

Development of Clinical Trials in Turkey After the Adoption of Clinical Drug Research Regulation

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ABSTRACT

Objective: This study aims to investigate the effects of Turkey's adoption of clinical trial (CT) regulations and international guidelines on CTs conducted in Turkey over the course of the 24 years.

Methods: The ClinicalTrials.gov website and its advanced filtering were used to identify registered CTs performed in Turkey during four six-year intervals. Various characteristics of the CTs, such as design, phase distribution, participant age, and type of funding, and the percentage of surgery-related CTs, were analyzed.

Results: The number of CTs conducted in Turkey increased exponentially during the 24-year study period, from 23 studies between 01/01/1994 and 01/01/2000 to 1930 studies between 01/01/2012 and 01/01/2018. Phase distribution analysis showed that there were more late-phase CTs than early-phase CTs in Turkey during the study period.

Conclusion: Modernization of Turkey's regulations for CTs facilitated the relevant growth of CTs in Turkey. Considering Turkey's unique geographic location, technological advancements, and ease of patient recruitment, the observed exponential increase in the number of CTs performed is not surprising. The higher number of late-phase CTs, as compared to early-phase CTs in Turkey, indicates that late-phase CTs may be more common in developing countries because they are less expensive to conduct than early-phase CTs and the pool of potential participants are naive.

INTRODUCTION

A clinical trial (CT) is a type of experiment that aims to improve a conventional technology or to generate a completely innovative way to improve the practice of conventional medical treatment, based on studying the effects of administering a particular treatment or product to selected groups of participants. Large groups of participants with related complaints are selected to achieve significant results concerning the benefits and side effects of an innovative treatment/product.^[1] CTs are interventional studies of innovative surgical procedures, drugs, nutritional products, and medical devices. ^[1] Observational studies, on the other hand, are based on retrospective analysis and epidemiological investigation. Unlike observational studies, CTs are prospective interventional studies that are designed to determine the probable clinical outcomes of a treatment/product be-

fore its release.^[2] During a CT of a medical product or procedure, many steps (or phases) must be successfully completed. All CTs include the same four phases, and the number of the participants required to effectively evaluate the clinical outcome of an innovative treatment/product increases dramatically with each progressive phase of a CT.^[3] The large number of participants required for a late-phase CT generally forces researchers to conduct CTs in countries with a limited number of potential participants to seek recruitment of participants from other countries.^[4] In contrast to CTs, observational studies do not include phases.^[5]

CTs require strong financial support and a large participant pool to achieve significant results. Financial support is generally provided by governments and sponsors.^[6] Sponsors include such organizations as industrial companies, healthcare institutes, and universities, as well as individuals.^[5] Worldwide, the industry is a major source

of funding for CTs that generally aim to identify optimal methods for profit. Feasibility studies precede CTs and play a crucial role in informing the authorities that perform and/or support CTs about the future of a project and the steps required for smooth progress.^[4] Another factor that facilitates CTs is guidelines that standardize the phases of a CT and protect the rights of participants. The International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guideline is a globally approved and known to accelerate the phases of innovative medicinal research, and facilitates rapid and continual investigation of related products, and industrialization.^[7] Countries with a sufficiently structured research network and optimized research guidelines are considered valuable to those with treatments/products ready for CTs. Furthermore, CTs can contribute positively to a country's GDP.^[8]

Turkey's geographic location and high-quality research facilities and researchers make it an attractive locale for the utilization of innovative technologies.^[9] Moreover, the overall number of registered CTs performed in Turkey renders it as a leader in the Middle East and North Africa (MENA) region. Before the adoption of ICH-GCP guidelines and laws, CTs in Turkey were not properly designed or performed.^[10] In 1993, the primary outline for drug research was formed by accepting of clinical drug research regulation. This regulation is very similar to the initial ICH-GCP guidelines it replaced as the primary Turkish regulation concerning CTs.^[10] In 1995, globally approved guidelines (Good Clinical Practice (GCP), Good Laboratory Practice (GLP), and Good Manufacturing Practice (GMP)) were adopted in Turkey, which, together with technological advancements, resulted in an exponential increase in the number of CTs conducted in Turkey.^[5,10]

