Clinical Research Association: A Leading Civil Society Organisation in Turkey

PEER REVIEWED

Introduction
As seen in all areas, civil society organisations and initiatives are of key importance in clinical research. In order to translate the ideas and requirements raised by any stakeholder into structured and constructive policy initiatives, societies, non-profitable organisations and associations are actively involved in activities in clinical research around the world. The Society for Clinical Trials (http://www.sctweb.org/public/home.cfm), the Association of Clinical Research Professionals (http://www.acrpnet.org/), and Develop Innovate Advance (http://www.diaglobal.org/) in the United States, and the Institute of Clinical Research (ICR) in the United Kingdom are some major examples of such civil organisations. In Turkey, a similar organisation, the Clinical Research Association (Klinik Arastirmalar Dernegi – KAD) is the important initiative which deals with the improvement of clinical trials in Turkey.

Founded in 2006, the Clinical Research Association is the first and only civil society organisation in Turkey in the human clinical research field, which is open to all clinical trials professionals from all stakeholders. It is a not-for-profit organisation, guided by a Board of Directors who are elected by the membership and are based at its head office in Ankara, the capital city of Turkey.

The association assembles the pharma industry, academy, regulatory authorities, clinical research organisations, other academic and civil associations and all professionals involved in this area[1]. The board is made up of three academicians, two CRO executives, one SME (subject matter expert), and one pharmaceutical company clinical research director.

The idea of building up the KAD came from the multidisciplinary contribution to improving clinical trials in specific areas, some of which are listed below:

- Alignment of all stakeholders in the country in regard to the regulatory and operational aspects
- Coming together, sharing experience, discussing the areas of improvement, generation of action plans
- Enhancing clinical research quality standards with appropriate training and conferences
- Providing a web portal and website as a common place for reference information for local and international members
- Enabling communication between all involved parties
- National and international networking and learning from others
- Increasing public awareness of clinical trials
- Optimising the predictability of the clinical research regulatory timelines
- Increasing the attractiveness of the country and region for clinical trials, comparable with EU countries
- Contributing to local innovative medicinal products research and development in Turkey

Members are involved in the regulating, controlling, designing, management and conduct of industry sponsored or academic clinical trials on humans, and they are engaged directly and/or indirectly in all aspects of work in clinical research.

The mission of the association is to contribute to the conduct of clinical trials in Turkey to the highest international standards, and to organise comprehensive educational supportive activities to reach this goal, and the vision is to bring the academy, industry and regulatory authorities together.

The aim of this paper is to provide detailed information about the Clinical Research Association's structure and activities, and the value it has been adding to the clinical research area and the future perspective in the light of clinical research milestones in Turkey.

1 Membership and Board

The KAD has regular Board of Directors meetings to determine and prioritise the activities. Since it was founded in 2006, there have been regular board meetings taking place to enhance the quality and the number of clinical trials conducted in Turkey.

The number of KAD members which are individuals rather than organisations, as per the association charter, has increased throughout the years. The details of membership profiles are demonstrated in Figure 1 and Figure 2, including the distribution and the origin of the members. As seen in the membership profile, KAD has a multidisciplinary and heterogeneous population of members which in turn supports the information exchange, networking, sharing experiences and discussion of ways to make it smoother for clinical research in the country from different insights. Among the members

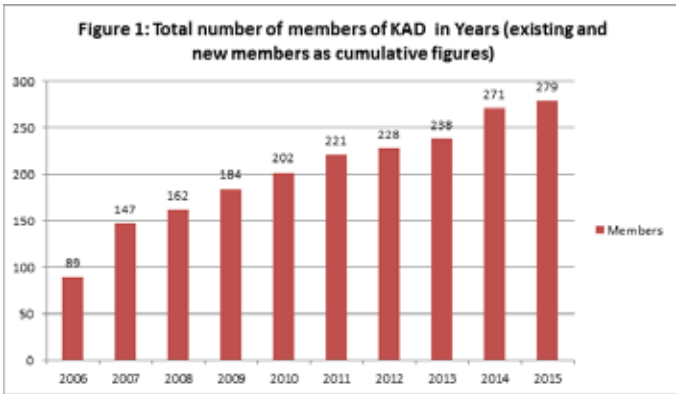

Figure 1

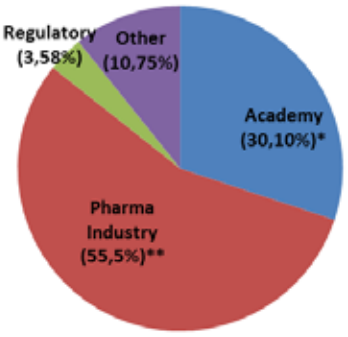

Figure 2: Origin profile distribution of KAD members (as of March 2016).
*Academy includes all academic members including law, medicine, pharmacy, and dentistry.
**Pharma Industry includes the pharmaceutical companies, contract research organizations, and direct vendors.

