

Clinical Trials Journey of Turkey-Long and Thin Road

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Abstract

The history of the clinical trials started at the beginning of 20th Century, and evolved with several milestones of the improvements with the ultimate goal of the compliance with ICH-GCP rules and European Directives. This paper aims to summarize the journey of Turkey in clinical trials giving the historical and current status highlights as well as country specific considerations, and to evaluate the potential and future insights.

Introduction

With its unique geographical location creating a physical, cultural and commercial bridge between East and West, Turkey has been displaying an exponential growth in the number of sponsored clinical trials. The history of clinical trials started at the beginning of the 20th century, and evolved with several milestones of improvements with the ultimate goal of ensuring compliance with ICH-GCP guidelines and European Directives. Due to a lot of variables including, but not limited to, the regulatory framework, clinical environment and social and cultural factors, this adventure of harmonization can be defined as a long and thin road along which stakeholders from different origins are 'cruising'.

This paper aims to summarize the journey of Turkey in clinical trials giving historical and current status highlights, as well as country specific considerations, and to evaluate potential and future insights.

Major Regulatory Milestones

In the young Turkish Republic, the Code of Pharmaceutical Products and Preparations was published in the Official Gazette on 26 May 1928 where the statement 'experimental drugs can be used in a patient only by his/her permission' appears for the first time [1,2]. Those days, there was a lack of established processes and systematic oversight of clinical trials; as a result of this, the design and control of clinical trials were overlooked.

The Fundamental Law that followed this Code of Health Sciences that was published in the Official Gazette on 15 May 1987 (law no 3359); this covered the basic regulatory processes for providing health services to the public. Within this law, the statement 'the scientific research with licensed or not licensed medicines on human subject cannot be done if the Ministry of Health (MOH) approval and the relevant patient's consent are not in place' was included [3].

Upon growing demand from the clinical research industry, with increased number of trials, widening understanding of patient rights to have access to the medicines at any step of development, unmet

medical needs that have to be addressed with research and development of new treatment options in the country, and growing demand from clinical investigators for harmonization of clinical trials, the regulatory environment stepped through the new modern age with the first Bylaw on Clinical Trials published on 29 January 1993 with number 21480 [4]. This became the main document regulating clinical trials in Turkey. Two years later, the GCP Guideline was released by the MOH as a first country specific GCP guideline with major similarities to the international GCP Guideline [5,6].

Between 2008 and 2009, with the enormous interest and the efforts of the MOH, the EU CT Directive principles were adapted within the Turkish Clinical trials Regulation with the Regulation dated 23 December 2008 with number 27089 that was published in the Official Gazette [7]. As in this regulation, the regionally established MOH-accredited 'central Ethics Committee (EC)' concept is accepted, all local ECs were closed and the regional central ECs started to work. Timelines and transition period were well defined by the MOH to facilitate the change and minimize any risk arising from the change, however this was followed by some regulatory challenges. The Turkish Medical Association filed a lawsuit against the MOH that resulted in the suspension and return of all submissions based on Council of State decision on 12 Jan 2010 [8]. As an impact of this suspension, all MOH initial clinical trial applications were returned to the applicants and the re-submissions meeting the expectations of the Council of State request were prepared by the applicants. This request concerned mainly the fact that the consenting physicians need to be independent of the study team at site thereby taking into consideration and ensuring the unbiased for the trial subjects. In order to overcome this conflict and to re-initiate the applications, MOH published a revision to the regulation on 11 March 2011. With this revised regulation, within MOH, a central EC and an Advisory Board were established and started to operate. At this stage, the final adjudication was given by the Assembly of the Administrative Chambers at Council of State and it was concluded that the MOH do not have the authority to release a regulation on CTs as there is no legal basis. Pursuant to this decision, the central EC at MOH was retired; Clinical Trial Applications (CTAs) and substantial amendment submissions were

put on hold, not discussed further and returned to the applicants. With the add-on article 10 which was implemented in the valid by law on 6 April 2011, the legal basis for the MOH to rule and regulate the clinical trials was accepted.