The present study aims to highlight improving the effects of adopting CT regulations and international guidelines on the number of CTs conducted in Turkey over the course of 24 years. Despite the historical developments in Turkey, to our knowledge, how these developments affected the numbers and types of CTs conducted in Turkey has not been studied previously. This study tracked the numbers of registered CTs conducted in Turkey between 01/01/1994 and 01/01/2018 and classified these CTs according to type, phase, funding, participant age, and treatment/product.

MATERIALS AND METHODS

Number of the CTs conducted between 01/01/1994 and 01/01/2018, according to the ClinicalTrials.gov database

ClinicalTrials.gov is the largest worldwide CT registry; the database includes approximately 305,000 CTs conducted in 209 countries.^[5] Before public access was given, the website only contained NIH-specific trials; however, beginning on 01/01/2000, the public was given access to the website and it began to also include privately funded CTs.

^[11] Advanced search filters provided by ClinicalTrials.gov

were used to analyze various aspects of CTs conducted in Turkey between 01/01/1994 and 01/01/2018.

Research criteria

Using the advanced filtering options, Turkey was selected as the region for the study's ClinicalTrials.gov search. To determine if there was an increase or decrease in the number of CTs in Turkey, the 24-year study period was divided into four time intervals of six years each, using 01/01/1994 as the initial time stamp and 01/01/2018 as the last. Next, the CTs were categorized according to phase via additional filtering. Among the types of CTs, only interventional and observational trials were considered. Participant age was categorized as follows: child (birth-17 years) for pediatric trials and adult (18-64 years) plus older adult (≥ 65 years) for adult trials. Funding sources were grouped as industry-funded studies versus other funding via selecting all options other than "Industry" from the "Additional Criteria" section. Concerning CT participants, they were analyzed as surgical and non-surgical.

Limitations of this study

The search of ClinicalTrials.gov identified some of the same CTs when the child (birth-17 years), adult (18-64 years), and older adult (≥ 65 years) filters were used, which indicates overlapping results in the case of age filtering. The total number of the CTs was integrated into a graph depicting study types, alongside observational versus interventional studies. Moreover, in addition to ClinicalTrials.gov's enormous database of registered CTs, it also includes unregistered CTs.^[12,13] For a more comprehensive investigation of the development of CTs in Turkey, registries other than ClinicalTrials.gov should also be analyzed;^[14] however, it is not expected that such an expanded study will significantly change the findings presented herein, as ClinicalTrials.gov includes the vast majority of all CTs conducted worldwide. Lastly, despite the careful use of filtering during the search of ClinicalTrials.gov, a negligible number of relevant CTs may not have been found and included in the present study's analysis.

RESULTS

There was a significant increase in the number of CTs (both observational and interventional) during the 6 year of 01/01/2012-01/01/2018, reaching the maximum total number of 1930. During the 24-year study period, there was a nearly 84-fold increase in the number of registered CTs performed in Turkey, from 23 studies between 01/01/1994 and 01/01/2000 to 1930 studies between 01/01/2012 and 01/01/2018 (Fig. 1). The number of CTs with different phases increased significantly during the 24-year study period (Fig. 2). Among all CT phases, phase III trials were the most common in every time period followed by phase IV, phase II, phase I, and early phase I CTs (Fig. 2). There were not any early phase I or phase I CTs conducted in Turkey between 01/01/1994 and 01/01/2006,

