

**The establishment of a national clinical research infrastructure:
Turkish Clinical Research Infrastructure Network (TUCRIN)**

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List of abbreviations

TUCRIN	Turkish Clinical Research Infrastructures Network
ECRIN	European Clinical Research Infrastructures Network
EU	European Union
FP-7	EU Framework Program 7
MoH	Turkish Ministry of Health
MoD	Turkish Ministry of Development
MoSIT	Turkish Ministry of Science, Industry and Technology
TITCK	Turkish Ministry of Health Drugs and Medical Devices Agency
TUBITAK	The Scientific and Technological Research Council of Turkey
GCP	Good Clinical Practice
IT	Information Technology
EC	Ethics Committee
SOP	Standard Operating Procedure
ESFRI	European Strategy Forum on Research Infrastructures

Abstract

TUCRIN is Turkish Clinical Research Infrastructure Network, founded under Rectorate of Dokuz Eylul University, Izmir. TUCRIN is a partner of ECRIN, a European Union Seventh Framework Programme project. TUCRIN is planned to consist of clinical trial centres and clinical reserach units, spread across Turkey. Each TUCRIN member is supposed to locally support investigators, sponsored by public funds or industry, in conducting and coordinating clinical trials and to provide consult and training. TUCRIN has been founded to improve the quality of clinical research conducted in Turkey and the safety of participants. In this report, current situation of clinical research in Turkey is summarized and the establishment of a national clinical research network, TUCRIN, is reported.

1. Summary of the Current Situation of Clinical Research in Turkey

1.1 History of Clinical Research in Turkey

The first legal document related to clinical trials occurred in Turkey many years before the Helsinki Declaration or Belmont report; issued in 1928, the Code of Pharmaceutical Products and Preparations No. 1262 law carries the statement: "Experimental drugs can be used in a patient only by his/her permission". Then the other regulation is the Regulation on Medical Deontology, dated 1960, and still in force. Article 10 and 11 of this Regulation address physicians and dentists who are conducting research. After periods of misconducted and ill-designed studies, the modern era of clinical trials began in 1993 with the introduction of the "Drug Research Bylaw". This document was directly influenced by the initial drafts of ICH-GCP Guidelines, and some parts were very similar. This became the main document that regulates the conduct of clinical trials in Turkey. A good clinical practice (GCP) guidelines document was added in 1995. On the other hand, an amendment made to Article 90 of the New Turkish Penal Code No. 5237 of 26 September 2004 envisages that in conflicts between international treaties concerning basic rights and freedoms and national laws, priority will be given to the international treaties. Therefore, in Turkish law, international treaties concerning basic rights and freedoms are given precedence as compared with national laws and other regulations.

1.2. Current data of clinical trials in Turkey

There has not been any national clinical trial registry in Turkey. However, a national database development studies were started within the frame of TUCRIN –TITCK collaboration agreement signed on July 3, 2013 <http://tucrin.deu.edu.tr/index.php/en/>

The number of international clinical trials in Turkey that was obtained from the Clinicaltrials.gov web site shows that most of the clinical trials (65 %) are funded by industry (Fig 1). However, we have to consider that almost 60 % of the clinical trials of Turkey is registered to the Clinicaltrials.gov web site. According to the data from Turkish Ministry of Health Drugs and Medical Devices Agency(TITCK), distribution of clinical trials with drugs shows that phase III and IV studies are dominated (Figure 2).