there are professionals from an academic environment from medical, dentistry, and law, professionals from the pharma industry (pharma companies, contract research organisations and direct vendors), members of ethics committees and professionals from the Turkish Health Authority (Turkish Medicines and Medical Devices Agency - TMMDA - under the Turkish Ministry of Health). The Board of Directors, some of whom are co-authors of this paper, are also from academia and industry, and regularly interact with the regulatory authorities, ethics committee members, key opinion leaders, and other civil society organisations.

2 Activities Over 'Three Cs': Cooperation, Collaboration, Communication

Prioritising the enhancement of cooperation and collaboration amongst the clinical research stakeholders, facilitating smooth and clear communication, and targeting local clinical trial activities to contribute to harmonising country and global principles, KAD has been involved in several activities and initiatives. KAD sees that the 'Three Cs' are the key elements of the adoption of the innovation in global clinical research and development into local expertise and know-how.

2.1 Web Portal as a Milieu for Information Exchange:

Internet use is a fundamental part of modern society. Web portals for different target user profiles and different aims have been used increasingly over the last decade. A web portal is a website or service that offers a broad array of resources and services, such as e-mail, forums, search engines, and on-line shopping malls. In recent years, many health portals have emerged which offer services to lay people or health professionals. The use of the portals was also reported in medical literature[2]. The portals may be designed for assisting patients[3] or providing organised resources for professionals[4, 5, 6].

Recognising this interesting and powerful modern life tool, KAD began to provide its web-user members with the association's official web portal (klinikara tırmalar. org.tr), regardless of whether they are official members of the association or not. KAD also has a web portal for English-speaking members (www.klinikarastirmalar.org/en). The web portals have been:

- offering real-time regulatory updates from the country and from all over the world
- hosting a repository for the regulatory reference documents
- announcing and/or organising conferences, congresses, seminars
- offering a forum environment for discussions
- linking with the clinicaltrials.gov website's Turkey-specific data.

News is offered from the country and all over the world in regard to regulatory changes, recent updates, and any publication or written opinion that contributes to increasing quality on an ongoing basis. The news sharing started in the KAD website very early, right after the establishment of the association, and supported the spread of information across the country. In Figure 3, the numbers of news items shared per year between 2006 and 2015, and the origin of these items, are illustrated. The released news and alert information lines reached a peak in 2008-2009, and during 2013 and 2015. These dates are the ones when regulatory changes occurred.

Figure 3

Between 2008 and 2009, among enormous interest from and effort by the Turkish Regulatory Authority, the EU Clinical Trials Directive principles were adapted within the Turkish Clinical Research Regulation with Regulation number 27089 dated 23 December 2008, 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 periods were well defined by the MOH to facilitate the change and minimise any risk arising from the change; however, this was followed by some other regulatory challenges which are elaborated in another article published recently[8]. 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 was revised on 25 June 2014 and 13 September 2015, in compliance with agreed international acts, EU standards and the Good Clinical Practice rules as confirmed in Article 1 of the regulation. Both documents are available for reference in the MOH web page [www.titck.gov.tr]. The health authority continuously requests official opinion and comments on the clinical trials' specific regulatory process documents, including the regulation amendments and guidelines set up from the stakeholders, which the Ministry of Health recognises as respectful collocutors.

KAD is one of these collocutors as it is recognised as a main stakeholder of the clinical trial industry. The Clinical Trials Regulation dated 2013 and its amendments from 2014 and 2015 are the major documents that can be given as examples for the regulatory document which KAD contributed with association opinions.

Releasing the news and alerts, KAD took the web portal communication as an opportunity to share recent updates across the country, and being read by all stakeholders contributed to minimising the regulatory risk that might have arisen from the regulatory changes.

Data about the news and alerts is recorded and kept perpetually in a database which is maintained by an IT company (Pleksus IT, Ankara, Turkey), and the personal data of the users is not shared with the sponsor companies or any third parties. By the end of May 2016, there are 4397 members registered to the KAD web page, and 431 of them are registered to the English webpage.

