in the questionnaire prospectively based upon their active trials. Local studies were not included in this study as informed consent details/criteria for national clinical trials are generally not similar to the international clinical trials in terms of content, complexity and length.

Results

A total of 39 investigators from university or state hospitals located in eight different Turkish cities responded to the survey. Sixty-four per cent of the sites were located in two big mega cities; Istanbul and Ankara (Table II). The distribution of therapeutic areas among respondents is shown in Figure 1. Based on their reports, the total number of trials was 87.

Collectively, investigators entered information on 410 patients in the questionnaire. Of these patients, 244 (59.5%) were male and 144 (35.1%) were female, while gender was unspecified for a further 22 (5.4%) (missing data).

The median age of 388 patients whose information could be gathered from questionnaire was 62 (age range 12-89), although information regarding age was missing for remaining 22 patients. Six patients were in the pediatric age group (<18 years), 17 patients in the young adult category (18-25 years), and 156 patients (40.2%) were identified as over 65 years of age.

Based on the criteria in the questionnaire in Table I, 306 out of 410 patients were considered eligible for the trials.

Based on information gathered from the investigators, 80 out of 306 eligible patients (26.14%) refused to sign the informed consent form. Only one reason was mentioned by 68 patients, while for 11 patients investigators selected more than one reason; one patient did not indicate any reason.

The influence of patient relatives (36.7%) and the risk of adverse events (27.8%) were the two most common reasons for refusing participation in a clinical trial (Figure 2). The need for additional visits and/or tests (18.9%) was seen as the third most common reason, followed by the risk of being treated with inactive agents (15.2%) and the possibility of being treated with unknown (i.e. products under investigation) products (12.7%). For one patient no reason for refusal was specified. Reasons concerning the length and complexity of informed consent and health insurance coverage were not ticked by investigators for any patients.

Discussion

The present study is the first survey that explores the decisions of Turkish patients offered a chance to participate in an international randomized clinical trial. The study was planned to gather data prospectively through investigators, from their potential patients who were candidates for any on-going trials regardless of sponsor. However, during the creation of this questionnaire, information about the details of clinical trials (e.g. phases, investigational drugs or biologics, registered or unregistered investigational products, long or short-term trials and objectives of the trials) was deliberately omitted, due to the confidentiality of the trials. Also, we did not increase the number of questions since this might have had a negative impact on responses from researchers but even with these lower numbers of question, we still have missing information on the age and the gender of some patients . The design of the trial may be considered

as a limiting factor of this survey. However, the gathered data is almost similar with the literature which is discussed below to give some perspective for further investigations in this area. A second step could therefore be implemented to evaluate the impact of trial details, as well as general patient perceptions of trial participation.

In a recent study, of the attitudes toward clinical trials of patients who had been admitted to outpatient clinics of research hospitals in Istanbul, it was shown that 33.7 per cent of the survey group indicated that they may agree with participating in a clinical tria[5]. Although that study gave valuable information about the Turkish population, the data of the present study adds important information to it with the patients who had been invited to participate in a real international randomized clinical trial.

Informed consent is a legal doctrine that has been developed by the courts over a number of years. The doctrine of informed consent was derived from the Nuremberg Code in 1947, which required that doctors obtain the voluntarily informed consent of the subject prior to conducting medical experimentation[6]. The principles established by this code for medical practice have now been extended into general codes of medical ethics.

It is widely recognized on a global basis that many patients prefer to play an active part in the decision-making process in daily practice. This paradigmatic shift can be attributed to several developments, such as the availability of more alternative treatments and recognition of the patient as an active health consumer and autonomous decision-maker. Weinfurt explored this shift in oncology research and concluded that new outcome measures might be needed to assess the effects of cancer comprehensively[7].

In the present survey, patients' relatives were the main cause of non-participation in clinical trials. This may be related to community perceptions of clinical research. The Nuremberg case (the practices of Nazi doctors) and the thalidomide case served to create negative perceptions of clinical research many years ago. This perception by patients or relatives is one of the main barriers to enrollment. Not only in Turkey but worldwide the media also feeds the perception of patients as 'guinea pigs' in clinical trials[8].

Diane Simmons, president and chief executive of the Center for Information and Study on Clinical Research Participation (CISCRP), is fully aware that it does not help to refer to clinical trial volunteers as 'guinea pigs' and has urged newspaper staff to consider using more respectful terms in future[9]. The term she had in mind was 'medical hero' based on evidence from a CISCRP campaign showing that public perceptions of clinical trial participants have a significant impact on recruitment. The CISCRP campaign resulted in a 38% increase in patient recruitment over the control group[10].

Informed consent protects the patients by providing them with complete information on which to make an informed decision. Investigators or research staff should explain the purpose and expected duration of the subject's participation, describe the procedures that subjects will undergo during the study, and identify any procedures which are experimental. Informed consent should also feature a description of foreseeable risks or discomforts to the subject, as well as any benefits to patients or others. Similarly, a disclosure of appropriate alternative procedures or courses of treatment if there are any that might be advantageous to the subjects should be included in the informed consent form[2]. In this survey, adverse events and risks related to new investigational treatments were found to be one of the most frequent reasons for refusing participation.

