Turk J Hematol 2007; 24:1-3

REVIEW ARTICLE

Clinical research in Turkey

Hamdi Akan

Department of Hematology, Ankara University School of Medicine, Ankara, Turkey
✉ *akan@medicine.ankara.edu.tr*

The History of Clinical Drug Trials in Turkey

The history of clinical trials in Turkey dates back to the beginning of the 20th century, but many years had passed with studies done with no compliance to the Good Clinical Practice (GCP) guidelines. This was not due to the lack of legal documents. On the contrary, the first mention of clinical trials in a legal document occurred in 1926; "The Code of Pharmaceutical Products and Preparations No. 1262" law carried the statement: "Experimental drugs can be used in a patient only by his/her permission."

After periods of misconducted and ill-designed studies, the modern era of clinical trails began in 1993 with the introduction of the Drug Research Bylaw [1]. This document was directly influenced by the initial drafts of the ICH-GCP Guidelines, and some parts were very similar (Figure 1). This became the main document regulating the conduct of clinical trials in Turkey. A GCP guideline document was added in 1995 [2], followed by Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) guidelines also published and issued by the Ministry of Health [3-4]. Although these were quite early and impressive achievements, the growing number of different clinical trials and clinical investigators over time increased the need for new and updated regulations. This demand was partly covered by documents such as regulations on compassionate use, observational trials, patient rights, and articles in the Turkish penal law. During that time, major changes in Turkey's national policies occurred, as it turned its face dramatically toward the European Union (EU), and a new period began that required a complete revision of all legal documents and adaptation to EU rules and principles.

The Current Situation

The potential for conducting clinical trials in Turkey is huge. There are 94 universities, 59 medical schools, 1190 hospitals and 200,000 hospital beds. 95,100 medical doctors are in practice and 46% are specialized. If we look at the number and distribution of Research and Development (R/D) personnel, they can be broken down as follows: 37% technological sciences, 19% math, physics, life sciences, 19% social sciences, 14% medical sciences, and 11% agriculture. The goal is to have 40,000 people working in this area in 2010. The annual budget reserved for clinical trials by the pharmaceutical companies in Turkey was 27.5 million US dollars in 2005 [5-7].

To conduct a clinical trial in Turkey, especially a drug trial, is a matter of time, effort and finances. As usual, the steps are designing the trial, finding the sponsor and preparing the documents necessary for an ethical committee approval. Currently, all Phase I, II and III clinical trials are subject to both local and central ethical committee approval. Phase IV trials are handled by local ethical committees. Phase I trials are very rarely performed in Turkey, as they require specialized infrastructure and institutions. Figure 2 lists the number and distribution of clinical trials submitted to the Central Ethical Committee, which reflects the fact that Phase III and Phase IV trials are dominant [8,9]. After submission of a protocol to an ethical committee, it takes approximately 100 days to obtain an approval. The time limit between the first day of an approved study protocol and the day of the first patient in the trial is roughly 160-210 days. The main reason for this long delay is that in order to submit a study protocol to the Central Ethical Committee, an approval

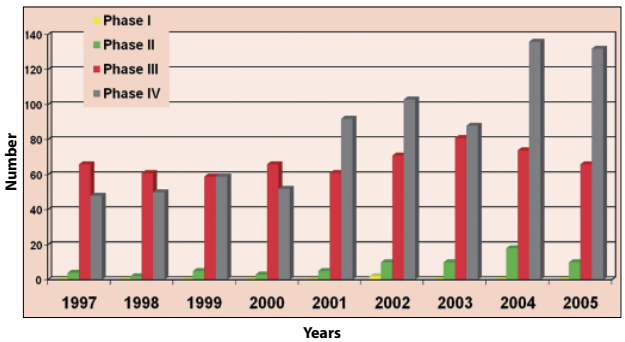

Figure 1. The distribution of clinical trials in Turkey according to phases and years.