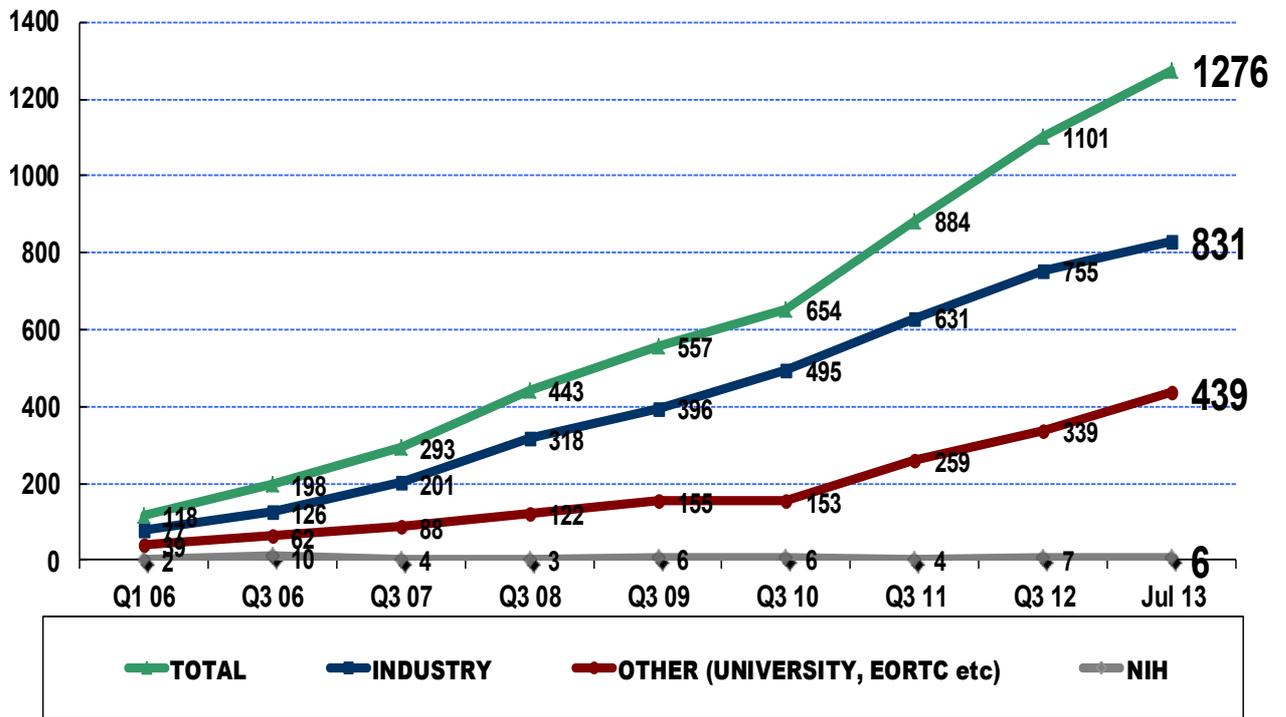


Figure 1. Distribution of the clinical trials in Turkey that were registered Clinicaltrials.gov according to the sponsors.

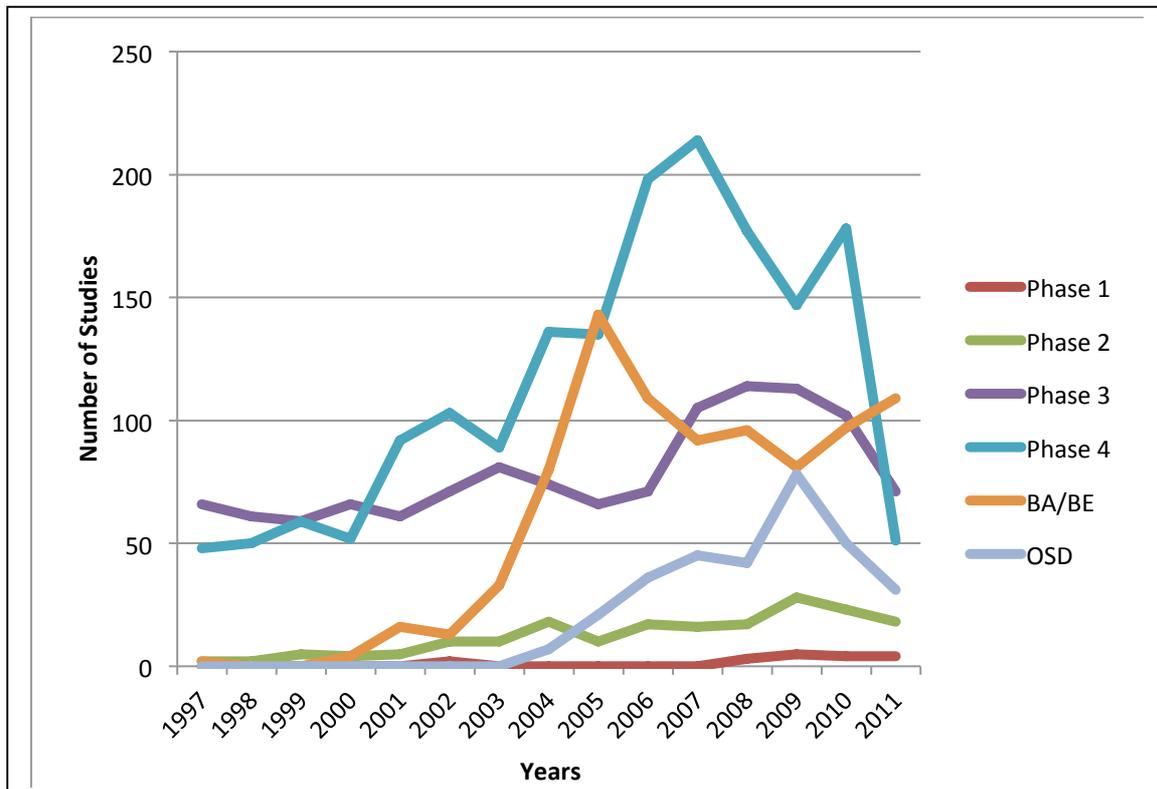


Figure 2. Distribution of clinical trials in Turkey according to types, phases and years (data obtained from TITCK). BA/BE: Bioavailability/bioequivalence studies, OSD:Observational studies on drugs

1.3. Legislative regulation and ethical governance of clinical research in Turkey

1.3.1. Human participation for clinical research

- **Advanced Therapy Medicinal Product:** a gene therapy medicinal product, a somatic cell therapy medicinal product, a tissue engineered product, or a combined advanced therapy medicinal product manufactured industrially or by a method involving an industrial process.
- **Industrial Advanced Medicinal Product:** an advanced therapy medicinal product from a single source which is derived from human/animal cells or tissue for use in multiple humans beings, or which, even if prepared for use by a single person, contains an unauthorized industrial product/gene therapy product.
- **Nonindustrial Advanced Medicinal Product:** live tissue products and autologous tissues prepared according to special quality standards for use solely in the country concerned, which may be administered at a hospital under specialist supervision, is dispensed on prescription or upon a patient-specific order, and contains no industrial constituents whose manufacturing license does not include approval for this use.
- **Traditional Herbal Medicinal Product:** any medicinal products whose medicinal herbal ingredients are bibliographically shown to have been in use anywhere in the world for a period of at least thirty years preceding the date of the application, including at least fifteen years in Turkey or in a member state of the European Union, and which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a physician for diagnostic purposes or for prescription or monitoring of treatment, and which have specific indications appropriate to traditional herbal medicinal products, and which are exclusively for administration in accordance with a specified strength and posology, and are an oral, external or inhalation preparation.
- **Noninvasive Clinical Trial:** any trial not involving direct intervention in the patient by a physician, including observational studies, surveys, retrospective archive studies using files and image records, studies with biochemical, microbiological, pathological and radiological collection materials like blood, urine, or images or other materials obtained during routine examination, testing, analytical or therapeutic procedures, studies with cells or tissues, studies with diagnostic genetic materials not having the nature of a gene therapy clinical trial, studies performed within confines of the nursing function, dietary studies with food additives, studies on body physiology like exercise, studies conducted based on anthropometric measurements, or studies to evaluate daily habits.
- **Gene Therapy Clinical Trial:** studies aimed at treating disease in human beings by eliminating deficiency of genes whose genome is known and functional investigations have been completed.
- **Observational Drug Study:** an epidemiological study to collect data on a medicinal product, spontaneously prescribed, in patients undergoing treatment in the indications for which the product has been approved in Turkey according to the current diagnostic and therapeutic guidelines of the Ministry.
- **Observational Medical Device Study:** an epidemiological study to collect data on a medical device bearing the CE marking, spontaneously used for its purpose of use as described in its user manual.

