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Clinical Scientific Research Potentials in Turkey

Along with policies and visions for scientific and technological development put forward by the European Union (EU) in the mid-1990s, Turkey has taken major steps toward harmonizing with the EU in the field of clinical research and drug trials.

Although clinical research in several disciplines of medicine—including cardiology, infectious diseases, oncology, hematology, nephrology, endocrinology, pulmonary diseases, and surgical branches—has been ongoing in Turkey for almost half a century, many studies did not completely comply with good clinical practice (GCP) guidelines. Along with policies and visions for scientific and technological development put forward by the European Union (EU) in the mid-1990s, Turkey has taken major steps toward harmonizing with the EU in the field of clinical research and drug trials.

The Bylaws for Drug Trials was introduced by the Ministry of Health on January 29, 1993. Two years later, the ministry's Directorate of Drug and Pharmacy published the first edition of the *Good Clinical Practice (GCP) Guidelines*. This booklet covers all the essential rules and regulations for clinical trials to be conducted on human subjects, including informed consents, research and clinical ethics, and the establishment of local and central ethical research committees.

Since 1993, this important document has been adopted by all universities and state and social security hospitals involved in clinical trials to protect the rights of patients and normal volunteer subjects, data acquisition, data protection, reliability, monitoring, and reporting. In Turkey, all sponsors now ask the researchers to comply with the GCP guidelines throughout the clinical trial, without any exception. The trials can be initiated only after written approval from the ethical committees, with signed agreements from the primary investigator and members of the clinical research team. As required by the GCP guidelines, 72 institutions have now established their local ethical review committees (see Table 1).[1]

As is well known, most Phase I and Phase II studies are performed in the United States and Europe. Clinical research centers in Turkey mostly participate in multicenter Phase II/III, Phase III, and Phase IV trials, the majority being prospective drug trials and registration-directed studies performed according to GCP guidelines. Today, many Turkish clinicians are enthusiastic about testing new drugs in Phase III or Phase IV trials conducted according to GCP rules. The number of clinical trials submitted for approval to the Central Ethical Committee of the Ministry of Health is shown in Table 2.[1]

After the launch of the GCP guidelines, at first only a few pharmaceutical companies decided to conduct trials with limited manpower resources, resulting in outsourcing various activities. Thus, in the period of 1997 to 2000, local contract research organizations (CROs) were founded.

Healthcare

In Turkey, most inpatient and outpatient healthcare is provided by hospitals under the auspices of the ministry of health, universities, social security insurance system, municipalities, and private enterprises. In 2000, current health expenditures (CHE) represented $12.6 million of the Gross Domestic Product (GDP) with a CHE:GDP ratio of 6.3. The public share of the CHE was 61.8%, and the private share was 38.2% that year. Social security funds accounted for 35.8%, and the government employees' retirement fund shared 26%. Hospitals constituted 39%, 18.7% of which was university hospitals. Interestingly, the share of total pharmaceutical expenditures was 33.5%. According to the data analyzed by the OECD 2004 Health Database, Turkey allocates 6.6% of her GDP to the health system, compared to an average of 7.9% for all OECD countries.

Economic Indicators

During the last 80 years the Turkish Republic has made very important and visible improvements in all aspects of its society, including its cultural opportunities, economic vitality, and infrastructure. The Gross National Product (GNP) per capita increased from $2,828 in 1999 to $3,383 in 2003, and the GNP growth rate in 2004 was 9.9%. The population grew to 70 million at an average annual growth rate of nearly 5%. Although in 1955 agriculture accounted for 39% and industry contributed 16% to the GNP, in 2001 these figures changed to 12% and 24%, respectively. All these parameters indicate that, within the last 50 years, Turkey has moved from an closed agricultural economy to a relatively industrialized country with a more open-market philosophy. Currently more than two-thirds of the population lives in urban areas.