19 August 2011 was the date when another new regulation was published and effective. This was the regulation which provided the detailed and final definition of the ECs

- Medicines Clinical Trials Ethics Committee
- Bioavailability and Bioequivalence Ethics Committees
- Non-Medicines Clinical Trials Ethics Committee

The ability of applying to any EC located nearby, in cases where there was no EC at the location of the sites was also covered in this regulation.

The regulation allowed for parallel submission enabling EC and MOH applications to be done at the same time, and stated a specific timeline for the review of the dossiers submitted; 30 days for both EC and MOH which was hardly achieved due to the high workload of the ECs and MOH.

Current Clinical and Regulatory Environment

Turkey has been considered among the top ten countries in terms of potential study subject populations; these consist of U.S., China, India, Brazil, Russia, Japan, Mexico, Germany, Turkey and Thailand [9]. Turkey's potential is supported by well-established, fully equipped medical facilities where clinical trials can be conducted at a high standard, and by the well-trained and experienced academicians and specialized physicians who are willing to contribute to the clinical trials. Looking into the figures of the in-patient medical facilities in Turkey, there is a dramatic growth in recent decades (Figures 1a and 1b). Figure 2 demonstrates the number of health care professionals in Turkey [10].

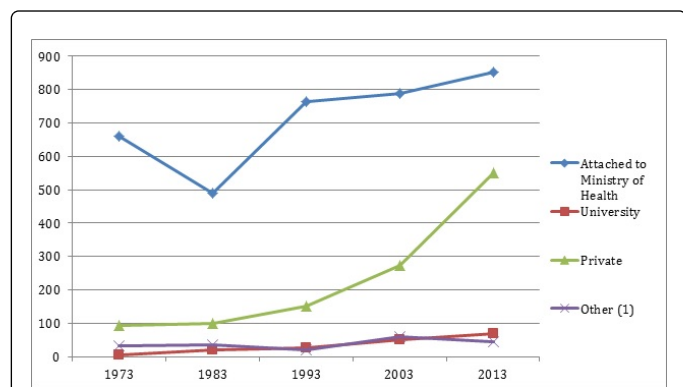


Figure 1a: The numbers of the in-patient medical facilities and their distribution in Turkey.

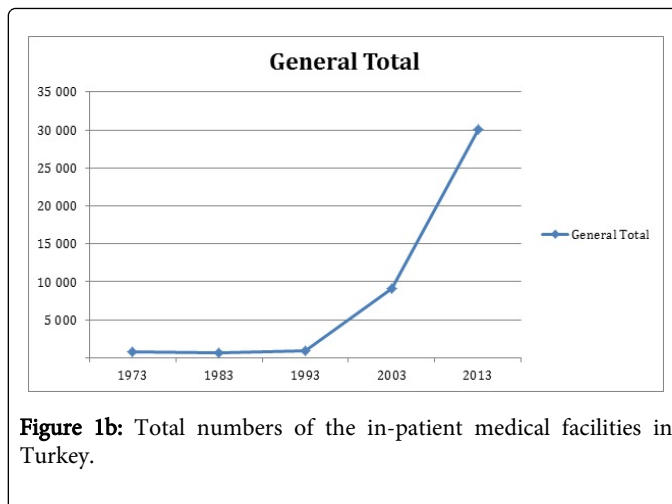


Figure 1b: Total numbers of the in-patient medical facilities in Turkey.

Note: Data obtained from Turkish Statistics Institution as of December 2014. Data source is the MOH. Under the "Other" group, inpatient medical institutions owned by the municipalities are covered. In addition, Ministry of Defense hospitals are included in this group for the year 2002 and onwards. The numbers of Community Health Centers, Family Medicine Units, Tuberculosis Dispensaries, MCH/FP Centers, Cancer Early Diagnosis, Screening and Training Centers are included in the total. Values are updated retroactively. Reliable data in compliance with the description could not be obtained before the year 2000.