No clinical trial may be conducted in children, pregnant women, postpartum or breastfeeding women and vulnerable individuals. However, in cases where the volunteers are expected to directly benefit from the trial and the trial carries no serious foreseeable risk to the well-being of the study volunteers, permission may be granted to a trial in children or vulnerable individuals or during pregnancy, lactation or the postnatal period, with the

approval of the ethics committee and permission of the MoH, provided that the volunteer's consent form has been obtained according to the applicable procedure.

Clinical research involving pregnant women, fetuses and infants

When research involves pregnant women, a perinatologist or a gynecologist/obstetrician, or in the case of a trial in postpartum or breastfeeding women, a neonatologist or a pediatrician who is a member of the ethics committee must determine that the study poses no unfavorable effect on the on the fetus or infant.

Clinical research involving children

Children are defined as individuals up to 18 years of age. Pain, distress, fear, and parental separation should be prevented and minimized when unavoidable. Children should not be the volunteers of clinical trials when the research can be conducted with legally competent adults. The least vulnerable among children should be included (i.e., older children). There must be no financial inducement to enroll the child in the clinical trials.

The EC should evaluate the protocol with respect to protections for children.

The EC must notify the TITCK if it is informed of a violation or non-compliance with GCP.

- The scientific validity of the study should be verified. It is recommended that the trial design be set following consultation of the children from the age groups to be involved in the trial or from representatives of the children. Uncontrolled trials for demonstration of efficacy should be avoided. The size of the trials should be as small as possible but large enough to demonstrate the appropriate efficacy with sufficient statistical power. The use of control groups and placebo groups should be based on equipoise.
- Trials replicating previously conducted trials with the same purpose should be avoided.
- Protection and safety of children is ensured (including minimization of risks, fear, pain and distress) and appropriate pediatric expertise is available at all trial sites.
- A justification is provided for the inclusion of children to achieve the trial objectives and for the choice of age groups. Depending on age groups, inclusion/exclusion criteria may need to include a pregnancy test. Genetic diversity should be taken into consideration.
- Appropriate non-clinical data are available before the use of the product in children.
- Extensive and comprehensive review of available evidence (including relevant publications) and experimental work on the investigational medicinal product should be available and reviewed to justify the initial hypothesis, the safety and the evaluation of expected benefit, and the age ranges of children to be included.
- The quality of the performance of the trial is such that it ensures that the results will be interpretable; monitoring, audit and quality assurance should be described.
- The trial uses age-appropriate formulations of the medicinal product(s).
- An Independent Data Monitoring Committee involved in the conduct of clinical trials in children is specified, unless provided otherwise in the protocol.
- There should be provisions in the protocol for systematic independent publication of results, within a reasonable timeframe, including when results are unfavorable.
- The protocol should include provision of the medicinal products to children involved in trials after the completion of the trial where appropriate, unless the benefit to risk balance of the medicinal product tested proves negative.
- The EC ensures that the sponsor regularly monitors and reviews the balance of risk and benefit of the research so that the health and wellbeing of the children enrolled are safeguarded.
- For randomized trials there should be equipoise at the beginning of the trial and no participants should receive care known to be inferior to existing treatments.

Healthy children should not be enrolled in research that can be performed in adults, except for research such as palatability test for a new flavored medicine.

Clinical research involving disabled persons

When research involves disabled persons, a psychiatrist or physician specialized in a field relevant to the research who is a member of the ethics committee must determine clinical, ethical, psychological and social issues associated with the trial poses no unfavorable effect on the disabled person.

- Disabled means any person who meets the criteria for disability described in Article 405 and 408 of the Turkish Code #4721 of 2001, and includes patients under intensive care and privates and corporals conscripted for military service.

Clinical research involving vulnerable individuals

Clinical trials can not be conducted with on vulnerable individuals. However, where the subject of clinical trial is directly related to the vulnerability or is a clinical condition that can be investigated only in the vulnerable population and all therapeutic options available to treat the vulnerable individuals have been exhausted, it may be permitted to conduct a clinical trial in the vulnerable as long the written consent of the legal representative is obtained.

TITCK is the responsible authority for the accreditation of Ethics Committees (ECs).

