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Turkey's Position Regarding Clinical Drug Trials

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ABSTRACT

In clinical drug trials it is essential in terms of Medical ethics to study on patient's and subject's rights, to discuss on physician-investigator/patient-subject relations, and to evaluate the dynamics inherited within these relations. In order to have internationally acceptable trials, besides the existence of methodological and semantical harmony, it is also necessary to standardize ethical principles, as well. For different societies in which production of scientific knowledge take place, it is possible to speak about the existence of different cultural factors. On the other hand, free from the fact that to what extent they differ from each other regarding the level of economical and sociological development, there should be some "universal ethical principles" binding scientists from different geographies of the world. In Medical researches the term "universality" has started to be cited more, and it has been obvious that a common consideration on basic values that direct these researches is needed. Only when these are taken into account, the researches that are conducted in different countries may have the same level of scientific and ethical standards. Since, the patient-physician relations in Turkish society and its reflections on clinical drug trials, and regulations about clinical drug trials in Turkey should be evaluated.

Key Words: Medical ethics; Clinical drug trials; Subject and patient rights; Researcher/physician-subject relations; Ethical principles.

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TURKEY'S POSITION REGARDING CLINICAL DRUG TRIALS

Physician-Patient Relations in Turkey Within Sociological and Cultural Context and Its Reflections on Clinical Drug Trials

The determinants of physician-patient relations are not only the expectations of physicians and patients, but also the duties and responsibilities of the physician, informed consent procedure, and either the practice in question is suitable in terms of ethical and legal norms. In such a relation, the objectives of physician-patient interaction, duties of the physician, the role of patient's values, and patient's autonomy are essential.

Is there a communication model that is preferred or should be preferred regarding physician/investigator-patient/subject relation? It is obvious that this question could not be answered easily, because it is supposed that for different clinical conditions and different societies, different models should be employed. Indeed, in different times, different communication models could lead the physician or the patient.

As it is true for some other countries in which paternalistic attitude shape sociological structure, it is also true in our country, as well: the physician has the role of authority in physician-patient relation. Thus, whether it fits to the nature of regarding field or not, a relation in which one controls the other is more valid than a physician-patient relation. Since the society faces often with the different types of such a relation, and develops a norm in time upon this, it is impossible for the society to find this relationship odd, and force the existing system to change (1).

Regarding Medical practice in our country, the patient generally is not in the position of ''the one who gets information and actively takes place in the treatment'', but plays the role as the one who gives information about himself and who does not aware of what physician is responsible for his treatment to what extent, and who does not know about his rights. However, while it is pre-conditional for a ''mutual participation'' type of relationship that the physician should choose the method of treatment by taking the values of his patient into account, and should inform patient about possible risks, on the other hand, there are some other pre-conditions i.e.; the patient asks for such information, chooses the method of treatment which suits best to his values, knows about his rights. The term ''patient rights'' in the field of clinical Medical ethics and ''subject rights'' in the field of research ethics are the products of the relationship, which has reshaped on the grounds of ''mutual participation'' type of relationship between physician and patient. Educational, cultural and economical levels of the patient have impacts on his attitude about taking over the responsibility of his own health care. Therefore, the patient/patient's relatives should be instructed in a manner to improve the level of responsibility over their problems, and to improve their behaviors, to help the patient perceive the concept of autonomy.

Most of us might have encountered authoritarian parents, teachers, administers and employers, who use reward-punishment methods in order to control our behaviors. Thus, it is reasonable to observe physicians who cannot establish a relationship with their patients, which is based on ''mutual participation'', and the patients who never expect such a relationship. Most of the patients perceive physicians as people who get the control. They neither expect such a mutual relationship, nor they know how to behave in such a relationship. Since, it is not expectable to have such a demand from

patients; it is essential that the physicians should start it. But, first of all, the physicians should be convinced about the usefulness of such a relation, and essence of active participation of the patients. However, if physician-investigators/subject-patient relationship were examined in clinical drug trials, it would generally be observed that the subject is in passive position. Because, the investigator is the competent one who possesses education, knowledge and experience, and this ''acquired authority'' keeps him active in this relationship.