Science and Technology

The Turkish Republic has always shown a strong commitment for socioeconomic development through education and industrialization. During the last 25 years, the liberal economic policies of several governments have opened the Turkish markets to foreign investors and helped Turkish entrepreneurs to participate in foreign markets, and there has been more emphasis on innovation-oriented national science and technology policies.

In 2004, the Supreme Council for Science and Technology of Turkey decided to raise the share of R&D expenditure gradually to the EU average of 2% of GDP by the year 2010. In addition, the council decided to take all the necessary measures to have a full-time research workforce of nearly 40,000 by the year 2010.

Turkey's total number of universities has grown to 92, including 23 established by private foundations. Activities at these higher education institutions represent 60% of Turkey's total

R&D expenditures. There are approximately 150 public research centers currently working on forestry, agriculture, mining, materials, energy, environment, and biotechnology projects. According to the Turkish Scientific and Technological Research Council (TUBITAK), R&D personnel are divided among the fields of science as follows:

- 37% in technological sciences
- 19% in mathematics, physics, life sciences
- 19% in social sciences, architecture, arts
- 14% in medical sciences
- 11% in agriculture

Scientific Publications

Turkey has made significant progress in scientific publications covered by the Science Citation Index (SCI), as indicated by its world rank of 19th in 2005. The total number of scientific publications from Turkey, as indexed by SCI, rose from 6,066 in 1999 to 17,300 in 2005, with articles in medical sciences constituting nearly half of the total publications.

Public and Private Funding

In Turkey, almost $100 million in public funding is provided annually for academic research. TUBITAK has been the major public institution funding and promoting research and development. The Council provides financial support for research projects, research centers, scientific meetings, and undergraduate and postgraduate scholars.

TUBITAK also finances industrial technological activities and contract research, and has played a very important role in the process of the nation's association with the EU-Sixth Framework Programme (EU-FP6). According to the reports published in April 2004 by the European Union, European participation in EU-FP6 and shortly in EU-FP7 will encourage and promote science and technology collaborations between Turkish research institutions and European counterparts.

The Turkish Academy of Sciences (TUBA) grants scholarships to promising young scientists and awards to established scientists. The State Planning Organization also provides funding for academic research projects and contract research, and the Ministry of Finance allocates funds to state universities representing 40% of the total public funding for academic research.

However, financial support for clinical drug trials is most often obtained from private sources, especially from pharmaceutical companies. Other private sources for research financing include foundations, charities, endowment funds, and nongovernmental organizations.

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Table 1. Local Research Ethics Committees

Institutions	Number
Medical Schools	36
Ministry of Health—State Hospitals	25
Social Security Hospitals	9
Private Medical Centers	2

There are five major CROs providing services mainly to sponsors. Their principal activities include preparation of application files for the research ethics committees, study monitoring, data collection, and reporting. During the last six years, with the steady increase in numbers of patients enrolled in international trials from Turkey, CRO activities have also increased considerably. Along with this development, mainly due to global contracts asking for Turkey's participation, there have been new incentives and operations of local subsidiaries of prominent global CROs. In addition, a few CROs provide services in conducting bioequivalence studies for the generic pharmaceutical companies in Turkey as well as for some western European companies.

AKADEMIKA[R] Program

There is a growing need to prepare and train clinicians and allied health workers for careers in patient-oriented clinical research. In Turkey, for the last 10 years, many medical schools and pharmaceutical companies (including Sanofi-Aventis, Pfizer, and Roche) have been organizing courses and seminars on clinical research training.

In December 2003, the AKADEMIKA[R] Program was created to address the need to train practicing clinicians and academicians in all the essentials of GCP according to European Union standards.[2] Research nurses, data managers, monitors, and officials from the Ministry of Health can also apply for this program free of charge.