1.3.2 Laws and regulations about clinical trials

	ISSUE DATE
LEGISLATION	
LAW	
Turkish Healthcare Act, Additional Article 10	06.04.2011
Turkish Penal Code	26.09.2004
<u>Turkish Civil Code</u>	22.11.2001
CHARTER	
Medical Deontology Regulation	09.02.1960
REGULATION	
Regulation on Clinical Trials	13.04.2013
Regulation on Patient Rights	01.08.1998
Convention on Human Rights and Biomedicine	12.01.2005
<u>GUIDELINES</u>	
Good Clinical Practice	
Guideline on storage and distribution of investigational products used in clinical trials	
Guideline Regarding independent Data Monitoring Committees DATA APRIL 2013	

Guideline for Developing a Training Program and Evaluation Principles
Guideline for Observational Studies Conducted on Drugs
Guideline Regarding the Principles and the Essentials for GDP of Advanced
Therapy Medicinal Products
Guidelines for Archiving in Clinical Trials
Guidance on the format of Applications to the Ethics Committee
Guideline on Site Organization Management Principles in Clinical Trials
Guidance on the Format of Applications to the Ministry for a Clinical Trials
Guidance Relating to insurance Coverage in Clinical Trials
Guideline Regarding Collection, Verification, and Submission of the Reports of
Adverse Events/ Reactions Occuring in Clinical Drug Trials
Guidance on Ethical Approaches for Clinical Trials Conducted with the Pediatric
Population

EC FORMS

Non-interventional Studies Ethics Committee Control And Report Form (For
investigator)
Informed Consent Form Contents (Sample)
Republic Of Turkey Dokuz Eylül University Faculty Of Medicine Clinical Trials
Ethics Committee Drug Trials (For Specialty And Academic Purposes)New
Application
Republic Of Turkey Dokuz Eylül University Faculty Of Medicine Clinical Trials
Ethics Committee Drug Trials New Application
Republic Of Turkey Dokuz Eylül University Faculty Of Medicine Non-interventional
Clinical Trials Ethics Committee New Application
Certificate Of Relation Of interest
Non-interventional Studies Ethics Committee Dokuz Eylül University Application
Form
Dokuz Eylül University Non-interventional Studies Ethics Committee Special Study
Module Application Form
Application File Requirements Checklist
Research Monitoring Form
Informed Volunteer Consent Form Assessment Form
Research Protocol Assessment Form
Non-interventional Studies Ethics Committee Flow Chart
Clinical Trials Ethics Committee Flow Chart
Ethics Committee Members General information Form
Confidentiality Agreement And Letter Of Undertaking For The Ethics Committee
Non-interventional Studies Ethics Committee Control And Report Form (For
investigator)
Non-interventional Studies Ethics Committee Special Study Module Application
Form
Protocol Amendment Notification Form
Non-interventional Studies Ethics Committee Control And Report Form (For
Reporter)

EVALUTION FORMS

Ethics Committee Chairman And Deputy Chairman Appraisal Form
Ethics Committee Chairman And Deputy Chairman Self-Appraisal Form
Ethics Committee Members Appraisal Form
Ethics Committee Members Appraisal Form

1.3.3 Ethics Committees and approval process

Ethics committees (EC) are organized as;

1. Ethics Committee for Clinical Research
2. Ethics Committee for Bioavailability/Bioequivalence Investigation.

Ethics committees are comprised of not less than seven (7) and not more than fifteen (15) members with at least one (1) of them a non-health care professional and one (1) a jurist, and the majority consisting of health care professionals holding a doctorate or medical residency degree. Ethics committee members convene with the two thirds majority of total number of members, and adopt decisions by the favorable vote of a simple majority of its full membership. At least three members of an ethics committee are selected from outside the institution where the committee's secretariat is located. An ethics committee member may not sit on more than one ethics committees. Senior executives of clinical research sites may not sit on ethics committees. Ethics committee members who are affiliated with the study sponsor or have a role in the study being reviewed may not take part in ethics committee discussions and nor in the voting on the study concerned, nor may they have their signature under the committee decision.

Members of an Ethics Committee for Clinical Research must meet at least the following qualifications:

- a) Specialist physicians who have previously taken part as an investigator in an international clinical trial conducted preferably according to good clinical practice, who are preferably specialized in different branches;
- b) Pharmacists holding a doctoral degree in pharmacology or a medical doctor specialized or holding a doctoral degree in pharmacology;
- c) A person holding a doctoral degree in biostatistics or a public health specialist or a medical doctor holding a doctoral degree in public health;
- d) ç) A biomedical engineer or specialist, or, if unavailable, a biophysicist or physiologist;
- e) A jurist;
- f) A non-healthcare professional;
- g) If available, a person holding a doctoral degree or specialized in medical ethics or deontology;
- h) If available, a clinical pharmacist.

Members of an Ethics Committee for Bioavailability/Bioequivalence Investigation must meet at least the following qualifications:

- a) Specialist physicians who have previously taken part as an investigator in an international clinical trial conducted preferably according to good clinical practice;
- b) Pharmacists holding a doctoral degree in pharmacology or a medical doctor specialized or holding a doctoral degree in pharmacology;
- c) A person holding a doctoral degree in biostatistics or a public health specialist or a medical doctor holding a doctoral degree in public health;
- d) A pharmacist preferably holding a doctoral degree in biopharmaceuticals, pharmacokinetics or pharmaceutical technology;
- e) A pharmacist holding a doctoral degree in pharmaceutical chemistry or analytical chemistry, or a chemist or chemical engineer holding a doctoral degree in said fields;
- f) A jurist;
- g) A non-healthcare professional,
- h) If available, a person holding a doctoral degree or specialized in medical ethics or deontology.

As of today, there are 85 different Ethics Committees (EC) in different cities. In multi-center clinical trials, the scientific and ethical approval will be obtained of the ethics committee independent from the locality where the coordinating center is located. Notifications are made to ethics committees in places where the other sites are located.