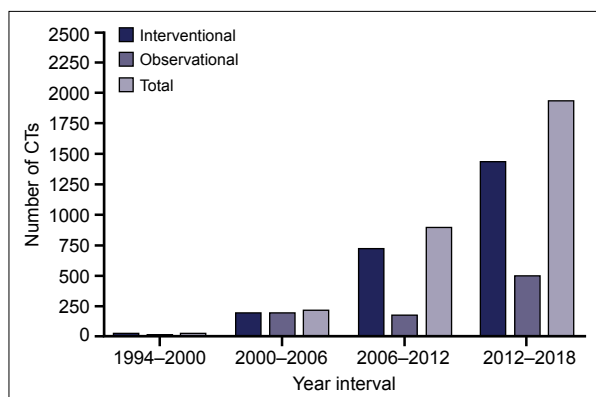


Figure 1. Distribution of the CT types and the total number of the CTs in Turkey, according to each 6-year interval. The ClinicalTrials.gov database was analyzed using Turkey in the “country” section, alongside the 24-year study period divided into 6-year intervals in the “Study start: from-to” section. A separate analysis was conducted by selecting observational and interventional studies from the “Study type” section and for each of 6-year interval. The total number of the CTs was analyzed by leaving the “Study type” section blank.

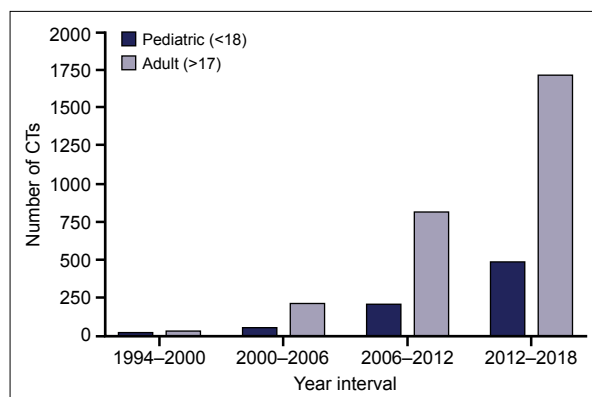


Figure 3. Distribution of the pediatric CTs versus adult CTs in Turkey, according to each 6-year interval. The ClinicalTrials.gov database was analyzed using Turkey in the “country” section, alongside the 24-year study period divided into 6-year intervals in the “Study start: from-to” section. Pediatric studies were analyzed by selecting the “Child (birth-17 years)” option, whereas adult CTs were analyzed by selecting the “Adult (18–64 years)” and “Older Adult (≥65 years)” options at the same time from the “Age” section.

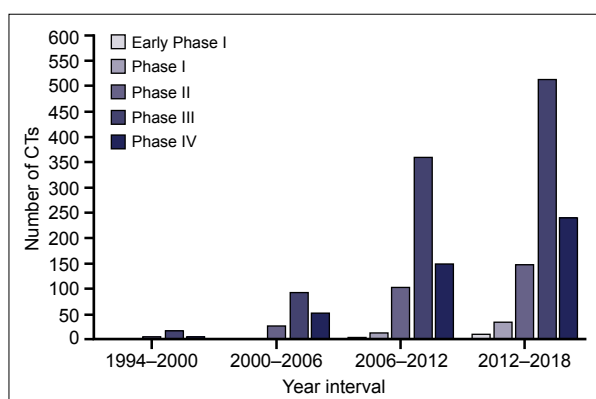


Figure 2. Distribution of the CT phases in Turkey, according to each 6-year interval. The ClinicalTrials.gov database was analyzed using Turkey in the “country” section, alongside the 24-year study period divided into 6-year intervals in the “Study start: from-to” section. Distribution of the CT phases was analyzed separately by individually selecting each phase from the “Phase” section. The “Not applicable” option was ignored during analysis.

whereas after 01/01/2006, there was an exponential increase in the number of early phases and late phase CTs; however, the shortage of early phase studies is preserved despite the overall increase.