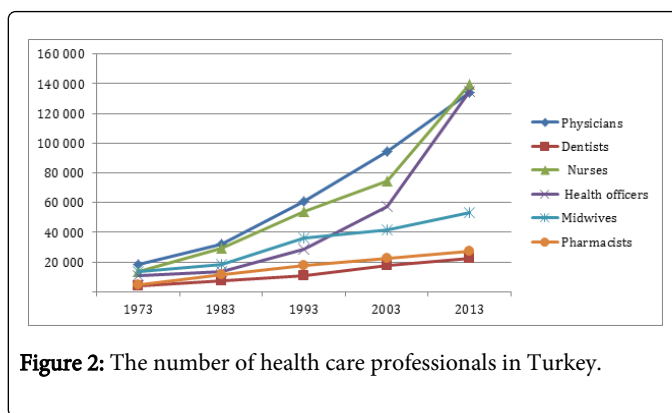


Figure 2: The number of health care professionals in Turkey.

Note: Data obtained from Turkish Statistics Institution as of December 2014. Data source is the MOH.

The Regulatory Authority between 1982 and 2011 was the General Directorate of Pharmaceuticals and Pharmacies. On 2 Nov 2011, the authority structure was evolved into the Turkey Medicines and Medical Devices Agency. Within the Agency, there is a Clinical Trials Department that has been maintained with specialized sub-departments as follows

- BE/BA Trials Evaluation Unit
- Academic and Observational Trials Evaluation Unit
- Data Record and Safety Maintenance Unit
- Initial Applications Evaluation Unit
- Substantial Amendments Evaluation Unit

Currently clinical trials with human subjects using investigational medicinal products are initiated, conducted, ruled and controlled

under the valid regulation dated 13 April 2013, which has a revision on 25 Jun 2014. Both documents are incorporated and are available for reference in the MOH web page [11].

Medical device studies however, are being managed by the Medical Devices Division in the Turkey Medicines and Medical Devices Agency, and their conduct falls under the regulation dated 6 September 2014 with number 29111 which is available in the MOH web page:

www.ieg.gov.tr/UnitDetails.aspx?DetailId=OCRwl2afhhI=&UnitId=l7xS8LqxdKw

DetailId=OCRwl2afhhI=&UnitId=l7xS8LqxdKw

As per this reference, the applicant (either the sponsor or the authorized Contract Research Organization (CRO) domiciled in Turkey) can perform the parallel application to an EC and MOH. The EC can be any EC of the participating sites and only one EC review

and favorable opinion is enough covering all sites. General approach is to select the national coordinating investigator and his site for a study, and proceed with this facility's EC thereby receiving the investigator's support. The Regulatory Agency's approach is to start reviewing the dossiers submitted, and wait for the EC favorable opinion to be submitted to them; the Agency does not issue the final approval if EC favorable opinion is not in place and submitted to them. The timelines stated in the regulation is 15 days for EC approval, and 30 days for MOH approval. Practically the regulatory bodies have been making great efforts to meet these timelines; however the backlog and the correspondence on revision requests that are generated realistically take time therefore giving prolonged timelines. The schematic summary of the regulatory submissions and approval process diagram of Turkey can be seen in Figure 3.

