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**Review Article**

# Clinical trial ethics in Turkey in the context of some expectations and predictions

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## ABSTRACT

Why is so much attention now being given to the ethics of clinical trial? Why does debate continue over the ethics and regulation of research involving human subjects? Are there societal duties to support the conduct of clinical research? Why was this protocol good enough for X, or Y, or Z, but not good enough for this university or institution? What is the rationale for public bioethics? As shown even though all the rights and obligations of all parties of clinical trial – the researching physician, the volunteering patient, the industry, research institution- have been assured with ethico-legal regulations, there still exist many problems in the world of clinical research, and suggestions of solutions to the said problems. It is obvious that medical trials on human beings, on the one hand, accelerate developments in medicine and offer benefits for the present and future generations, but on the other hand, they can lead to acts that may endanger human dignity and human value. The objective of this paper is to discuss the rights of human subjects in clinical drug trials; to review the researcher-physician/subject-patients relationship from several aspects; to consider the dynamics which exist in this relation; and to reach some practical solutions that might be conveyed to the applications in the context of medical ethics in Turkey.

**Keywords:** Clinical trial, Ethics, Turkey, Biological material of human origin

## INTRODUCTION

It is a reality that the ethical problems existing in scientific research, particularly in biomedical research, can reach considerable limits. In order to be acceptable at an international level, the related ethical principles as well as the harmonization of methodology and semantics, must be specified in scientific research activities. In various countries in which the production of scientific knowledge has become possible, the existence of different cultural characteristics can be observed. Nevertheless, to whatever extent their culture and the level of their social and economic development may differ from each other, there should be "universal ethical principles" which would be binding for scientists living in different geographies. In medical research activities, accordingly, the concept of "universality" has come to the fore in recent times. And there is a need now for a consensus about the fundamental values which govern these activities. Only in such a way would it be possible to have common ethical principles in terms of research carried out in different countries.

In clinical drug trials in medicine, the principal element is the "human" component. This concept covers the investigator himself as well as the patient-subject, who is the research material. The aim of the biomedical research involving human subjects is to develop the diagnostic, therapeutic and/or preventive procedures or to explain the etiology and pathogenesis of disease. This research may involve the diagnosis and treatment of a patient; or may be carried out on experimental subject solely for "pure" scientific purposes. Thus, while the patient in the first category is both an "object" or "end" and a "means" or

"tool", the experimental subject in the latter is only. In clinical drug trials, to distinguish between the ends and means thus becomes of utmost significance from an ethical point of view. And the limits of the rights of the voluntary healthy subjects become more comprehensive.

The physician involved in drug trials on patients is not just a "physician" but a "researcher-physician". And it is due to this role that he becomes the subject of the Declaration of Helsinki, of the guide for "Good Clinical Practice", and national and international regulations as regards drug trials. The activities of the physician, governed by the rules therein, stem from his identification and role as a "researcher", with no ensuing intervention with his function as a physician. And whether his research is therapy-oriented or not, a medical doctor conducting a clinical drug trial should not consider himself as a physician with his "ordinary" function. Nor should a patient presume that the research or trial activity is integral part of his treatment; otherwise, his decision, made upon such a consideration, and his informed consent given accordingly, will be invalid.

In clinical drug trials, all measures should be taken to prevent patient from any foreseeable risks. The patient as an experimental subject, without knowing that he will be better or worse off, is basically exposed to a particular risk on behalf of other human beings; this is an instance of altruistic behavior. If needed, in order to decrease the level of risk to a minimum, part of the knowledge to be obtained from the research may be given up, although it would ultimately be to the benefit of other people.

As we know, ethical research norms are global in nature and do not vary from place to place. Further, commercial sponsors have very strong incentives to ensure that their investments in clinical research will be accepted by regulatory agencies in the developed countries where they earn the vast majority of their revenues. Indeed, companies that work exclusively in the clinical research field can easily be forced out of business by market forces that demand strict compliance with these ethical rules. The advance of medical science is leading to more clinical trials and these trials are increasingly complex, time-consuming and expensive.[1-3]

Trials in emerging countries are subject to the same standards that prevail in the developed world. To be relevant and responsible, research ethics must be informed by and appreciative of the ethically justifiable purposes and ends of the institutions and individuals who are expanding the reach of research. Clinical research on humans is subject to certain ethical and regulatory norms. To understand the implications of conducting trials in developing countries, it is important to first understand these global norms.[4,5]

Evaluation of the impact of health policies is of greater importance today when the demand for health care services exceeds what the available resources are able to finance. Today's clinical research/trial is tomorrow's health care; therefore, there is a need for national policies and future planning. Efforts to discover new treatments and drugs have become priority investment areas both in developed and developing countries.