2.2 Congresses and Conferences Organised and Hosted

Clinical trials have been conducted in Turkey since 1993 with the first clinical trials regulation having been issued. Growing the number of clinical trials and the interest of the regulators and stakeholders enabled the European Union-compliant Clinical Research Regulation to come into force as of December 2008[8].

One of the most inspiring events KAD organised is the First National Clinical Research Congress, with international participation by speakers and attendees. This event was held on 2-4 May 2013 in Istanbul. The Congress, being the first scientific congress on clinical trials, gathered all stakeholders from all over the country, enabled verbal and poster presentations, and served as an open venue for specific and fruitful panel discussions. There were 37 verbal, and 61 poster presentations shared during this event. The presentations' topics varied, including almost all aspects of the clinical trials, including but not limited to biosimilar products, medical herbal products, medical cosmetic, medical devices, investigational medicinal products research, and development opinions and review papers[9].

It is worth noting that KAD prepared the 'Very Firsts in Clinical Trials Area – Achievement Flow' and this was also appreciated by all congress participants (Table 1). This Achievement Flow was a sort of time-machine, demonstrating the evolution of the clinical trials industry in the country and the leaders inspiring and driving the evolution.

With high interest from the clinical research professionals, the Second National Clinical Trial Congress followed the first Congress two years later, taking place on 27-28 March 2015 in Istanbul, with 24 verbal and 39 poster presentations. During the meeting, the presentations were evaluated and accepted by the organisation committee per the main discussion points such as logistics, quality, data handling, operational challenges, regulatory highlights, medical device and biosimilar drug studies, and cosmetic and herbal clinical trials, as well as the social, legal and ethical considerations[10].

The board members of the KAD participated in the Clinical Research Workshop organised in February 2015 by the Turkish Ministry of Health and the Medicines and Medical Devices Agency as invited panel speakers. The KAD members participated in the discussions and brainstorming sessions, and recommendations were compiled in different panel desks. All outcomes of this workshop were published in a workshop report, and professional opinions and suggestions by the regulatory decision-makers in Turkey were taken[11].

For the first time in Turkey in the clinical research area, KAD organised and hosted the open-access web-based live panel meeting called 'Ethics Committees Are Inquiring' on 4 April 2016. The meeting was moderated by the KAD Chairperson, Prof. Dr Hamdi Akan, with accompanying conference speakers from the Turkish Ministry of Health, and the Ethics Committee Chairperson and members. A total of 207 participants attended the meeting interactively, asking specific questions and getting relevant advice from the speakers. Open live sessions let all the parties involved in clinical research freely and directly communicate with the regulatory authority and ethics committee delegate to determine the way to proceed in the studies.

2.3 Book and Publication Contributions

Being dedicated to adding value to the clinical research environment in Turkey, KAD board members contributed to a number of books in Turkish published in different years. Some of these are:

a. Clinical Trials Book, Bilimsel Tip Yayinevi, by Hamdi Akan, Hilal Ilbars, Nursah Cetinkaya
b. Good Clinical Practice Handbook, 2015, Bilimsel Tip Yayinevi, Clinical Research Association
c. Clinical Trials Dictionary, Bilimsel Tip Yayinevi, by Hilal Ilbars
d. Good Presentation Skills Book, 2014, Bilimsel Tip Yayinevi, edited by Hamdi Akan
e. Clinical Trials Methodology and Design Book, 2016, Bilimsel Tip Yayinevi, edited by Hamdi Akan

Since being published, these books were represented as reference sources for all stakeholders with different roles and origins.

KAD board members also prepared the articles on specific research and development considerations and regulatory highlights which were published in several journals. Interest in the publications has been remarkably high, as proven by the citation of these in other papers, and their use as references for several conferences with the data included in[7, 12, 13].