CTs were categorized as pediatric (participant age: birth-17 years) and adult (participant age: >17 years) (Fig. 3). There was an exponential increase in both age categories during the 24-year study period, from 15 pediatric and 23 adult CTs between 01/01/1994 and 01/01/2000 to 478 pediatric and 1707 adult CTs between 01/01/2012 and 01/01/2018. The distribution of CT funding sources during the 24-year study period was also analyzed (Fig. 4). Between 01/01/2012 and 01/01/2018, industry-funded CTs

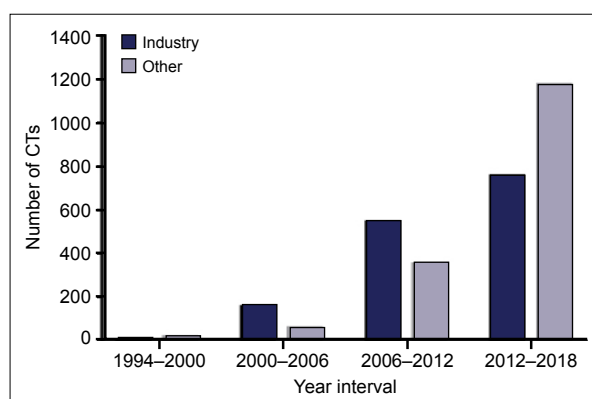


Figure 4. Distribution of the industry-funded CTs versus other-funded-CTs in Turkey, according to each 6-year interval. The ClinicalTrials.gov database was analyzed using “Turkey” in the “country” section, alongside the 24-year study period divided into 6-year intervals in the “Study start: from-to” section. Funding sources were investigated by selecting the “Industry” option and by selecting the “Other” options in the “Funder type” section.

were less common than other-funded CTs in Turkey; however, between 01/01/2000 and 01/01/2012 industry-funded CTs accounted for the 63% of CTs conducted in Turkey. In between 01/01/1994 and 01/01/2000, there were three industry-funded with 20 other-funded CTs performed in Turkey, versus 756 industry-funded CTs and 1175 other-funded CTs between 01/01/2012 and 01/01/2018.

Surgery-related trials accounted for 17.4% of all CTs conducted in Turkey between 01/01/1994 and 01/01/2000, and during the next 18 years that percentage decreased significantly as the overall number of CTs increased significantly (Fig. 5). There were four surgery-related CTs between 01/01/1994 and 01/01/2000, followed by 11,

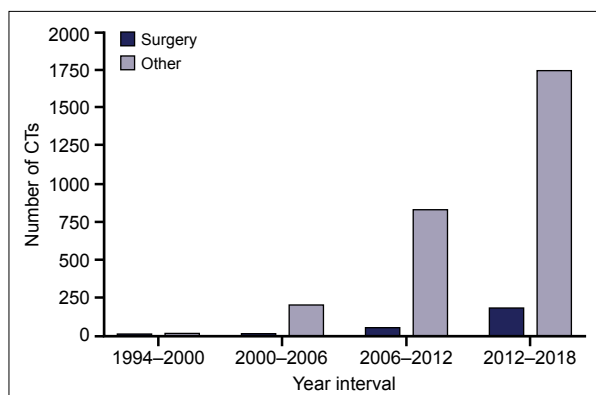


Figure 5. Distribution of the surgery-related CTs versus other CTs in Turkey, according to each 6-years interval. The ClinicalTrials.gov database was analyzed using “Turkey” in the “country” section, alongside the 24-year study period divided into 6-year intervals in the “Study start: from-to” section. Surgery-related CTs were analyzed by typing the keyword “Surgery” and “Surgical” in the “Condition or Disease” section. Studies not related to surgery were analyzed by extracting the number of surgery-related CTs from the total number of the CTs for each 6-year interval.

62, and 184 CTs during the next three interval periods, respectively; yet, the percentage of surgery-related CTs conducted in Turkey was only 9.5% between 01/01/2012 and 01/01/2018.

