ANALYSIS OF THE NEW REGULATORY BIOETHICAL REVIEW FRAMEWORK FOR CLINICAL TRIALS IN TURKEY

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Abstract
We conducted a descriptive study of the existing research ethics committee (REC) review structure in Turkey with respect to clinical trials and discuss what can be expected in the future under the new regulation that came into effect in April 2013. We identified 78 RECs in Turkey under the Ministry of Health (MOH) as of September 2012, categorised under geographic location, type and institution. We identified REC member lists from the MOH in the same month and further characterize them under: membership number, gender, and speciality. MOH, universities, national nongovernmental organizations such as the Turkish Medical Association and the Turkish Bioethics Association, as well as clinical research and pharmaceutical bodies are intensively interested in the enhancement of the current system of research ethics review in the country. The European Union and Council directives have been important sources that have guided new developments. Proper evaluation of the existing system and introduction of new regulatory framework are expected to further clarify the obstacles and offer opportunities for institutions, researchers, REC members and administrators.

Key words: Ethics Committees, Bioethical Review, Clinical Trials, Turkey

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There has been an important evolution in the review procedures of bioethical medical research in Turkey over the past 20 years. These changes are relevant to researchers in biomedical fields in general and in the conduct of clinical trials in particular. The establishment of such a new framework is highly pertinent in sustaining and promoting human rights of research subjects through governmental regulations as elsewhere in the developing world. Prior to the establishment of this new Regulation on Clinical Trials by the Ministry of Health (MOH) that came into effect on 13 April 2013 (1), five prior discrepant regulations governed the bioethical research review system in the country. The review structure under the auspices of the new regulation provides better guidance with respect to particular situations including redefinition of adverse effects, inclusion/exclusion of special subject groups, and greater specification of review procedures. These changes also highlight arguments for the necessity of future amendments regarding the new regulation especially with respect to higher degree of independence and transparency of Research Ethics Committees (RECs) as well as implementation of further steps to ensure confidentiality of documentation and more structured training and credentialing of reviewers and researchers in principles of bioethical medical research.

The establishment of RECs in Turkey dates back to 1986 (2). In Turkey clinical trials may only be conducted at centers for health practice and research. These currently include the public and private universities under the Council of Higher Education (YOK), the university-affiliated and MOH approved centers for research and development, the Gülhane Military Medical Academy (GATA) in Ankara and Istanbul, and the numerous provincial MOH teaching and research hospitals (3). According to Kansu et al (2006) clinical research centers in Turkey participate in multicenter Phase II/III, Phase III efficacy and safety testing, and Phase IV post-approval studies, the majority of which are prospective. Most Phase I pharmacodynamics and pharmacokinetics and Phase II safety screening studies are performed in the United States and Western Europe. The MOH emphasized the importance of promoting not only clinical trials and post-marketing of drugs in the country, but also the increase of direct involvement in early phases of drug research (4,5).

In size, the Turkish drug market is currently ranked sixteenth in the world and 36th according to drug export and research and development. The objective of increasing the share of Turkey as a drug research and production enterprise is strongly expressed by the Turkish Drug and Medical Device Institute. By Vision 2023 document, Turkish Government stated the objective to increase drug research investments to 3 percent of gross national savings by 2023 on the centennial of the republic’s founding. The performance of RECs is seen as critical in enhancing faster and more efficient reviews and compliance with the US and EU guidelines, but also in improving economic savings (6,7).

This study was undertaken as a preliminary step by the Fogarty International Research Ethics Initiative Turkey/Central Asia, funded by National Institutes of Health, aiming to advance the contemporary status of
bioethical review processes in Turkey especially with respect to consistent application of legislative changes, as well as structures, composition, and geographic spread of RECs in the country.

**Method**

According to the legislation in force during the acquisition of data, RECs were established with the approval of MOH within universities upon the proposal of the rector, or at teaching and research hospitals upon the proposal of chief physicians. The regulations included detailed information on the type of RECs and their membership. The Drug and Medical Device Institute in the MOH disseminated information on such functional RECs in the country. For the purposes of this study the identified RECs were all published on the MOH website in September 2012.

We classified the RECs according to the geographic location, institution and content type. Membership number, gender and representation of specialties and professional characteristics were further examined. All RECs are expected to report to MOH, nevertheless, potential inconsistencies in announcement intrinsic to the MOH comprise the limitations of the study.

**Current Domestic Legislation**

The Regulation on Clinical Trials prepared in 2013 came into effect in accordance with the European Parliament and Council directives concerning good clinical practice (2001/20/EC, 2005/28/EC) (3) This new regulation was dependent on the 10th supplementary article of the law entitled Health Services Fundamental Statute as of April 6, 2011 (8).

Conducting clinical trials outside the jurisdiction of domestic legislation is interpreted as a violation of the 90th article of Turkish Criminal Law (9). Administration of these statutes are supported by additional seventeen MOH documents published by the Turkish Drug and Medical Device Institute referring to application procedures, insuring recruitment of volunteers, good clinical practice, guidance on clinical trials with pediatric populations, and adverse event/reaction reporting, inspection, auditing and monitoring procedures, and archiving (10).