Subject-patient has accepted the physician as ''authority'', who has knowledge, experience and expertise. He supposes that he does not have the right to ask questions, but he has to answer all kinds of questions, and has to accept the particular treatment physician proposed. He does not even consider asking for details of the medicine, which is going to use or to be tested on his own body or he never asks about the methodology of research. On the other hand, the investigators suppose that sociological-economical and intellectual levels of the patients are low, thus it is unnecessary and time-consuming effort to get their informed consent: the physician always decides on behalf of the patient; and patient's social security system do not offer sufficient alternatives of treatment. Most of the subject-patient is not aware of their rights regarding research. However, the subject-patient must take the responsibility of knowing, finding out and seeking for his rights, as well. The first requirement for this is having prepared the ''informed consent forms'' in a manner that they can be understood and recalled easily, and they are open and free from details. The information that is given to the patient to get his informed consents differs from the information, which is given during the treatment in one aspect; the former one is an activity to which the patient is free to participate.

It is significant to stress on the responsibility of the physician-investigator to give information regarding research method. Quite a lot of investigators may claim that it is an unnecessary activity that causing the patient's mind confused and leading the patient as a subject in making a decision (2).

Are the priorities and evaluation of ethical principles regarding clinical drug trial and research ethics in our country different from those of Western countries? Should the activities that have been developed in Western World like informed participation and respect for individual authority, be understood as universal values in terms of intercultural biomedical researches and in clinical drug trials? Or, should they be left to cultural interpretation and application?

When we review these questions in lights of basic ethical principles, we may conclude that those principles that have been developed in Western World should be taken as universal values. We cannot leave the necessity of regarding basic ethical principles to the interpretation and application of the culture itself. In order words, the structure and the interpretation of ethical principles in our country cannot be different from those of USA, Canada and Western Countries. Medical ethicists will keep fighting for this. However, the priorities and weights given to the principles may differ. For example, ''do not harm and beneficence'' principles in our country may have priority over ''respect for authority'' and ''justice'' principles, because of the reasons stem from our socio-cultural structure, custom, and tradition. The concepts like age, power, and liability are as highly significant in our country as in other countries, in wich authoritarian and dependent relations shape the social structure. The relation between the physician and the rest of the society is not a

relation depending on co-operation, but a relation respectful to the one who has the power.

The Legal Grounds Regarding Clinical Drug Research in Turkey

Legal regulations related to clinical drug trials on human beings in our country are quite new. The earliest regulation is the Regulation on Medical Deontology, dated 1960, and still in force. Article 10 and 11 of this Regulation are addressing physicians and dentists who are conducting researches. Article 10 states that "A physician or a dentist who conducts a research cannot apply or suggest a diagnosis method that he discovered before having convinced himself by testing the method sufficiently to prove that it is free from harm and is useful. However, a researcher can offer a method that has not been tested sufficiently only if it is stated that the method is still being tested or if the precautions to be taken are clarified when it is being applied." By this explanation, the article states that a physician really can test new methods.

On the other hand, the Article 11 of the same Regulation states; "Any practice having a purpose of experiment on human beings are not acceptable, besides any biological, chemical and physical treatment cannot be applied." The Article goes; "If classical methods have been proved to be useless for the patient clinically or chemically in laboratory experiments, a new method which has been proved to be useful by animal experiments can be applied. However, it should be probable that it would be useful for the patient and even if it were not be successful, the results would not be worse that those of the routine treatment methods." Despite the fact that this article seems confusing, it allows clinical trials. It is possible to state that, this Regulation dated 1960, is aiming at regulating classical physician-patient and physician-physician relations, thus it mostly deals with physicians who runs their own officers, and as other fields of medicine that have not been considered in the Regulation, the part regarding Medical researches is far from giving a guidance (3).

Turkish Physicians Association (TPA) that comprehends the essence of the issues that do not take place in the Regulation has started to prepare a modern and more sufficient draft, and these efforts have given fruits. The manual named "Rules for Professional Ethics in Medicine" had been prepared by having discussed all the issues in different platforms, and having considered social and scientific developments in Turkey and in the World, as well. It consists of 7 parts (4):

1. Objective. Scope and Definitions,
2. General Rules and Principles,
3. Physician-Physician Relations,
4. Physician-Patient Relations,
5. Physician and Human Rights,
6. Medical Researches and Publication Ethics,
7. Miscellaneous Provisions.

The Part 6 regarding Medical researches deals with; research on human beings (Art. 40), informed subject and informed consent (Art. 41), individuals who are not adult and not rational (Art. 42), and protection of the subject (Art. 43) (4).

The other essential text dealing with legal regulations on drug trials conducted on human beings is Article 34 of the Law on Health Services numbered 3359, which came into force on May 7, 1987. The article states; ''The drugs and compounds that did not have permission or license cannot be produced, imported or sold, or even those had permission or license are forbidden to be used in scientific research purposes on humans without consent of the particular individual and the Ministry of Health.''(5)

Finally, the Directive on Drug Researches, which was published in Official Gazette numbered 21480, and came into force on January 29, 1993, establishes the legal foundations of conducting drug researches in our country that fit international standards, and legal rights of the researchers and volunteers are guarantied (6).