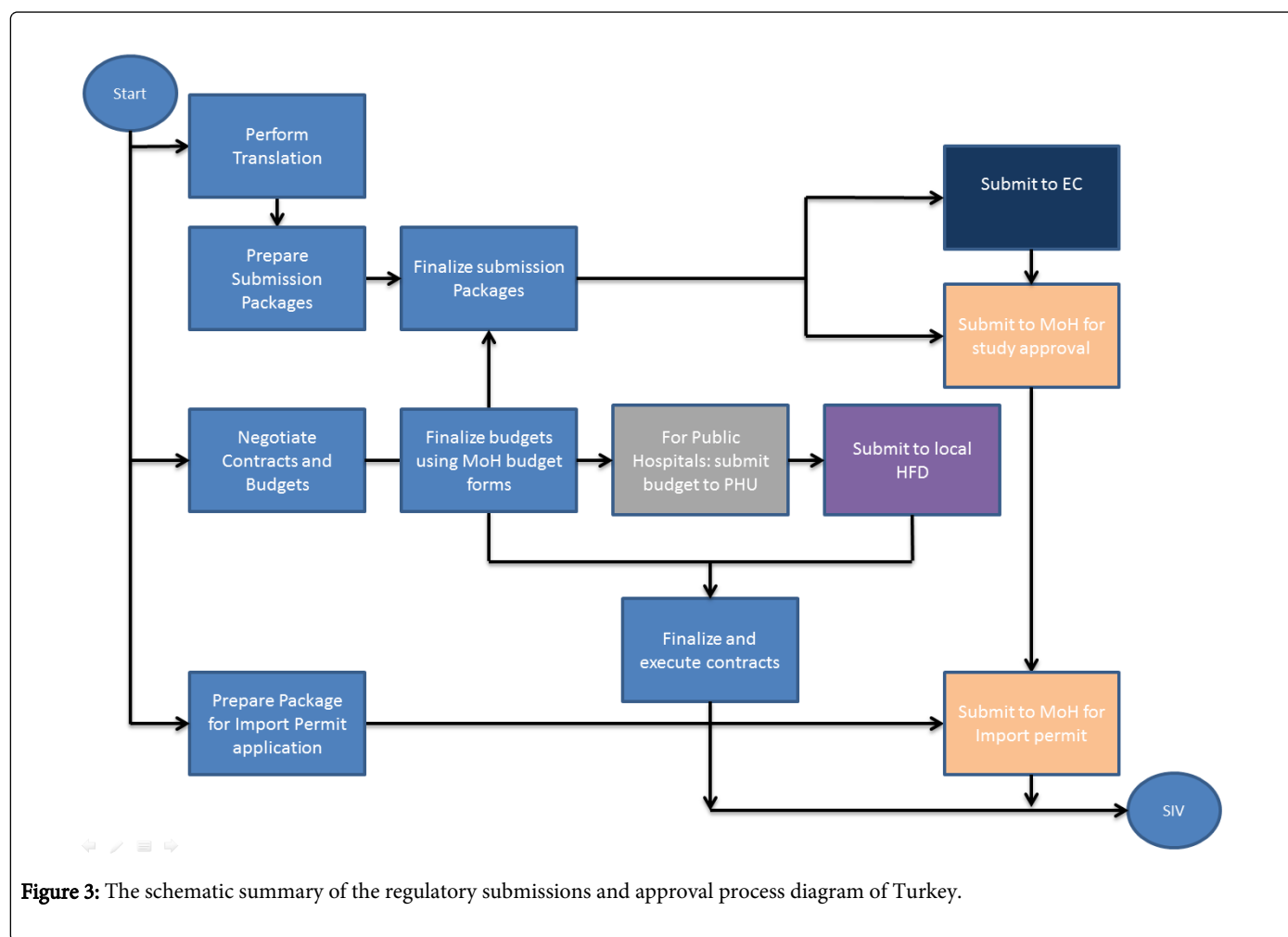


Figure 3: The schematic summary of the regulatory submissions and approval process diagram of Turkey.

The regulation covers the trials on special populations, including pediatric population, pregnant, puerperal or breast feeding women, disabled population, intensive care and unconscious subjects; the coverage defines the requirements that the preliminary trials' data is sufficient to support the target subject population, conditions that there should be no known risks to the minors, and explains other requirements in detail in the relevant articles.

One of the striking new requirements recently implemented is the registration of the clinical trials in a publicly available database, with

the clinical trial data privacy protection; this opens a transparency path within the industry and constitutes a big revolution in enhancing public awareness on clinical trials.

Stakeholders and Country Specific Aspects

Without any doubt, the main stakeholder contributing to the research and development of new medicines is the Turkish government, specifically the MOH, Development Agency, and Social Security Institution. The Medicines and Medical Devices Agency

provided the industry with high standard clinical regulations, supporting guidelines and even submission templates with the ultimate goal of EU compliance and complete harmonization. The current numbers of clinical trial applications with investigational medicinal products and the distribution in trial phases are seen in Figure 4a. Figure 4b demonstrates the medical devices studies that were approved in Turkey between 2009 and 2014. These numbers clearly show an increase in the volume of both medicinal products and medical devices clinical trials and the potential underlying efforts that contributed to this.