Ethics committees are independent in their function of reviewing and approving clinical trial applications from a scientific and ethical perspective. The decisions of an ethics committee is not approved separately by the rector, the dean, or the chief physician.

Making a parallel application to the ethics committee and the Agency simultaneously is allowed, to obtain authorization for conducting a clinical trial falling within the scope of the Regulation. Permission of the MoH is required to commence a clinical trial that has been approved by ethics committee.

The application for a clinical trial is made to the relevant ethics committee or TITCK by the sponsor, consisting of natural/juristic person(s), or by a contract research organization domiciled in Turkey appointed by the sponsor. If the sponsor has no representative domiciled in Turkey, the application for a clinical trial must be submitted through a contract research organization domiciled in Turkey. If there is no sponsor application is made by principal investigator or by coordinator in multi-center trials.

EC approval

Application is made to the related Ethics Committee for the purpose of receiving approval scientifically and ethically for clinical trials. According to kind of clinical trial, application is made to the related Ethics Committee with the application form and cover letter samples prepared considering the appropriate application form and application cover letter samples published at the website of TITCK (<http://www.iegm.gov.tr/Default.aspx?sayfa=anasayfa>). Ethics Committees for Clinical Research will notify their opinion to the applicant within not more than fifteen days, and Ethics Committees for Bioavailability/Bioequivalence within not more than seven days after the application date. In the case of non-drug clinical trials and clinical trials with cell therapies using products containing genetically modified organisms or products involving gene therapy, the fifteen-day timeframe specified for ethics committee approval may be extended for an additional thirty days. For multicenter trials, the decision of a single ethics committee is sufficient.

TITCK permission

Permission of the TITCK is required to commence a clinical trial that has been approved by an ethics committee. The study sponsor makes an application to the TITCK to obtain permission of the MoH. In order to receive MoH permission after the received scientific and ethical approval application is made to TITCK for clinical trials to be conducted with medical devices, for bioavailability/bioequivalence (BA/BE) studies, for comparability studies of biosimilar products, for Phase I, Phase II, Phase III, and Phase IV drug clinical trials, for clinical trials to be conducted with advanced treatment medicinal products, for observational drug studies, for observational medical device studies, for efficacy and safety studies to be conducted with cosmetic raw materials or products, and for clinical trials to be conducted with traditional herbal medicinal products. In order to receive MoH permission following scientific and ethical approval, for clinical trials to be conducted with non-industrial advanced medicinal products application is made to TITCK for clinical trials to be conducted with industrial advanced medicinal products, for gene treatment clinical trials, for stem-cell transplantation trials, for organ and tissue transplantation trials, and for new surgery method trials.

Requirements for (research) ethics committees to review the compensation arrangements for study subjects handled

Insurance coverage is provided against any bodily injury or death of a volunteer taking part in a clinical trial due to the investigational medicinal product or any procedures applied at the

time of the clinical trial. It must be documented, therefore, by the sponsor of the trial that all patients and healthy volunteers taking part in a clinical trial have been provided insurance coverage by the sponsor of the clinical trial against any injury associated with taking part in the clinical trial concerned. Accordingly, the relevant ethics committee and the TITCK must be presented with an insurance policy or, in the case an insurance policy cannot be submitted, a certified authentic copy of the insurance policy or certificates of insurance clearly indicating the terms and conditions of insurance in reference to the insurance policy concerned.

Ongoing quality assurance process for research ethics committees

For ethics committees to function in a standardized manner, the TITCK establishes an Ethics Committee Standard Operating Procedure and post it on the TITCK website, updating it as necessary. Ethics committees carry out their functions according to these set of standards. Ethics committees who fail to operate in line with the ethical guidelines, or fail to meet the requirements laid down in the Ethics Committee Standard Operating Procedure, or found in a TITCK audit to be lacking the space, secretarial services, archiving services or equipment essential to fulfilling the function of an ethics committee is issued a warning by the TITCK. The approval may be withdrawn if the ethics committee fails to address the issues that gave rise to the warning within the prescribed timeframe.

Clinical trials being conducted, trial sites, sponsors and contract research organizations, manufacturing sites of investigational products, laboratories where analyses relevant to the trial are being performed, and ethics committees may be inspected in and/or outside of the country by the TITCK, with or without advance notice, to determine compliance with this Regulation and other applicable regulatory provisions.

Clinical trial sites, standards, and applications for authorization

Clinical trials may only be conducted at centers for health practice and research established within universities, approved centers for research and development within universities and teaching and research hospitals of the MoH, including Gülhane Military Medical Academy and military teaching and research hospitals, preferably at locations dedicated to clinical research, which are suitable for and which possess appropriate staff, equipment and laboratory means that enable ensuring the safety of research subjects and proper conduct and monitoring of a clinical trial, and appropriate emergency care should it be necessary.

Phase I clinical trials and bioavailability/bioequivalence studies are conducted at healthcare institutions and research and development centers approved by the TITCK, subordinate to the MoH or universities, and equipped with the necessary means to perform emergency interventions when necessary and meeting standards set individually for each of them.

Sites where clinical trials are conducted on the basis of the Guideline for Good Clinical Practice must minimally have:

1. the necessary staff and equipment at an adequate level, appropriate to the nature of the study,
2. the facilities and means necessary for storing and dispensing the investigational product in a manner appropriate to its nature,
3. the means and equipment to provide appropriate care to subjects, including cases requiring emergency care,
4. the sufficient means and equipment to enable transferring subjects to a more advanced health institution/organization, where necessary,
5. the sufficient means and equipment to retain the data and documents relating to the clinical trial and subjects, for the period prescribed in the Guideline for Good Clinical Practice, after the study is completed.