The full two-day program, held for 40 participants at a time in the Executive Development Unit of the Sabanci University outside Istanbul, includes presentations on important issues related to the implementation of study protocols and clinical research methodology, including phases of trials, randomizations, monitoring, data reporting, quality control, quality assessment, ethical issues, and publications. Moreover, trainees are divided into small groups with mentors for interactive sessions with short movies.[2]

The feedback and comments obtained from the participants have been quite positive, and the program has been a regarded as one of the most successful in clinical research available in Turkey. To date, 320 trainees have attended. AKADEMIKA[R] will continue to be organized three times a year. (For more information, please visit www.akademika.org.)

Assessment

Turkey is in the review phase to join the EU and has undergone many important reforms involving patients rights, criminal law, and specialized biotech drug-dispensing acts. Although more than 300 clinical trials have been conducted in the country over the last three decades, many early trials were not registered, in part because there were no law-enforcement mechanisms. More recently, the annual number of clinical trials has risen but remains relatively low (in the range of 100-150 per year) compared to international trends.

However, several pharmaceutical companies continue to sponsor clinical trials in Turkey to acquire data for their multicenter international studies. In general, these trials have served as a vehicle for reforming the standard practices of researchers. GCP was conceived in 1993 as a way to make the most promising clinical trials accessible to more clinical centers. GCP legislation allowed physicians to bear responsibilities for patient care in clinical research trials. This type of practice gradually increased the number of clinical centers participating in clinical trials and created a competitive scientific environment.

Other benefits have included training of technical staff, establishment of hospital-based registry and full recording systems, awareness of patient insurance documents, reliance on Institutional Ethics Committees, and a uniform requirement of informed consents for patient enrollment. In addition, attention to data monitoring, data protection, and privacy issues has increased. In the early 1990s, the acute myeloblastic leukemia remission induction therapy trial with idarubicin, the recombinant human erythropoietin (rhEpo) trial in patients with anemia and cancer, and EORTC trials conducted in Turkey are considered to be excellent case studies for the management of ethical, credible, and scientifically qualified clinical research trials.

Some important strengths of conducting clinical research studies in Turkey include the presence of well-equipped and high-level university hospitals, as well as well-trained and competent specialized clinicians. In addition, lower costs associated with ethical reviews, regulatory approvals, and investigator compensation compared to the U.S. and Europe can also be highly advantageous for sponsors who would want to place a clinical trial in Turkey. Higher success rates for patient recruitment are another positive trend in this regard.[3]

Table 2. Clinical Trial Projects Submitted to the Central Ethical Committee

	1999	2000	2001	2002	July/2003
Phase I	—	—	—	2	—
Phase II	5	3	5	10	4
Phase III	59	66	61	71	52
Phase IV	59	52	92	103	56
Total	123	121	158	186	112

On the other hand, disadvantages for sponsors initiating trials include an inefficient patient-referral network, which leads to a patient overload in the hospitals. This sometimes squanders the time and effort of trial physicians, causes reluctance on the part of regulatory authorities to accept trial data, and raises concerns about the political stability of the region. Other problems include a torpid bureaucratic atmosphere for protocol approvals and activations; an inadequate infrastructure for some clinical centers in terms of logistics, equipment, research nurses, and data managers; and difficulties in reimbursement for protocol-required laboratory tests. As recently pointed out by Schilsky and Harousseau during the last ASH Meeting (2005) in Atlanta, these problems still exist in many European countries as well.[4]

While many U.S.- and Europe-based pharma/biotech companies are looking for novel sites for clinical trials, Turkey with her increasing number of medical schools and highly specialized trained clinicians and scientists is becoming even more attractive as an investment and professional site for clinical trials. Additional encouragement comes from the new Turkish government decision to increase R&D expenditures by 2% by the year 2010.

The current estimate that drug trials comprise around $10 million in activity for Turkey annually is still considered to be quite low compared to many European countries, but the gradually increasing number of trials is expected to have a significant impact on medical, scientific, and economic progress. Meanwhile, we believe that more trained clinicians and practical and applicable regulations, as well as efficient collaboration between researchers and administrators, are needed for the improvement and advancement of clinical scientific research in Turkey.

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