Several factors are no doubt important in the formulation of health policies, including identification of priorities; effective, efficient and equitable management of resources in the provision of health services; policymaking based on the accurate and current information; planning and organization; infrastructure- and institutional capacity-building; and implementation of required legislative regulations. Evaluation of the impact of health policies is of greater importance today when the demand for health care services exceeds what the available resources are able to finance. Today's clinical research/trial is tomorrow's health care; therefore, there is a need for national policies and future planning.

With the increase of health expenditures all over the world, it is attempted to bring drug expenditures under control. The rise of chronic diseases, in particular, has extended the period of medication, and as a result, it leads to an increase in the budget sensitivity of repayment organizations. It is expected in the upcoming period that the pricing approach will change and the importance of pharmacoeconomic evaluations will increase. Different methods for the purpose of drug expenditure control have come to the fore throughout the world, for example rational use of drugs, regulations on prescribing, awareness for preventive and protective treatment, promotion of generic drug use, etc.

The need for health care services and clinical trials has risen as a result of the increase in the elderly population in the world, health problems that may be encountered in the old age due to the prolongation of life expectancy, an increased risk of exposure to chronic diseases, and socio-economic changes. It should be noted that clinical research is an indispensable part of the development of innovative medicines and therapies that improve the quality of life. Only by means of clinical research can current ways of treatment be improved and can new treatment options be offered to patients.

Efforts to discover new treatments and drugs have become priority investment areas both in developed and developing countries. Thousands of researchers and administrators, hundreds of thousands of research volunteers, millions of dollars, promotions, profits and promises, hopes. These are the main elements of clinical drug research in the last years. Academic career and professional reputation of researcher-physicians are associated with their access to strong financial resources as well as their studies and publications. The notability of medical research institutes and medical researchers is based on their abilities to develop significant research programs, to attract researchers of high level, and to go into commercial and technology transfer partnerships

with the pharmaceutical industry. On the other hand, the long-term needs of pharmaceutical, drug-device and biotechnology companies depend on the 5 features of medical centers; patients, prestige, patents, publications and personnel. For the purpose of completing this cycle, the governments of developed countries, particularly the United States, Canada, Germany, and France, consider medical technology and strong biomedical industry as an important factor to improve the trade balance, to increase the economic competitiveness, and to make life easier for citizens.[6,7]

China, Brazil, Russia, India and Turkey referred to as emerging economies in the pharmaceutical industry continue to attract the attention of global pharmaceutical companies both due to their potential and the size and growth rate of the industry. Pharmaceutical companies, because of cost advantages and high growth prospects, have strengthened their presence in emerging economies and shifted their activities such as production and R&D to emerging economies.

Global pharmaceutical industry grows in line with the demand while national pharmaceutical sectors have differences in setting priorities. Some give weight to Reseach & Development, and some become prominent in export or clinical trials. Germany, France, United Kingdom, Spain, and Italy generally referred to as the EU-5 countries have strong indicators in the industry. The United States and Japan have also risen to prominence. China, India, Russia, Brazil, and Turkey have been recently referred to as "developing countries" competing with developed countries with the growth they have achieved, and these countries are expected to become more competitive in the future.

## CLINICAL TRIALS IN TURKEY

In the last 20-30 years in Turkey, the number of applications to physicians has increased has six times, and the average life expectancy has increased by 25% depending on increased access to new therapies and drugs. Considering the clinical research world with respect to competitiveness, which is important for sustainable development, it seems clear that related government policies are shaped based on the fact that Turkey has fallen behind “pharmerging” markets such as Brazil, Russia, India, and China.

To understand the global industry and better evaluate the position of Turkey, the indicators related to countries address the EU-5 countries and the BRIC (Brazil, Russia, India, and China) countries as well as Singapore, Ireland, China and South Korea with best practices benchmarked. The share of our country in the total clinical trials was 0.8% in 2011 (the number of trials 978) while it rose to 0.95% in 2015 (the number of trials.746). In this four-year period (2011-2015), Turkey advanced from the 36$^{th}$ rank to the 31$^{st}$ rank with respect to its share in the total clinical trials of countries; however, it is not considered sufficient (https://clinicaltrials.gov/).[8] Turkey is also expected to take place in the first 10 such as South Korea and China.