Conduction of a clinical trial

Clinical trials subject to the Regulation is conducted with a team appropriate to the nature of the study, led by a principal investigator. Phase I clinical trials and bioavailability/bioequivalence trials is conducted by a team with sufficient training and experience in good clinical practice and a doctor of medicine specialized or holding a doctoral degree in pharmacology.

The sponsor or the principal investigator or the physician or an investigator who is a dental practitioner takes any urgent safety precautions necessary to protect subjects against risks that may arise in the event of new circumstances emerging during the conduct of a clinical trial or in connection with development of the investigational product, which may impact on subjects' safety. The principal investigator or the sponsor notifies the relevant ethics committee and the TITCK on these new circumstances and the precautions taken. Otherwise, the TITCK will suspend the study.

If, despite approval by the TITCK, a study has not been initiated on the date specified in the application file, reasons for not initiating the study is reported to the TITCK within ninety days.

The sponsor may delegate some of its duties to a contract research organization operating according to scientific guidelines and good clinical practice, provided that a written contract is executed and information is given to the TITCK. Delegation of duties to a contract research organization is not annul a sponsor's potential civil and penal liability in connection with such delegated duties. The sponsor and the contract research organization have joint responsibility for the contracted activities and their outcome.

1. 4 Funding for Clinical Research in Turkey

In Turkey, almost \$100 million in public funding is provided annually for academic research. The Scientific and Technical Research Council of Turkey (TUBITAK) has been the major public institution funding and promoting research and development. The Council provides financial support for research projects, research centers, scientific meetings, and undergraduate and postgraduate scholars. TUBITAK also finances industrial technological activities and contract research, and has played a very important role in the process of the nation's association with the EU-Seventh Framework Programme (EU-FP7). The Turkish Academy of Sciences (TUBA) grants scholarships to promising young scientists and awards to established scientists. Turkish Ministry of Development (MoD) also provides funding for academic research projects and contract research, and the Turkish Ministry of Finance allocates funds to state universities representing 40% of the total public funding for academic research.

However, financial support for clinical drug trials is most often obtained from private sources, especially from pharmaceutical companies. Other private sources for clinical research financing include universities, foundations, charities, endowment funds, and nongovernmental organizations.

1.5 Problems and bottlenecks of clinical research in Turkey

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, nonstandardized 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. 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.

2. ECRIN-IA Project and a national clinical research network (TUCRIN) establishment

2.1 What is ECRIN?

The European Clinical Research Infrastructures Network (ECRIN) is a sustainable, not-for-profit infrastructure supporting multinational clinical research projects in Europe. ECRIN is based on the connection of coordinating centres for national networks of clinical research centres and clinical trials units, able to provide support and services to multinational clinical research.

2.2 What is TUCRIN?

TUCRIN is Turkish Clinical Research Infrastructures Network, founded under Rectorate of Dokuz Eylul University, Izmir. TUCRIN is a partner of ECRIN, a European Union Seventh Framework Programme project.

TUCRIN is planned to consist of clinical trial centres and clinical reserach units, spread across Turkey. Each TUCRIN member is supposed to locally support investigators, sponsored by public funds or industry, in conducting and coordinating clinical trials and to provide consult and training.

TUCRIN has been founded to improve the quality of clinical research conducted in Turkey and the safety of participants.

As a partner of ECRIN-IA Project, Dokuz Eylul University is responsible for connecting Turkey to ECRIN by developing a national network (WP2, Task 2.1 Expansion). The decision of connecting will be made, during the course of the project, by the Network Committee after a visit assessing if Turkey fulfils the following objectives for connection to ECRIN:

1. To set-up a national infrastructures network as a single coordinating hub, either national co-ordination of clinical research centres or clinical trial units or a national coordination of clinical research networks,
2. To receive a support from national ministries or funding agencies to secure expected financial contribution,
3. To be able to provide support to any category of multinational clinical research, in any disease area, with a single coordinating hub that will be used for connection to ECRIN,
4. To be in contact with the relevant Ministry and ESFRI delegate to plan the ECRIN-ERIC membership,
5. To collect all the necessary information on regulatory, ethical and insurance requirement, to organise a quality assurance system, and to provide an extensive description of the structuring of clinical research in Turkey,
6. To organise a quality assurance system

The presence of the Turkish European Correspondent for one year is expected to act as a bootstrap, allowing Turkey to meet these criteria to connect ECRIN.

2.2.1 Mission and objectives

Mission of TUCRIN includes:

- Promoting clinical research in Turkey,

- Improving the quality of clinical research,
- Improving the safety of participants,
- Supporting training of clinical researchers,
- Coordinating clinical research and providing standardization,
- Improving public health.

Main objectives of TUCRIN are:

- to facilitate integration of Turkey to Europe via ECRIN (offering multinational clinical research initiatives and clinical trial partnership)
- to facilitate communication between stakeholders of clinical research
- to help national clinical research SWOT analysis, roadmap and policymaking
- to provide up-to-date information on clinical research by developing a national clinical trial, clinical investigator and clinical trial unit registry.

2.2.2 Establishment process

In the beginning, Turkish National Clinical Research Infrastructures Network (TUCRIN) was developed by a small founding team consisting of 6 academicians dedicated to clinical research in Turkey (Table 1).