The primary authority who can convince a patient to take part in a clinical trial is the physician. Tanai et al, reviewed the characteristics of and the outcomes for patients with advanced non-small-cell lung cancer who declined to participate in randomized clinical chemotherapy trials[11]. They retrospectively evaluated patients' characteristics and outcomes from two randomized clinical trials for patients who had not received chemotherapy for advanced non-small cell lung cancer. Among the background patient characteristics, the only variable associated with trial participation or refusal was the frequency of physician visits for patients ($p<0.001$). There was no evidence to suggest any difference in the characteristics and clinical outcomes between the two groups. It was concluded that trial designs and the doctor-patient relationship may have an impact on patient participation in randomized trials.

Informed consent is a legal condition whereby a person gives consent based upon a clear appreciation and understanding of the facts, implications and future consequences of an action. This is a particularly complex decision in clinical trials, because there are often unproven benefits and increased risks associated with the experimental treatments being offered. Complications and drug side effects are commonly referred to in research studies as adverse events. Adverse events that are already known to occur from past experience with the treatment or drug under study (e.g. from trials at an earlier phase) are called suspected (anticipated) adverse events. On the other hand, unexpected complications may still arise and they are called unsuspected (unanticipated) adverse events (e.g. any new complications that appear during Phase III trials). In this survey, the risk of being faced with an adverse event is the second most frequent reason for declining participation. Weckstem et al, also suggested that possible side effects are the most frequent reason for declining a trial by cancer patients[12].

Coverage of all treatment and trial specific evaluation costs is an ethically important point in clinical trials. Economically disadvantaged patients may be considered vulnerable subjects[13]. In Turkey, total social security coverage is as high as 94%[14], and some investigators have frequently mentioned that some of their patients had refused to participate as they were covered by social security. However, health insurance coverage was not cited as a reason for declining participation in a trial in this survey.

Informed consent can be complex to evaluate, in this case because it was unclear whether either the expression of consent or an acknowledged understanding of its implications was genuinely comprehended by the patients. Contrary to expectations, the terminology and length of the informed consent form appeared to have no impact on the survey results. As information about the patients' understanding of the informed consent process is lacking in the present study, the issue could be addressed in a second wave of ClinRec projects. Although not conclusive, available data suggest that research participants may frequently not understand the disclosed information. Failure to understand the details and risks of the trial may not only compromise participation, but also the process of informed consent. It is important to understand the psychosocial outcomes related to the decision-making processes in individuals who are eligible for, and are considering participation in clinical trials, and specifically to consider factors such as : knowledge about treatment options, expectations of treatment outcomes, satisfaction with decision-making, and regret over treatment decisions[15]. It has been suggested that making a truly informed decision requires that

participants receive and weigh information from a variety of different sources, which may not be possible if consent is given quickly. Stryker et al, conducted a survey to understand the psychosocial outcomes related to decision-making processes in individuals eligible for participation in clinical trials[15]. The survey, which covered 50 individuals eligible to participate in selected clinical trials, measured satisfaction with decision-making, decisional regret, and timing of consent (early versus late signers). The authors concluded that participants who enroll in clinical trials quickly may believe they do not fully understand the implications of trial participation, and emphasized that more effort is needed to ensure that clinical trial participants fully understand the risks and benefits of participation and are satisfied with their decision to enroll in a trial prior to signing consent forms. Efforts to improve understanding through the use of multimedia and enhanced consent forms have had limited success. Flory and Emanuel concluded that having a study team member or a neutral educator spend more time talking one-on-one to study participants appears to be the most effective available way of improving research participant's understanding[16]. Nowadays, decision-aids are being explored for use in clinical trials; and it has been cited that more than 90% of patients found this helpful in terms of trial participation and understanding of the information sheet[17]. Decision-aids typically contain evidence-based information presented in a simple, graphical form and lead patients through a process of clarifying their values and weighing the pros and cons of the options before decision making[18].

New technologies (internet communications tools –e.g. Facebook, Twitter- and mobile tools such as Short Message Service) are under evaluation as a means of reaching patients and building patient trust of clinical research. Utilization of these tools by patients for communicating with other patients, and by advocacy and support groups is growing exponentially. Many such groups have made it known that they would positively welcome news about trials that might affect the health of their members. These web based tools are also used frequently to share experience. Using these new technologies and communication tools in a preplanned, prospective way may help recruitment to clinical trials.

Conclusion

Patient barriers for enrollment include the 'guinea pig' perception held by patients and /or relatives, anxiety caused by uncertainty, additional demands of the trial, and concerns about information and consent. Having dedicated research staff on hand to support clinical staff and patients during the informed consent process may help to overcome these barriers, as time constraints faced by the investigator are one of the main barriers in enrollment. Additional work is needed on simplifying the informed consent form and properly evaluating strategies to further overcome enrollment barriers. A short and a long term communication campaign to present scientific information about clinical trials from academicians/professionals to the public will also help to improve recruitment in clinical trials in Turkey.

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