DISCUSSION

Before 1994, Turkey did not have sufficient organizational ability to conduct CTs.^[10] The first law in Turkey related to CTs was passed in 1926 and specially addressed experimental drugs.^[10] A search of ClinicalTrials.gov showed that before 1994, there were only four CTs conducted in Turkey.^[5] Despite Turkey’s potential for clinical research, the low number of Turkish CTs before 1994 is an indication of the negative effects of the lack of Turkey’s adoption of globally approved CT guidelines. The present findings show that after Turkey adopted ICH-GCP universal guidelines in 1993 alongside GLP and GMP, the number of CTs conducted in Turkey increased dramatically, rendering Turkey a top producer of CTs in the MENA region.^[14]

The small number of observational CTs shown in Figure 1 draws attention. However, the present study’s observational and interventional CT distribution rates shown in Figure 1 are similar to earlier reports of global distribution rates.^[5] As mentioned earlier, in contrast to observational CTs, interventional CTs are phased trials that aim to introduce and to test an innovative medical treatment/product.^[1,5] Worldwide, interventional CTs are conducted nearly 4-fold more frequently than observational CTs.^[5] Similarly, Figure 1 shows that the number of interventional CTs conducted in Turkey was 5-fold higher than that of observational CTs.

Figure 2 shows the distribution of CT phases according to each of the present study’s 6-year periods. It was reported

earlier that late-phase CTs are more common in Turkey than early phase CTs,^[14] which is typical for a developing country with a large pool of potential participants for late-phase CTs. Early phase studies generally conducted in regions that they were introduced, generally in developed countries.^[3,14] In contrast to the findings shown in Figure 2, phase II CTs are the most common globally, followed by phase I, phase III, phase IV, and early phase I CTs.^[5] This is further evidence that researchers in developing countries prefer conducting late-phase CTs. The present findings show that the most common CT phase in Turkey was phase III, followed by phase IV, phase II, phase I, and early phase I; however, Turkey’s adoption of globally approved CT guidelines together with technological advancements increased the overall number of CTs conducted in Turkey, even though the distribution of the CT phases remained the same.

The high and young population of the MENA region is an asset for the CT researchers.^[15] Simultaneously, the region’s high prevalence of disease due to poor healthcare is indicative of the need for innovative medical interventions for both pediatric and adult patients.^[16] Figure 3 indicates that the distribution of pediatric and adult CTs conducted in Turkey is similar to the global distribution; globally, the number of adult CTs is approximately 4.7-fold higher than the number of pediatric CTs.^[5] The modernization of Turkey is observable with an increased number of pediatric studies as well as adult studies since 1994. However, due to the large young population in the MENA region, it is expected that the number of pediatric CTs in Turkey would increase. However, 01/01/2012–01/01/2018 interval in Figure 3, indicates that the difference between pediatric studies and adult studies increased.

CTs require complex and expensive cost analyses and budget planning,^[6,17] which often exceed the budget of individual stakeholders, especially in the case of late-phase CTs; this makes securing financial support crucial for conducting a CT. Despite its for-profit nature, the industry is a critical source of funding due to the depth of its financial resources. Accordingly, the present study evaluated industry-funded CTs in Turkey separately from other-funded CTs (Fig. 4). Figure 4 shows that the distribution of CT funding changed during the 24-year study period; between 01/01/1994 and 01/01/2000, there were only three industry-funded CTs in Turkey versus 20 other-funded CTs, whereas between 01/01/2000 and 01/01/2012, there were 702 industry-funded CTs in Turkey, versus 414 other-funded CTs. The observed increase in industry-funded CTs in Turkey might be associated with the simultaneous expansion of the pharmaceutical market in Turkey; nonetheless, between 01/01/2012 and 01/01/2018, there were 756 industry-funded CTs conducted in Turkey, versus 1175 other-funded CTs. This latest change is most likely related to the expansion of academic and government funding in Turkey that targets drug development. Globally, industry funding and other funding each account for approximately 50% of all CTs (5), which is similar to the present study’s

findings for 01/01/2012–01/01/2018 (industry-funded to the other-funded ratio of 1:1.55).