**Types of Research Ethics Committees (RECs)**

Regulation on Clinical Trials governs studies on human subjects except retrospective studies. The 2nd article of this regulation applies to “clinical trials, including studies to investigate bioavailability and bioequivalence, with drugs, medicinal products, or herbal medicinal products, whether authorized/licensed or others, or non-drug clinical trials conducted on humans, as well as the centers where clinical trials are conducted, and the natural or legal persons who conduct them. This Regulation does not apply to retrospective studies.”

Two types of REC’s defined: 1) Ethics Committees for Clinical Research for scientific and ethical assessment of studies except bioavailability and bioequivalence studies; and 2) Ethics Committees for Bioavailability and Bioequivalence Investigation (1). The RECs currently comprise minimum 7 and maximum 15 members with the requirement that at least one member is a non-health care professional and one is a legal
professional (‘a legal advisor’). Other members can be health professionals, majority of whom hold doctoral degrees. A member can only serve one REC. The RECs are required to include at least 3 members who do not work in the same institution. A given member of a REC is appointed for a two year term and this can be renewed indefinitely. Mandatory members of each REC include: preferably doctoral level pharmacist, or a chemist or chemical engineer with respect to the review of bioavailability and bioequivalence studies (1).

The new regulation has decreased the time limit for reviews by more than fifty percent. RECs also oversee compliance issues on approved studies. The simultaneous application to Drug and Medical Device Institute in the MOH and to the REC for review is now permitted under the new regulation. Applications are made by the study sponsor or the contracting research organization appointed by the sponsor. The time limit for response to a proper application is 30 days. For clinical trials that include therapy involving products containing genetically modified organisms or products involving gene therapy, and for non-drug clinical trials, there may be an extension granted for an additional thirty days. Adverse event reporting is also another important subject for regulatory oversight. The investigators have to report immediately all serious adverse events and laboratory findings identified as critical safety concerns to the sponsor, who is obligated to urgently report to MOH and to the REC within eight days. The adverse events are characterized in the protocol and/or the study brochure by the principal investigator and those that are deemed not to require immediate reporting are still expected to be reported to the sponsor (1).

An Advisory Board on Clinical Trials in the Drug and Medical Devices Institute gives opinion on matters referred by all the parties to a clinical trial requiring expert view including the RECs; this body is chaired by the MOH undersecretary or a deputy. The Board comprises 3 physicians (surgical, internal medicine and basic sciences) with additional masters or PhD degree, a clinical psychologist, a divinity member, and the primary legal advisor of the MOH or designee. Each member of the Board serves for two years and this can be renewed (1).

Existing Contemporary Research Review Structure

Currently, seventy eight RECs are distributed across 34 of 81 provinces in the country. Istanbul province has the highest number (19), followed by Ankara (12), and Izmir (6), situated in public universities (43), private universities (10) and MOH Research and Training hospitals (25) (11).
According to the previous regulation the RECs were grouped in four jurisdictional categories: Clinical Drug Trials (4); Bioavailability and Bioequivalence Trials (4); Non-Drug Clinical Trials (8); and General Clinical Trials (62) (11,13).

At the time of the study, there were a total of 977 REC members across the country. As the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) guidelines specify the need for representation of females (14), in Turkey the figure was 328 (33.6%). The median of membership size of RECs was 13. There were 26 RECs with a maximum of membership size of fifteen individuals. There were 35 ethicists serving who were also permitted to serve in more than one REC. The most frequently represented medical and public health specialties included: pediatrics, 85 (8.7%); internal
medicine 79 (8%); pharmacology, 74 (7.6%); and public health, 56 (5.7%). In addition there were 62 (6.3%) non-physician health professionals, and 212 (21.7%) from fields other than biomedical health sciences (11).

Administrative bodies of RECs consisted at most of three officers. Only two of the 78 RECs however had three officers. In institutions with more than one REC, the same administrative body served all the relevant RECs. At this time a total of 102 administrative staff served on RECs across the country: 10 with postgraduate degree; 35 with associate degree; 41 with bachelor's degree; and 16 with high school diploma (11).

Discussion

Since the initial document on regulation of RECs came into effect in 1993, there have been significant developments in research ethics review on clinical trials in Turkey. The regulations have been prepared to comply with universal scientific and ethical principles at all stages governance of clinical trials to protect the wellbeing and rights of human subjects. The regulations are within the scope of standards of European Union and especially with respect to recommendations on Good Clinical Practice (GCP).