Achievement	Information	Year
1st Bylaw (Regulation) on Clinical Trials	Released by Turkish Regulatory Authority (RA) (number 21480)	1993
1st Central Ethics Committee (EC)	Established by the approval of Turkish RA	1993
1st Good Clinical Practice Guideline	Released by Turkish Regulatory Authority	1995
1st RA Approval of a Clinical Trial		1995
1st Contract Research Organisation	Omega CRO	1997
1st Good Clinical Practice Training	Course on Clinical Trials in Psychiatry	1998
1st Bioanalytical Center	Novagenix	2000
1st Bioequivalence and Bioavailability Clinical Trials Center	Erciyes University Hakan Cetinsaya GCP Center	2000
1st Journal	IKU (Journal of GCP)	2001
1st FDA Clinical Site Inspection	Ege University Medical Faculty, Department of Gastroenterology	2004
1st FDA Inspected/Accredited EC	Ankara University Medical Faculty Ethics Committee	2004
1st Regulatory Authority Drug Safety and Pharmacovigilance Office	Turkey Pharmacovigilance Center	2005
1st Civil Society	Clinical Trials Association	2006
1st EMA bioavailability and bioequivalence center inspection	Erciyes University Hakan Cetinsaya GCP Center	
1st International Good Clinical Practice Training	Organized by Sanofi, Akademika	2008
1st EMA Clinical Site Inspection	Ege University Medical Faculty, Department of Surgery	2009
1st Book	Clinical Trials Book, Prof Hamdi Akan,	2009
1st CRO Association	SAKDER (Contract Research Organization Association)	2009
1st Regulatory Authority Clinical Trials Infrastructure	Department of Clinical Trials and Drug Safety under Turkish Ministry of Health, General Directorate of Drug and Pharmaceuticals	2009
1st RA Accredited Phase I Center	Ege University Drug Development and Pharmacokinetics Research and Application Center	2012
1st Government Regulatory Authority Agency	Turkish Medicines and Medical Devices Agency	2012
1st Dictionary	Clinical Trials Dictionary, Dr Pharm. Hilal Ilbars, PHD	2013
1st Congress on Clinical Trials	1st National Clinical Research Congress	2013
1st Advanced GCP Course	In the context of the 1st National Clinical Trials Congress	2013

2.4 Surveys

Surveys were performed prior to planned activities in KAD. The first survey in 2014 was organised for ethics committee members to understand whether online training is favourable. After the results were gathered, the KADUZEM online training module was prepared and released for use. The second survey was about an online live Q&A session for ethics committee members, with representatives from the authority. The interest was confirmed with survey results and the online live Q&A session was organised.

2.5 Facilitating Ongoing Training Sessions

KADUZEM is an online asynchronous webcast-based GCP education programme approved by the Ministry of Health. The programme consists of basic, advanced and clinical research nurse GCP education modules. By the end of May 2016, 400 participants had joined this programme.

There have been other training and educational meetings facilitated and organised by KAD. For the list of these meetings, please refer to Table 2. The ongoing educational support is one of the most important initiatives taken by KAD to make sure the regulatory risk is minimised and the current legal framework is correctly interpreted by the stakeholders country-wide. Detailed analysis and outcome of the educational and training activities of KAD will be the subject of another review article. The educational materials and the standards given are mainly based on the Helsinki Declaration and ICH-GCP, but also as per the specific guideline on organising and managing the training courses on clinical trials released by the Turkish Regulatory Agency.

KAD represented Turkey in the Bioconvention meeting in the United States in 2014, and during the convention, distributed the brochure that was approved by the Turkish MOH. It was a great opportunity to enable the networking in a large event with all participating countries and companies.

2.6 Transparency Issues

KAD cooperated with www.clinicaltrials.gov to post all the clinical trial activities in Turkey on the association webpage using the interface in Turkish (http://www.clinicaltrials-tr.org).

KAD is the first active supporter of the AllTrials clinical trials transparency initiative in Turkey (www.alltrials.net) and the voice of AllTrials activities in Turkey is via the association's webpage.

3 Future Perspective and Last Words

According to the analysis 'Challenges and Opportunities for Clinical Research in the Middle East'[14], amongst the

factors having an impact on the country's attractiveness, two very important ones dominate:

Table 2: Meetings facilitated and organised by KAD

Date	Meeting	Location
11 May 2007	Interpretation of Budget and Insurance Processes in Clinical Trials	Ankara
17 Nov 2007	Meeting for Evaluation of Development Processes in Clinical Trials	Istanbul
2009	Clinical Trials: The Story of Last Year, Updated Regulation and Future Insights	Ankara
13-14 March 2009	KAD-ECRIN Joint Meeting	Istanbul
3-4 May 2013	1st National Clinical Research Congress	Istanbul
13 Jan 2015	Good Clinical Practice Fundamental Training	Izmir
25 Feb 2015	Training for Ethics Committees	Kayseri
27-28 March 2015	2nd National Clinical Research Congress	Istanbul
4 April 2016	Online live broadcast 'Ethics Committees Q&A to Authority and EC Representative'	Ankara

- Relevant expertise (number of clinical research organisations, number of clinical trials, size and availability of labour force and relevant skills) (15 %) and
- Infrastructure and environment (protection of intellectual property, level of healthcare and country infrastructure, country risk factors) (15 %)[14].