When a SWOT analysis- Strengths, Weaknesses, Opportunities, Threats - is made on clinical trials in Turkey, it indicates that it has plenty of strengths and resources. The legislation on clinical trials in Turkey was drawn up in line with the principles of Good Clinical Practice (ICH-GCP), directives of the European Union, and the Helsinki Declaration. Thus, the latest and most advanced legislation applicable in the world is also in force in our country. International standards apply in clinical trials carried out simultaneously in multiple countries including Turkey. Therefore, there is no difference between the standards applied in the European Union and Turkey and these standards are strictly controlled.

Adverse effects that could endanger the health of volunteers are monitored and inspected by local and international health authorities, and all necessary measures including the termination of the trial are also taken. In accordance with both national and international legislation and rules, participation in a clinical trial is on a voluntary basis, and volunteers are involved in such trials by their own free will and without any incentives. A clinical trial cannot be undertaken in Turkey without the approval of an independent Ethics Committee and the permission of the Ministry of Health and without the free-will decision and informed consent of a participant. Our country has the apparent advantage in the conduct of clinical trials, including the population of nearly 80 million, the presence of different ethnicities, disease burden, the incidence of genetic diseases due to consanguinity, rare diseases and so on.

Considering the population affected by rare diseases in each country, policies formulated by governments play an important role in the research and development and marketing process of orphan drugs that needs to be produced. As it is stipulated in the Regulation on Clinical Trials, an application shall be made directly to the Ministry of Health for trials on rare diseases that have no known treatment and requires clinical trials, and on orphan drugs to be produced exclusively for such diseases. The pharmaceutical industry has very little interest in orphan medicinal products because of the small number of patients under normal market conditions. Therefore, the European Union provides incentives to pharmaceutical companies for research and development.

## FINANCIAL ISSUES AND INCENTIVES RELATED TO CLINICAL RESEARCH AND INNOVATIVE THERAPIES

Financial issues hold a key place in clinical studies of drugs and medical devices. In the past decades, a number of factors have been shown as a justification for the increasing importance of financial issues in the conduct

of clinical drug trials. In addition, a major place is also held by the increase in the number of researcher-physicians depending on the development of medical schools, and by extension, by the increase in their researcher attitudes have also. There has also been an increase in education programs in research methodology and research ethics generalized for young physicians. There have also been changes in the attitudes of many scientists and physicians towards working in the industry.

Many well-trained and qualified physicians for biotechnology companies and pharmaceutical companies left the academic institutions in which they worked. Clinical trials have become a tool to attract patients to medical centers and universities. Medical oncologists testing particularly cancer drugs in certain major centers have included most of the patients in the clinical trial protocols, and thus have made their research an integral part of standard medical care. It has routinized the clinical research not only for patients but also for students, hospital and other physicians as well as having actively encouraged drug producers to support clinical trials. It has become more difficult for clinical researchers (differently from basic laboratory researcher) to reach government funds and clinical trials have become more dependent on drug and medical device producers and insurance companies. Considering the supporters of clinical trials in Turkey, the industry ranks first as expected. While drug and medical device development studies are carried out with the support of the industry, it is clear that these studies are international and multi-centered.

Except for commercial trials on drug and medical device development, there are also noncommercial trials which are conducted by the researchers and research supporters without the contribution of the industry. Non-interventional clinical trials include research on the treatments of rare diseases (production of orphan drugs), comparative effectiveness studies for the optimum use of drugs, and so on. Such research is supported either by supporting public institutions (Scientific Research Units of Universities-BAB and TUBITAK) or by researchers themselves – as out-of-pocket payment especially in academic studies and thesis.

With the advancement of technology, R&D processes are supported and new technologies play a role in the development of new drugs and treatments. It is envisaged that, in the future, clinical research process will be shortened by means of computer-aided virtual metabolism programs, the rate of clinical trials will gradually decrease, some parts of the clinical research process will largely be conducted in a virtual environment and computer-aided drug design applications will become widespread. Personalized medicine applications will also be implemented as the availability of the genome applications increases. The evolution of molecular biology and biotechnology has led to the mass production of large amounts of drugs, especially pure proteins, and by extension, it has enabled a greater number of studies to be conducted in a short time. The development of biological research techniques has also allowed scientist to undertake trials, to the extent not possible before, in the fields of molecular and cellular biology as seen in the human genome project (HGP).