Alongside with the conventional techniques, the variation of CTs determines the amount of innovative approaches targeting the specific fields in a country. According to Figure 5, surgery-related CTs in Turkey increased from four studies between 01/01/1994 and 01/01/2000 to 184 studies between 01/01/2012 and 01/01/2018. Between 01/01/1994 and 01/01/2000, the percentage of surgery-related CTs to all CTs was 17.4%, while it drops to 9.5% between 01/01/2012 and 01/01/2018. However, the total number of the CTs increased between 01/01/2012 and 01/01/2018 (1930 CTs), so did the number of surgery-related CTs, which indicates that the innovations of surgery in Turkey have also increased.

CONCLUSION

Overall, there is an 83-fold increase in the number of CTs over a 24-year duration in Turkey after the adoption of clinical drug research regulation, starting with 23 studies between 01/01/1994 and 01/01/2000 and reaching 1930 studies between 01/01/2012 and 01/01/2018. However, late phase studies form the majority of all CTs in Turkey over the course of 24 years, which indicates the lack of local introductions of novel approaches in Turkey. Turkey resides in a very good position among the MENA region concerning the clinical trial conducting potential. However, when the unique geographical location, high target population alongside with its high-quality institutions with sufficient investigator potential is considered, it appears that there is no reason for the lack of conducting early phase studies in Turkey.

Ethics Committee Approval

This study is an analysis of publicly available database and therefore local ethics committee approval is not applicable.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: F.Ö., A.S., F.N.; Design: F.Ö., A.S., F.N.; Supervision: F.Ö., A.S., F.N.; Materials: F.Ö., A.S., F.N.; Data: F.Ö., A.S.; Analysis: F.Ö., A.S., F.N.; Literature search: F.Ö., A.S.; Writing: F.Ö., A.S.; Critical revision: F.N.

Conflict of Interest

None declared.

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Klinik İlaç Araştırma Yönetmeliğinin Kabulü Sonrası Türkiye’de Yapılan Klinik Çalışmaların Gelişmesi

Amaç: Bu çalışma, Türkiye’nin klinik çalışmaların yürütülmesi konusunda uyguladığı uluslararası yönetmeliğin etkilerini 24 yıllık bir dönem içinde göstermektedir.

Gereç ve Yöntem: ClinicalTrial.gov sitesi ve içerisinde sunulan filtreler kullanılarak klinik çalışma sayıları kategorize edilmiştir. Bu araştırmalar altı yıllık dört farklı zaman aralığı kullanılarak yapıldı. Çalışmaların çeşitleri, faz dağılımları, yaş aralıkları, sponsor çeşitleri ve cerrahi klinik çalışmaların tüm çalışmalara oranı incelendi.

Bulgular: Türkiye’nin konusu geçen 24 yıllık dönemine bakıldığında yürütülen klinik çalışmaların sayısının katlanarak arttığı gözlemlendi. 01.01.1994 ile 01.01.2000 tarihleri arasında kayıtlı 23 klinik çalışma, 01.01.2012 ile 01.01.2018 tarihleri arasında 1930’a yükselmiştir. Buna ek olarak, Türkiye’de geç fazlı çalışmalara, erken fazlı çalışmalara kıyasla daha büyük bir eğilim olduğu görüldü.

Sonuç: Türkiye’nin klinik ilaç araştırma yönetmeliğindeki reformu, inovatif tıp için uyumlu bir alan yaratmıştır. Türkiye’nin benzersiz coğrafi konumu, teknolojik gelişmeleri ve hedef hasta kitlesinin uygunluğu göz önünde bulundurulduğunda bu ivmeli artış beklenmedik değildir. Türkiye’deki geç fazlı çalışmaların sayısının erken fazlı çalışmalara kıyasla az oluşu, gelişmekte olan ülkelerde olası düşük maliyet ve tedavi edilmemiş hasta grubunun varlığı nedeniyle oluşan çekiciliği yansıtmaktadır.

Anahtar Sözcükler: Klinik çalışma faz dağılımı; klinik çalışmalar; Türkiye.