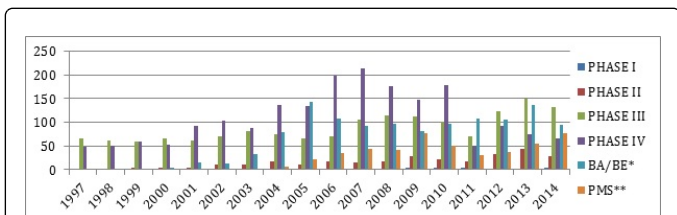


Figure 4a: Turkish MOH data on the clinical trials using investigational medical products between Jan 1997 and Dec 2014 ((BA/BE refers to Bioavailability and Bioequivalence Studies, and PMS refers to post marketing surveillance studies), (Source: Turkey Medicines and Medical Devices Agency, Clinical Trials Division.))

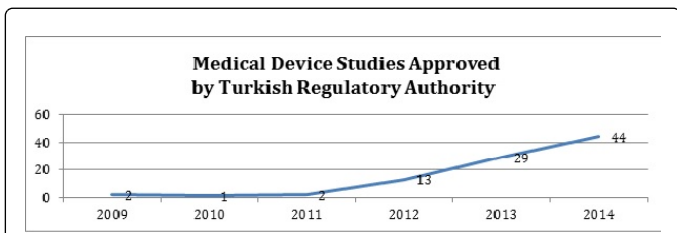


Figure 4b: The Medical Device Studies that were approved by Turkish Regulatory Authority (Turkey Medicines and Medical Devices Agency) between 2009 and 2014.

In addition to this, the number of inspections of the clinical sites in Turkey by foreign Regulatory Authorities demonstrates the active, massive and robust clinical data that is provided by the Turkish clinical investigative sites. Table 1 shows the list of the clinical site inspections performed by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in Turkey with years, departments and cities. Table 1 shows, the Turkish Regulatory Agency physically accompanied some of these inspections.

Year s	Regulatory Authority	Clinical Site	City
2004	FDA Inspection	Ege University, Medical Faculty, Internal Diseases Department, Gastroenterology Division	Izmir
2006	FDA Inspection	Istanbul University, Cerrahpasa Medical Faculty, Internal Diseases Department, Rheumatology Division	Istanbul
2006	FDA Inspection	Ege University, Medical Faculty, Chest Diseases Department	Izmir

2007	FDA Inspection	Ege University, Medical Faculty, General Surgery Department	Izmir
2007	FDA Inspection, Accompanied by Turkish Regulatory Authority	Dokuzeylul University, Medical Faculty, General Surgery Department	Izmir
2009	EMA Inspection, Accompanied by Turkish Regulatory Authority	Ege University, Medical Faculty, General Surgery Department	Izmir
2010	FDA Inspection	Istanbul University, Cerrahpasa Medical Faculty, Medical Oncology Department	Istanbul
2013	FDA Inspection	Yuzuncu Yil University, Medical Faculty, Pediatrics Department	Van
2013	EMA Inspection	Ankara University, Medical Faculty, Internal Diseases Department, Hematology Division	Ankara

Table 1: The list of the clinical site inspections performed by the US Food and Drug Administration and European Medicines Agency in Turkey.