## THE FINANCIAL INCENTIVES OFFERED FOR RECRUITING PATIENTS

Another subject never spoken in the world of clinical research in our country is that patients have no information about the incentives paid to physicians who recruit them in the research. Whether patients want to be informed or not, it is clearly thought-provoking to give incentives to a researcher in return for participation. It should be noted and declared that research funds create conflicts of interest for researchers who attempt to promote treatments that are less helpful or not needed in order to benefit from the payment.

Whether or not one wishes to inform the patient of the study's sponsorship or the incentives available to physicians who recruit them, it is clear that the incentives given to investigators for recruiting may be quite considerable. These funds are often used to pay for a significant number of other projects and/or individuals' salaries. It is the most appropriate solution for now that these payments are audited by the ethics committee of the organization and collected in a common pool to be used for research funding. Researchers often have difficulty in recruiting patients in their research. To increase such participation, various incentives are also offered to other physicians who work in the hospital and propose a voluntary patient. It is a longstanding and useful, according to some, practice to make a payment to those who find participants. However, there are also persons and institutions that find this practice unethical and illegal and even completely prohibit it. Such practices are still common in clinical drug trials, but patients are not aware of it.

## RESEARCH ON BIOLOGICAL MATERIALS OF HUMAN ORIGIN

One of the controversial issues in the clinical research field today and for the future is the use of biological samples of human origin. It is important to pay attention to the most helpful use of biological samples and other materials of human origin taken from participants.

Biological materials obtained from human beings for research purposes can be immediately used in a particular research project or be stored for use in projected future research. There is not a very precise distinction between the two usages; while some of the samples are used immediately, the rest may be stored for later use. Ethical issues about the use of biological materials of human origin in trials can be classified into two categories:[9]

- The first category addresses the removal of biological materials of human origin by an intervention on the body of a person. It comes up when, in the course of an intervention, the physical integrity of a person is at risk and additional protective measures needs to be taken at the same time (persons not able to consent).
- The second category involves the consent to the use and storage of obtained biological material and the protection of the confidentiality of medical data. This second group of issues requires serious attention and due care and are regulated by documents and guides published by many national and international institutions.

The relevant legal framework in Europe is based on the Oviedo Convention on Human Rights and Biomedicine (1997) and the Council of Europe's Recommendation Rec (2006) 4 on research on biological materials of human origin.[10,11] Article 22 of the Oviedo Convention stipulates that the biological material removed from human body may be stored and used for a purpose other than the specified only if this fulfills the appropriate information and consent requirements. Article 21 also indicates that the human body and its parts cannot be used for the purpose of financial gain. All these regulations do not prohibit the licensing/sale of intellectual property rights arising from scientific research using such materials, and this resembles other cases of intellectual property rights. However, it does not mean that persons donating biological materials do not need to be informed if biological materials of human origin are used for commercial purposes. Besides, researchers cannot sell such materials only for the purpose of financial gain and the owners of the materials and substances cannot act to obtain commercial profit. It can be compensated only by keeping the extended effort waste of time at a reasonable level.[11]

The Council's Recommendation Rec (2006) 4 regulates the removal and use of biological material from human beings for research purposes, and the principles regarding the materials of human origin to be stored and the management of biobanks – for instance, the rules for the use of residual biological materials obtained from clinical trials, scientific research, and forensic examination.[11]

The recommendation indicates research on biological materials and samples of human origin can only be conducted after an independent examination is made by a scientific and ethics committee and the informed consent of the person concerned is obtained in accordance with the principles of the Convention on Human Rights and Biomedicine. It also clarifies the identification of the persons concerned using biological materials and other data, which is a basic problem in the examination of ethics committee. Personal identifying information is accessible in general terms either directly by personal data stored in files or indirectly by a registration system entered with a password known by researchers or third parties concerned. Non-identifiable biological materials are those that do not allow the identification of the persons concerned even with considerable efforts. Assessing a project involving the use of biological material of human origin, a research ethics committee stipulates researchers explain in the project to what extent the personal data of participants will be accessed.