Table 1. TUCRIN Founding Team

Name	Title	Afiliation
Prof.Dr. Yeşim Tunçok	TUCRIN Coordinator, Network Committee Member and European Correspondent for ECRIN-IA	Dokuz Eylül University, School of Medicine, Dept. Medical Pharmacology, Izmir, Turkey
Prof.Dr. Murat Özgören	ESFRI delegate of Turkey, Vice Rector	Dokuz Eylül University, School of Medicine, Dept. Biophysics, Izmir, Turkey
Prof.Dr. Sedef Gidener	Head of Medical Pharmacology Department	Dokuz Eylül University, School of Medicine, Dept. Medical Pharmacology, Izmir, Turkey
Prof.Dr. Mehmet Ali Özcan	Past director of Dokuz Eylül University Hospital	Dokuz Eylül University, School of Medicine, Dept. Hematology, Izmir, Turkey
Prof.Dr. Isik Tuglular	Advisor of ARGE-FAR, the Clinical Trial Center of Ege University	Aegean University, ARGEFAR, Izmir, Turkey
Dr. Burç Aydın	Project assistant	Dokuz Eylül University, School of Medicine, Dept. Medical Pharmacology, Izmir, Turkey

As a result of regular TUCRIN founding team meetings twice a week, TUCRIN has been decided to be a National Clinical Research Infrastructure and Application Center under Dokuz Eylul University. Rector of Dokuz Eylul University approved the structure of TUCRIN.

Activities of TUCRIN founding team are listed below:

1. TUCRIN web site was developed and improved (<http://tucrin.deu.edu.tr/index.php/en/>). A [web site](#) both in Turkish and English is active. The web site uses the infrastructure of Dokuz Eylul University and is updated regularly with information on organisation (both ECRIN and TUCRIN), clinical trials, guidelines, general links, and training and career

links. Membership is also active for clinical researchers. Twitter accounts have also been created (@tucringlobal, @tucrinturkiye).

2. Meetings with Ministry of Health Drugs and Medical Devices Agency (TITCK), European Union projects Department of TÜBİTAK (The Scientific and Technological Research Council of Turkey) were performed in April 2012.
3. A TUBITAK Project proposal was prepared with 5 workpackages as listed below but it was not applied because of the proper call was suspended.

WP1: Organization and Promotion of TUCRIN

WP2: Development of a National Clinical Research Registry and Database

WP3: Development of Clinical Research Education and Training Modules

WP4: Quality Assessment Studies of TUCRIN

WP5: Development of a Clinical Research Tool Kit

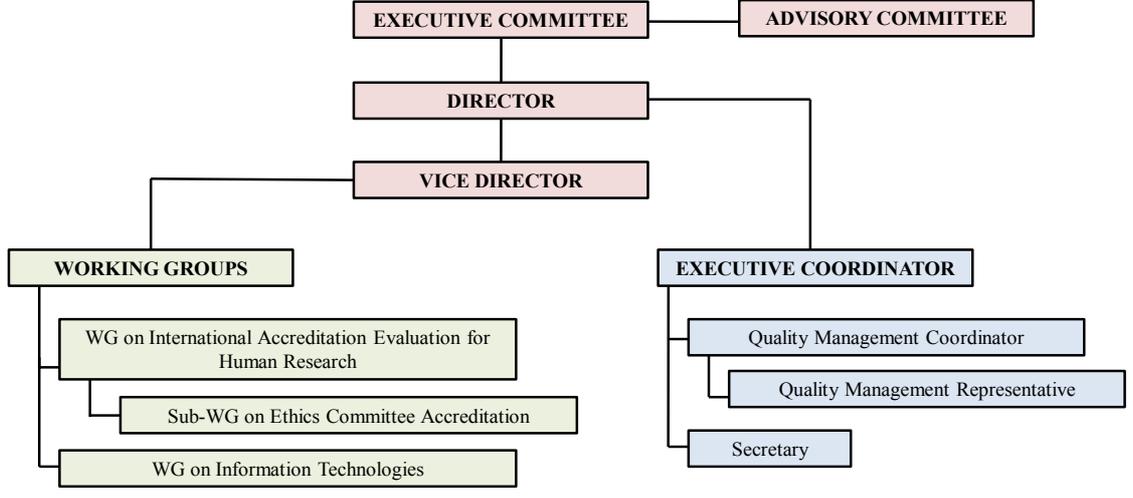
2.2.3 Legal Status

National Clinical Research Infrastructure and Application Center under Dokuz Eylul University has been approved by the The Council of Higher Education of Turkey and the regulation of TUCRIN has appeared in the official journal of Turkey on September 28th, 2012(Addendum 1). Director, vice director and executive committee members were appointed by the Rector of Dokuz Eylul University among the national candidates.

2.2.4 Organizational structure

Organization scheme according to the regulation on TUCRIN is as below:

Dokuz Eylul University
National Clinical Research Infrastructure Network (TUCRIN)
Application and Research Center
Organizational Chart



Color Codes



TUCRIN Executive Committee Members

Prof. Dr. Yesim Tuncok (Director)
Assoc. Prof.Dr. Mustafa Cenk Ecevit (Vice Director)
Emel Tetik, PhD(member)
Hilal İlbars, Pharm, MSc, PhD (member)
Prof. Dr. Işık Tuğlular (member)
Prof.Dr. Sedef Gidener (member)
Prof. Dr. Hamdi Akan (member)

TUCRIN Advisory Committee Members

Prof. Dr. Mehmet Ali Özcan
Prof. Dr. Şule Oktay
Prof. Dr. Ali Yağız Üresin
Prof. Dr. Aydın Erenmemişoğlu
Prof. Dr. Murat Özgören
Prof. Dr. M. Serdar Çelebi
Dr. Oğuz Akbaş
Dr. Ecz. Hülya Demirel
Emine Aygören
Betül Erdoğan Sarılıcan