In December 29, 1995, the General Directorate of Drugs and Pharmacy of the Ministry of Health issued a circular resulted in having two guides prepared namely ''Good Clinical Practice Guide'' and ''Good Laboratory Practice Guide''. These guides deal with researches conducted on humans with drugs, and explain in detail the rules stated in regulations, settle the rules to be followed (7,8).

Part 6 of the Directive on Patient Rights, which was published by the Ministry of Health in 1998, deals with ''medical trials'', as well. This part has following topics; consent in medical trials (Arts. 32), volunteer protection and information (Art. 33), method any way of having consent (Art.34), children's and irrationally situation (Art. 35), the use of drugs and compounds in researches (Art. 36) (9).

While the legal regulations have been modernized in our country, is the level of research and development activities on drugs sufficient? This is controversial. Most of the domestic firms deal with importing the drugs that have been developed by other firms and have patents, as drug substances that main cost component is synthesis expenditure, and produced by the firms located in countries that do not give patent right. Therefore, the studies are mostly phase 3 and phase 4 studies. There has been no firm in Turkey so far, which is able to obtain a substance that is eligible to be a drug, neither from natural resources nor with pure chemical synthesis. Hence, we do not have a problem like conducting clinical phase experiments (phase 1 to phase 3) to develop a drug, and indeed we do not even have experienced professionals and sufficient infrastructure. However, some phase 3 and most of phase 4 studies are conducted under supervision of clinicians and clinical pharmacologists in university clinics that have sufficient infrastructure.

The Regulation on Drug Trials, which was published in 1993, includes some articles that regulate conducting phase 1, 2, and 3 experiments. In the first years of this Directive, when there was insufficient number of pharmacologists, and when the infrastructure was incapable to conduct and evaluate analytical studies that were significant in phase experiments, there had been arguments taken place on the meaning of regulate those provisions in such a situation. Moreover, study and evaluation criterion of ethical councils, which are founded on the basis of this Directive in the research institutions locally and in the Ministry of Health centrally, have still been discussed.

During last decades, many academically motivated researchers have been conducting drug researches in Turkey, and the articles on those researches have been published in Medical periodicals that have their own publication rules. Considerations towards allowing the drug trials, especially phase 1, 2, or 3 trials,

on human beings to be conducted by hiding behind industry-university co-operation approach are irrelevant. These kinds of trials can only be conducted in clinics, which employs qualified personnel who has fulfilled basic pharmacology education and has specialty in clinical pharmacology, besides and as important as these, which has sufficient infrastructure. Another observation about the researches conducted in our country is doing unnecessary operation in diagnosis, treatment and rehabilitation of the patient, and applying unnecessary methods during the research and drug trial. These practices have ethical and material aspects, as well. Since, the patient is being directed by the physician/investigator on what is required for himself, he is ready for giving consent to the operations that he supposed to be necessary for himself and even ready to pay for these. Some of these unduly and excessive practices may be ''invasive''.

As related to the discussions, Ethical Council of TPA disclosed its study, ''View on Patients' Rights in Clinical Trials'' in 1996. Main points of the study are as follows: ''In a Medical point of view, it is required that the patient's health and care are primary aspects for the physician. Nothing will be allowed to precede this principle. This should be apparent in general Medical practice, and in trials, too. The patients and subjects who are left out of research should be treated as soundly and carefully as the others. It is suggested that the research team should separate research expenditures from treatment expenditures, and avoid unduly/unnecessary tests. Pre-determined ''optimum number'' for sampling is another factor limiting research cost.'' Moreover, in the study it is also stated that economical cost of the research/trial should not be paid by the patient himself, his relatives, or social security agency that meets health care expenditures.

In clinical drug trials projects, which are supported by the drug producers, there is another aspect needed to be evaluated carefully; whether the project will find answers to essential clinical questions regarding the use of drugs in treatment. It is also important that the physicians should be aware of ''marketing tactics'' like having the physicians accustomed to use a particular drug, or encouraging the drug to be added into hospital's drug list.

CONCLUSION

Therefore, based on the legal regulations summarized above, researchers and volunteers have attained rules and regulations that are fully compatible with international standards. In time, by doing some amendments on these legislation that are consistent with the conditions of the country, it will be possible to conduct clinical trials that are reliable and suitable to ethical norms on human beings in Turkey.

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