When a research ethics committee receives a project proposal on the collection of biological materials of human origin or the establishment of biobanks, a research ethics committee should carefully examine the following points: the project, first of all, should have a well-established reliable control mechanism, and the rules on the access to biological materials and samples for research purposes should be transparently and clearly expressed.

Many studies on ethics in experiments carried out on humans focused on, in the past, the issues related to volunteers and the performance of the clinical research. However, recently the focus has been neither on volunteers nor a researcher-volunteer pair, and there comes a new period of understanding and interpreting which involves a supporter and monitor (contract research organization). With this period, involved persons have had to deal with challenges not necessarily specific to clinical research but having a significant potential for a conflict of interest. As both physicians and patients are now aware of many situations where their interest conflict, some may think that biomedical research that grows outside but in parallel with the medical practice is better equipped to cope with such conflicts. However, I believe that the biomedical research world in our country is not resolute in the prediction and resolution of such conflicts despite the habit of recognizing such challenges.

Even though research ethics committees have been founded due to the thoughts on basic relationships that define clinical research, other related parties have undertaken roles that are important especially in financial issues and sometimes are incomprehensible. These parties and their interests, regardless of to what extent they have emerged and whether they have considered by ethical committees at various times or not, may directly or indirectly conflict in a certain research project or even they may not come together. The financial issues linking them together may be explicit or not. This debate starts with the expression of opinions on main relationships in clinical trials and brings financial issues to mind when other parties get involved in.

Considering the relationship of a healthy volunteer and researcher, the financial issue that often arises is the appropriate or "fair share" for the participation of volunteer in the research project. This is an issue that should be or could be addressed depending on the duration, effort, risk and anticipated discomfort of the activity participated. When such discomfort comes up, it may be interesting to observe individual ideas put

forward by members of the ethics committee. The age and financial situation of members are two factors that may affect the determination of attitudes. In this regard, first the question of “fair value” arises. What impact will individual ideas and values of members of the ethics committee have on the decisions of on the ethics committee? As each member of the ethics committee framed their own policy based on a variety of relevant financial factors, they are especially important when dealing with financial matters. If an ethics committee thinks that the price proposed for “a normal healthy volunteer” is too high or too low, problems may arise. In Turkey, the risk-benefit assessment is invariably undertaken for each healthy volunteer, and the research protocol may be rejected by the ethics committee if the unrequired risk is higher. It is also certainly considered whether such costs as loss of labor or power, transportation, meals, etc. are reflected on the research budget.

## CONCLUSION

In conclusion, it is safe to say that "a good biological science should have a code of ethics to be favored by a humanist. Factors that make new research scientifically acceptable are the same as those that make them ethically acceptable". Accordingly, it certainly applies to clinical drug trials conducted on humans. Trials conducted to developed new and effective drugs are today accepted and carried out in accordance with a set of well-established scientific standards and ethical rules common in all societies. It is obvious that medical trials on human beings, on the one hand, accelerate developments in medicine and offer benefits for the present and future generations, but on the other hand, they can lead to acts that may endanger human dignity and value in case of a malpractice.[12,13]

The accuracy or inaccuracy of a research protocol or ethical judgments on some aspects of such protocols is nonsense and invalid unless all the aspects of the research conducted are fully understood. Medical ethics evaluates clear and unclear reasons for conducting research with sick/healthy volunteers and provides a discussion platform to understand these reasons.

In the context of clinical trials, it primarily falls to bioethics to produce arguments required to reach a compromise on the globally valid principles of human action and on the conditions for a good life. The precondition for the fulfillment of this task by bioethics is to fully comprehend norms and values, which are adopted and respected by other cultures and accepted in practice, and to critically question both the practice of these norms and values in such cultures and their functions in guiding and regulating actions as well as inquiring how deep and far they can be valid on a global scale. Especially in an era that economy and technology determine all the goings-on, bioethics has undertaken a significant responsibility as a warner that becomes a critical mirror reflecting devastating effects and consequences of the interest pragmatism aims at rationalizing the biomedical research world with unilateral concerns. Contrary to the "quantitatifiying thought" focusing only on concerns that biomedical trials maximize benefit and success hunger, bioethics reminds us that there is also a resource offering purposes and targets that have qualities confirmed by the moral competence of practical mind as well as "qualitative values" that go beyond quantitative assessments. Bioethics is currently considered as the most convenient platform in terms of understanding, appreciating and comprehending supranational rules and norms that have the capacity to have interregional validity.[12,13]

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