The Clinical Trials Department within the Turkey Medicines and Medical Devices Agency is available for face to face discussions once a week with the CROs, and once a week with the sponsor representatives to receive any questions and provide advice on how to resolve issues. The Development Agency has been providing support to the Pharmaceutical R&D as one of the primary investment areas for Turkey. The Social Security Institution has been continuously analyzing the pharmaco-economic aspects of the clinical trials and providing feedback to the governmental bodies; this is attributing to opening the boundaries of the country more to the clinical trials. The scope of social security services increased with successful healthcare reform, as did patient satisfaction, access to services, and industrial indicators; this reform started in 2004 and was gradually implemented to provide the country with a centralized healthcare system [12]. Within the MOH, the Public Hospitals' Institution and its branches, called the Public Hospitals' Unions, have been involved in the preliminary budget approval for any clinical trial that will be conducted in public or governmental hospitals; this theoretically constitutes one additional step in the process, however in reality, contributes to the faster and more effective budget finalization at these clinical sites.

ECs are the other important stakeholders for whom the working principles and establishment rules are defined in the regulation. Generally the ECs meet twice a month, and depending on the meeting agenda, the initial feedback from ECs is received a couple of weeks following the meeting. ECs have not only been involved in the application dossiers review, but also in providing feedback on cases that are encountered throughout the life time of the clinical trial that are not specifically addressed in the written references. These contributions are of crucial importance for correct translations of the clinical trial documents and cultural adaptation of the translations and preparing the patient documents that have culturally acceptable terms and phrases.

The clinical investigators and their clinical sites are of key importance in Turkey as they are also in other parts of the world. Their potential can be seen by looking at the departments and clinics where the clinical trials are being conducted, and on the other hand the academic initiatives which are dedicated to serve the clinical trials

industry. At this moment, there are a lot of clinical trials divisions or rooms located in the clinical departments, where the access is limited, locked cabinets are in place and all infrastructures required for the conduct of the trial is set. A very good example is the Ankara University Medical Faculty Hematology Department Clinical Trials room, where a number of audits were hosted, including an EMA inspection without any facility or data finding. Another important example is the Clinical Trial room set in Ege University Medical Faculty Pediatric Hematology Department; this department also has MOH accreditation for Phase I Unit with complete equipment and personnel that is adequately educated and experienced. There are three MOH accredited Phase I facilities in Turkey to date; the other two are Ege University Pharmaceutical Development and Pharmacokinetic Research and Application Center (ARGEFAR), and Erciyes University Hakan Cetinsaya GCP and Research Center. Almost all of the clinical sites are involving site coordinators who are allocated by an external third party as per the request of the clinical investigators; this has become a routine practice in Turkey and it is proven that this supports patient enrolment, facilitates the trial related procedures at site and helps in getting the clinical investigators to be more involved in the protocol related scientific matters rather than the administrative issues. The Clinical Trials Department within the Turkey Medicines and Medical Devices Agency has released a guideline covering the process for this service and ensuring the site coordinators become members of the sites' clinical team.

It is worth stating that there are a number of civil initiatives including, but not limited to, Istanbul Clinical Trials Initiative (IKAI), Istanbul University Clinical Trials Excellence Center, Contract Research Organizations Association (SAKDER), Clinical Trials Association (KAD), Turkish Clinical Research Infrastructure Network (TUCRIN) which is the partner of ECRIN (European Clinical Research Infrastructure Network), and Association of Research-Based Pharmaceutical Companies (AIFD). These bodies have been organizing training meetings, press releases, congresses, conferences, panel discussions where all aspects of the clinical trials industry can be discussed and the new approaches to overcome the challenges are freely discussed by all the stakeholders shaping up the industry.

Looking to the Future

From 1993 onwards, there have been many regulatory and practical challenges encountered in the clinical trials industry. Throughout all the efforts to harmonize the Turkish clinical research industry with the world and approach compliance as closely as possible to the European Regulations; the confidence of the industry in the potential of Turkey has never wavered. This journey has been travelled by all stakeholders who have contributed with open minded ideas, continuous efforts and managed improvements. Currently, some of the main topics on which to focus could be the more predictable and consistent timelines in the regulatory process, more public awareness on the value of clinical trials with transparent access to the information, and more understanding of the country and its cultural specific factors by foreign sponsors. With a population of 74 million, well-established clinical sites and clinical investigators who have GCP experience, and with a clinical environment that is shaped by all stakeholders, Turkey serves as a promising plateau for clinical research.

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