Research enterprise is a rapidly developing and dynamic field in Turkey. Recently a cooperation agreement was signed between Dokuz Eylül University and Drug and Medical Device Institute on the establishment of the Turkish Clinical Research Infrastructures Network (TUCRIN). This national network will be a member of ECRIN (European Clinical Infrastructures Network) (15,16). A new draft law has been submitted to the National Grand Assembly in June 2013, including an article on inclusion of private health facilities in clinical trials under administrative directorship and coordination of governmental institutions (17). The establishment of Phase I research centers in Turkey that are using validated systems, accredited and in compliance with International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use and GCP, set forward important objectives. They provide standards for the design, conduct, performance, analyses, and reporting of clinical trials that provide additional assurance that the data and reported results are credible and accurate, and that the rights and confidentiality of trial subjects have been protected. Such expanded objectives requires new legislation, further education of professionals and infrastructure investments (18).

Bioethical research review needs to evolve as fast as the research enterprise. As the current analysis suggests there is a further need for better geographical distribution and enhanced dissemination on bioethical research review related work within discrepant institutions. The current regulations specify requisite expectations on the membership and administration of the RECs but there remains a great need for making the existing system more efficient and effective. There is no formal training, or certification expectations, expressed in the regulation for REC membership. Nevertheless, an interview with the General Director of the MOH Drug and Pharmaceuticals General Directorate (Turkish Drug and Medical Device Institute) and Deputy General
Director, indicated that over 2209 professionals have been educated through short-term training programs organized by the MOH since 2008 to serve on RECs as members and administrators (19,20).

The new regulation has further narrowed that terms related to excluded medical devices, revised definition of adverse events, and made exclusions with respect to certain groups such as Army recruits. A new chapter is governing the clinical trials with patients in critical care units. The Regulation includes terms to accelerate the review and approval period. The response time for Drug and Medical Device Institute for applications submitted in a procedurally correct manner is now reduced by more than a half. Simultaneous application to MOH and REC is also possible with the new regulation. These improvements emphasize the high priority given to the medical research enterprise, and sponsored research, and have implications that will impact the marketing and licensing dynamics. It is hoped that a more efficient system will increase foreign investments in the health research enterprise in the country.

An important aspect of the regulation on clinical trials has been to protect the social security system from inadvertent and/or unethical financial support of research. According to the new regulation, "The cost of all investigational medicinal products, devices or materials for use with the products, and the costs of all examinations, tests, analyses and treatments used in the trial will be covered by the sponsor. Such costs may not be recovered from subjects or from social security institutions". The governance of observational trials has also been adjusted due to financial concerns. Regulation narrowed the definition by adding the requisite that treatments should be applied in the posology and route of administration for which the product has been approved in Turkey.

The independence of RECs has also been better grounded by means of restriction of senior executives and managers in the institution form service. The new regulation includes self-governance with respect to improvements in accountability and document administration. Samples of the investigational product must be retained at least fourteen years. All records related to the clinical trial should be kept by the sponsor, principal investigator at least fourteen years. These procedures secure any escape from accountability depending on the slow jurisprudence system and erasing trace of the possible misconduct. The Regulation has a new article governing the oversight activities according to the standard operation procedure for RECs; if deficiencies are detected a warning is generated. In case of lack of compliance with such a warning, the Drug and Medical Device Institute may withdraw the approval for a REC and remove the chair from service for minimum two years. If used intrusively, such a mechanism can jeopardize the independence of a REC. The Drug and Medical Device Institute should show maximum respect and attention on such issues and universities and research institutions ought to be able to solicit appeal procedures.

In the future, additional legal amendments that enable the operation of RECs to be more independent from central authority of the MOH and from
any external influences that may be brought to bear through any external process are required. On the other hand, striking the right balance between the central authority guidance and run away practice in the country can prove difficult and remains a challenge. Additional administrative supports for the operation of local RECs in their day-to-day activities may ensure: greater oversight of review procedures; reduction of wait period for protocol review; implementation of steps to ensure confidentiality of documentation and communication with principal investigators; and greater transparency of the review process.

Ultimately, however, irrespective of whether such efficiencies can be readily achieved in practice in the near future, a fundamental question with respect to the new regulation is the limited emphasis on the collaborative relationship between the MOH and the universities in the service of greater transparency and ultimately greater independence in scientific research within the scientific community in the country. Such transparency and independence are also fundamental for longer term sustainability of good research practices and scientific progress in the country.

The new regulation also includes some simplified but questionable procedures; for example for multisite studies approval by one REC is deemed adequate and the requirement for reporting by regional RECs is no longer felt to be necessary. The time limit for reporting delays for beginning a trial after the date of the expressed intent in the protocol has also increased from 15 to 90 days. The reporting time for a premature end of clinical trials, increased from 7 to 15 days. The reports should include the reasons of stopping and maintenance of treatment of subjects. This extension can jeopardize the well being of the subjects depending on the type of treatment.

**Conclusion**

As an achievement of efforts over twenty years, Turkey has an established and developing bioethical research review system. The new regulation that came into effect in 2013 is purposefully intended to improve the review system to be more efficient with respect to clinical trials but also with inherent undertone for economic dividend as well as greater degree of privatization. Cross sectional view of the system reflects new opportunities for the development of domestic as well as international collaborative efforts in future years. Better standardization, independence, accountability, education, administration and geographical dissemination in the country remain ensuing objectives that is a welcome beginning.

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