The rapid and robust prosperity of clinical research will be possible by addressing the above-mentioned specific areas for improvement by all stakeholders, including the regulatory authority, academy, research institutes, associations and the pharmaceutical industry. In order to achieve this common goal, KAD keeps providing institutional opinions and ideas, upon request of the Turkish Health Authority, for setting up and improving the local regulatory processes of clinical trial conduct. Also, KAD is continuously engaging in efforts to increase communication, collaboration and cooperation amongst all parties with the publicly open scientific, social, and ethical platforms.

It is worth mentioning that with the valuable contribution of KAD, there has come the alignment of all stakeholders in the country, creatively planning and organising relevant meetings for all to come together and have a free and unbiased interaction environment. These, in turn, are seen as impacting on the following:

- Information and experience sharing to minimise the regulatory non-compliance risk in clinical trial conduct, via contributing to the set-up of the regulatory guidance documents
- Continuous training on the current and new rules and meeting organisations to maximise the relevant country expertise and to improve the infrastructure
- Optimising the predictability of the regulatory timelines.

All together, these represent the important activities for evolution and enhancement of relevant expertise, and enabling the driving of the best clinical research infrastructure set-up, as well as providing an important contribution to the journey of Turkey's clinical trials' successful harmonisation with the global principles of clinical trials.

With its establishment, ideas created, venues and opportunities provided, and remarkable efforts of the members, KAD represents a unique, pioneering, and leading civil society organisation in Turkey.

References

1. KAD Association Charter, available on klinikarastirmalar.org.tr
2. Pankaskie M, Sullivan J. Health care web portals. J Am Pharm Assoc (Wash). 2000; 40: 117-8.
3. Do N, Marinkovich A, Koisch J, Wheeler G. Electronic access to care system: improving patient's access to clinical information through an Interactive Voice Response (IVR) system and Web portal. AMIA Annu Symp Proc. 2003; 830.; Wald JS, Bates DW, Middleton B. A Patient-controlled Journal for an Electronic Medical Record: Issues and Challenges. Medinfo. 2004; 2004: 1166-72.
4. Aymard S, Falco L, Dufour JC, Joubert M, Fieschi M. Modeling and implementing a health information provider on the Internet. Stud Health Technol Inform. 2003; 95: 89-94.
5. Crass T, Antes I, et al. The Helmholtz Network for Bioinformatics: an integrative web portal for bioinformatics resources. Bioinformatics. 2004; 20: 268-70.
6. Cognetti G, Cecere L. E-oncology and health portals: instructions and standards for the evaluation, production organisation and use. J Exp Clin Cancer Res. 2003; 22: 677-86.].
7. Turkish Clinical trials Regulation dated 23 December 2008 with number 27089
8. Clinical Trials Journey of Turkey-Long and Thin Road, Ilbars, et al. J Clin Trials 2015, 5:2
9. 1. Ulusal Klinik Arastirmalar Kongresi Bildiri Kitabı, Klinik Arastirmalar Dernegi, (Abstract Book, 1st National Clinical Research Congress) 2013
10. 2. Ulusal Klinik Arastirmalar Kongresi Bildiri Kitabı, Klinik Arastirmalar Dernegi, (Abstract Book, 1st National Clinical Research Congress) 2015
11. Klinik Ara tırmalar Calistayi (Clinical Research Workshop) - Calistay Raporu (Workshop Report), 2015, Turkish Medicines and Medical Devices Agency, Hilal Ilbars, Gokhan Ozkan.
12. Ilbars H, Irmak DK, Akan H. Orphan Drugs: R&D Challenges with Updates from Turkey and Middle East Countries, Journal for Clinical Studies, Vol 6 Issue 2
13. Transparency in Clinical Trials, Nursah Omeroglu, Applied Clinical Research, Clinical Trials & Regulatory Affairs, 2015, Vol. 2, No. 2
14. Yoruk S, Tetik E. Challenges and opportunities for clinical research in the Middle East, Applied Clinical Research, Clinical Trials & Regulatory Affairs, 2014, 1, 83-87

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