years number	ICH-GCP Guidelines	Turkish Drug Research Bylaw (GCP Guidelines)
Approval	IRB/IEC approval	Competent Authority approval
Submission to IEC	IRB/IEC	First local IRB; after approval of central ethics committee
Notificatinon of the regulatory authority	Sponsor	Investigator
Nontherapeutic trials	Decision to be made by the IRB/IEC	Not defined
Ethical committee membership	At least one member whose primary area of interest is in a nonscientific area and at least one member who is independent of the institution/trial site.	No such member
Impartial witness for informed consent	Under specific conditions	For every informed consent
Adverse event notification	Sponsor	Investigator
Timetables: • SAE (fatal and life-threatening reporting)	7 days	24 hours
• AE (non-life-threatening) reporting	15 days	Not defined
• Retention of the source documents	2+years	15 years

Figure 2. Comparison of ICH-GCP guidelines and Turkish Drug Research Bylaw.

from a local ethical committee is mandatory. The new bylaw, which is expected to be effective in 2007, will reduce these numbers by 50%, as it introduces a system of double submission which enables simultaneous submission to both local and central ethical committees [10].

The number of international clinical trials in Turkey can be found on the webpage www.clinicaltrials.gov. Figure 3 summarizes the data and shows that the number of clinical trials in Turkey compared to the other parts of Europe is low. When we look at the distribution of these clinical trials, most of them are conducted in the field of hemato-oncology and neurology (Figure 4).

In the last 10 years, the number of physicians who want to conduct a clinical trial has increased, mainly due to an increase in the awareness of the importance of clinical trials and the increasing interest of pharmaceutical companies. This has caused an increase in the number of ethical committees in Turkey. At present, aside from the Central Ethical Committee working under the Ministry of Health, there are 82 local ethical committees in Turkey. These are formed mainly in the Universities and in major state hospitals. This increase has other reflections as well, such as in the number of GCP training programs mainly covering clinical trials put into practice and being applied by universities, pharmaceutical companies, clinical research organizations (CRO) and medical societies [11]. The heavy work load in this area necessitated the pharmaceutical companies to outsource their load. Now, there are around 15 CROs in Turkey, working mainly for the pharmaceutical companies.

These achievements not only resulted in an increase in the number of national and international clinical trials in Turkey, but they were also accompanied by a significant progress in scientific publications covered by the Science Citation Index (SCI), as indicated by Turkey's world rank of 19th in 2005. The total number of scientific publications from Turkey rose from 6,066 in 1999 to 17,300 in 2005 according to the SCI figures [12]. The articles in medical sciences constitute nearly half of the total publications.

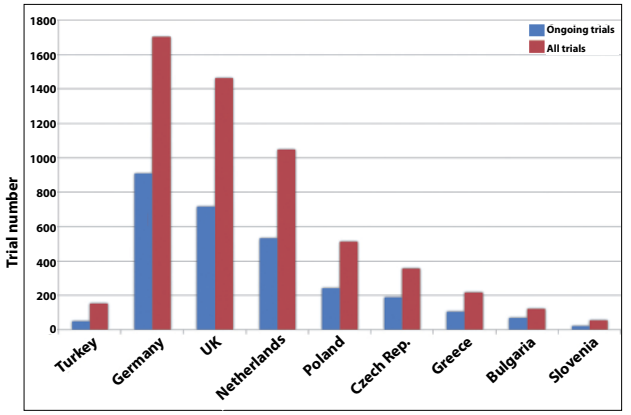

Figure 3. Clinical trials in Europe.

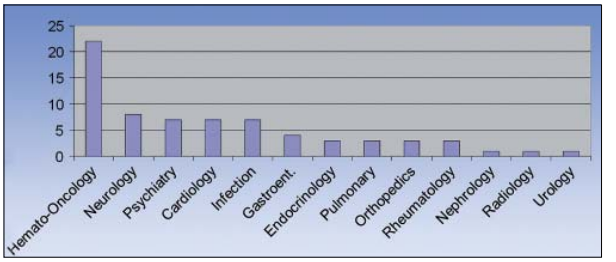

Figure 4. Clinical trials according to disciplines.