Executive Coordinator

Dr. Burç Aydın

Quality Management Coordinator

Ceylan Merve Binici

Quality Management Representative

Buket Erbayraktar

Working Groups of TUCRIN

1. **Working Group on International Accrediation of Human Research:** The preparatory phase of an international accreditation of human research in Dokuz Eylul University was started and ongoing as a pilot study. Final goal is TUCRIN counseling to be given clinical research centers that collaborates TUCRIN.
2. **Working Group on Information Technologies:** a national database development studies were started within the frame of TUCRIN –TITCK collaboration agreement signed on July 3, 2013 <http://tucrin.deu.edu.tr/index.php/en/>

2.2.5 Partners

There are 4 clinical trial centers that signed the framework agreement with TUCRIN

1. Erciyes University Center for Good Clinical Practice DEKAM, Kayseri(<http://dekam.erciyes.edu.tr/>)
2. Gaziantep University Center for Good Clinical Practice, FARMAGEN, Gaziantep (<http://farmagenarge.com/iletisim.html>)
3. Biocity, Istanbul (<http://www.biocitydevelopment.com/>)
4. Istanbul University School of Medicine, Department of Pharmacology, Drug Research Unit, (http://www.if.istanbul.edu.tr/index.php?option=com_content&view=article&id=544&Itemid=66)
5. Ankara University School of Medicine, Department of Internal Medicine, Division of Hematology <http://ichastaliklarihematoloji.medicine.ankara.edu.tr/>

2.2.6 Quality management system

A quality management system was established within TUCRIN and application for getting ISO 9001:2008 Certification was done.

2.2.7 Institutions can act as sponsors for TUCRIN

- **Ministry of Health Drugs and Medical Devices Agency (TITCK,** http://www.iegm.gov.tr/Default.aspx?sayfa=clinical_dep&lang=en)

A framework agreement between TITCK and TUCRIN was signed on July 3rd, 2013. There will be a big impact of the protocol agreement between TITCK and TUCRIN in the national level. We expect the positive implications on TUCRIN below:

1. TUCRIN is recognized officially by the Drugs and Medical Devices Agency (TITCK) of Ministry of Health that develops regulations for clinical trials in Turkey.
2. By signing this protocol, we agree with them to develop a national clinical trial registry containing both investigator and clinical trial data controlled by TITCK regarding the obligatory data entry by the investigators and/or Ethics Committee of Turkish Clinical Trial Sites.
3. TUCRIN will have easier access or applications to the national funds given by Ministry of Science, Industry and Technology because of the government-university collaboration.

4. TUCRIN will be attractive for the Clinical Trial Centers for new collaborations through this protocol.

- **Ministry of Science, Industry and Technology (MoSIT)**

MoSIT performed a meeting for preparing an “Action Plan on Strategy of Pharmaceutical Sector”. Draft of this document highlighted improvement of infrastructure of clinical research in Turkey. TUCRIN takes its place as a body responsible from implementation of the infrastructure of clinical research in Turkey. Currently, we are negotiating with the representatives of MoSIT for funding of TUCRIN to achieve the goals in the document in Turkey.

- **Local Development Agency (IZKA):**

There are several development agencies in Turkey belong to Ministry of Development. In Izmir, we had have an interview with the local Development Agency for funding of TUCRIN without any success.

2.2.8 Providing support to any category of multinational clinical research, in any disease area, with a single coordinating hub that will be used for connection to ECRIN

- In the scope of the ECRIN-IA project WP7 Transnational Access, there is one candidate as a partner of a clinical trial coordinated by Spain. We informed the clinical trial unit for requirement of the project and we are in contact with ECRIN-IA for supporting multinational clinical trials in Turkey.
- In TUCRIN project proposal, one of the workpackage is developing a clinical trial toolkit for both investigator-initiated and industry-sponsored clinical research.
- Capacity Building Questionnaire, Regulatory Submission Questionnaire and Medical Devices Questionnaire of ECRIN-IA project have been completed for Turkey. These questionnaires outline the basic structure of clinical research regulation and capacity of Turkey.

2.2.9. Contacting with the relevant Ministry and ESFRI delegate to plan the ECRIN-ERIC membership

- After negotiating the representatives of Ministry of Development, studies on implementing ERIC statute to Turkish law was started and ongoing.
- A high level meeting was performed to discuss ECRIN-ERIC statute and application of Turkey with TUCRIN to ECRIN-ERIC statute with the participation of high level representatives of TUCRIN, Ministry of Health, Dokuz Eylul University and ESFRI delegate on October 24th, 2013 in Kusadasi, Aydin, Turkey.

2.2.10. TUCRIN Activities

2.2.10.1 National Activities

Title of the activity	Date	Venue
Meeting on the information for a TUBITAK 1001 Research and Development Projects call " SB0104, Investigator-initiated clinical trials for new drug development"	August 22, 2013	Dokuz Eylul University, Izmir, Turkey
Workshop on a Project Proposal Writing for TUBITAK SB0104 call: theoretical and practical aspects.	October 2, 2013	Dokuz Eylul University, Izmir, Turkey
Workshop on clinical trial registry development organized by TUCRIN Working Group on Information Technologies	October 3-4, 2013	Dokuz Eylul University, Izmir, Turkey

2.2.10.2 International Activities

ECRIN Summer School organized by ECRIN and TUCRIN	October 23-25, 2013	Kusadasi, Aydin, Turkey
ECRIN WP 7- ECLIPSE Study Partnersip	January 2013-December 2014	TUCRIN

3. References

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