Clinical Trials on Children

Due to the arguments on conducting trials in children after 1993, the new Turkish penal law accepted by the Parliament in 2005 detailed the rules of conducting trials in children in accordance with EU directives. The paragraph on children includes issues that were absent in the current bylaw, such as assent of children, direct benefit and minimal risk, and the notion of no incentives or financial inducements except compensation. Also, a pediatric specialist is obligatory as a member of the ethical committees [13].

CONCLUSION

There are both advantages and problems facing the clinical trial arena in Turkey. The most important advantages are presence of well equipped and high-level university and state hospitals; well-trained specialized clinicians; lower costs associated with ethical reviews, regulatory approvals and investigator compensation; and good success rates for patient recruitment. The main problems are inefficient patient referral network (heavy patient overload), inadequate infrastructure in some centers (logistic, equipment, research nurse, and data management), lack of knowledge of GCP, non-standardized local ethical committees and problems in payments for investigator compensation.

With a population of 74 million and a developing under-structure, Turkey is a promising plateau for clinical research [14]. The forthcoming regulations and the EU integration process will provide a better future for clinical drug trials, and the GCP education programs will increase the number of qualified clinical researchers and ethical committee members.

References

1. Bylaw on Drug Research in Turkey (Turkish). Regulations of Drug Researches Turkish official gazette Date:29.01.1993, No: 21480. Available from: http://www.klinikarastirmalar.org.tr/dokumanlar
2. Guideline of Good Clinical Practice in Turkey (Turkish). Turkish Ministry of Health, Drug and Pharmeceutics Directorate, Good Clinical Researches Guide. No 51748 Available from: http://www.klinikarastirmalar.org.tr/dokumanlar
3. Guideline of Good Manufacturing Practice in Turkey (Turkish). Guideline for Pharmaceutical Products Good Manufacturing Processing Available from: http://www.klinikarastirmalar.org.tr/dokumanlar
4. Turkish Ministry of Health, . Ankara, Turkey Bylaw on Good Laboratory Practice and Accreditation of Test Laboratories in Turkey (Turkish). Available from:www.saglik.gov.tr
5. Turkey National Health Accounts 1999-2000. Basedon OECD System of Health Accounts. Ankara, Turkey: Ministry of Health, 2004.
6. Pak NK, Tankut T, Tümer T, Gürkan T. Turkish scienceand technology system vis-à-vis Europe. TUBITAK Report. 2004. Foreign Policy 29(1-2): 80-108. (Also available from www.foreign.policy.org.tr).
7. OECD. Main Science and Technology Indicators, OECD, 1998. Available from www.dtm.gov.tr.
8. Ilbars H, Yazgan S, Dagistanli S. Drug trials in Turkey (Turkish). Journal of Good Clinical Practice-IKU. 2004;7: 3-9.
9. Kansu E, Akbas O, Hayran M, Ayhan IH, Akova M, Akan H, Omeroglu N, Ari C, Tetik E, Taylan E. Clinical Scientific Research Potentials in Turkey. The Monitor, October 2006: 51-54.
10. Akan H, İlbars H, Ayhan IH, Kansu E, Akova M, Akbaş O, Omeroglu N, Ari C, Tetik E, Taylan E. New GCP Rules in Turkey. The Monitor, February 2007:41-44.
11. Akova M, Akan H, Ayhan IH, Kansu E, Akbas O, Ari C, Tetik E, Taylan E. Does training physicians in good clinical practice make a difference in quality of running clinical trials? 15th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark 2005. Abstract no. 877.
12. Onat A. Limited progress in 2005–scientific publications reaching 17,300. Rank 19th (Turkish). Cumhuriyet Bilim-Teknik, January 14, 2006, Issue: 982: 7.
13. Akan H, Akova M. Standards in clinical trials conducted on children (Turkish). In: Akan H, ed. Book of Clinical Research. Publisher, Bilimsel Tıp Yayınevi, 2007: 199-202.
14. Ott C. Turkey exhibits potential for clinical trials. Laboratory Talk, April 30, 2004 (news release from Chiltern International). Available from: www.laboratorytalk.com.