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In Taksim Square, Istanbul, children celebrate around a monument to Atatürk, the founder of modern Turkey; in years to come their children may view themselves as Europeans.

# Turkey's trial status

At last it seems Turkey's ambition to join the EU may be realised as membership negotiations are in sight. One area where Turkey is ahead of the game is its new clinical trial regulations, which will make it compliant with the EU Clinical Trials Directive. **Hilal Ilbars** and **Gülbin Ozelikay** explain

**T**urkey was formally accepted as a candidate for EU membership in December, 2004. This is a crucial step in Turkey's long campaign to become part of the European Community, however the journey is by no means over. In terms of the clinical trials sector, Turkey has already come a long way to meeting international standards.<sup>1</sup> Following several delays, Turkey was expected (at time of going to press) to implement the Regulations for Clinical Research on Human Medicinal Products on 16 July. This new legislation effectively meets EU directive 2001/20/EC requirements for the conduct of clinical trials in adults (see 'Conducting clinical trials in children', page 19).

The new legislation has a number of objectives: to speed up approval procedures, to motivate investigators, and to track the whole procedure precisely, all of which are essential prerequisites if Turkey is to realise its potential as a location for clinical studies. It should also ensure greater accuracy and reliability of the data collected in the clinical setting.

## Background

The regulation of clinical trials in Turkey is relatively recent, dating back to 1993, when the Regulation Relating to Drug Research was intro-

duced. This established guidelines for the testing of newly developed synthetic and biological substances and their manufacture for use in the prevention, diagnosis or treatment of disease, or for changing a physiological function.<sup>2</sup> It also established principles for the conduct of clinical trials involving healthy volunteers.

Of particular note, this regulation established a two-tier system for the ethical oversight of clinical trials. Protocols first had to be approved by the institution's own local ethics committee (LEC), and then submitted for approval by a central ethics committee (CEC) attached to the Ministry of Health (MoH). The format and procedures for submitting applications were set out in the legislation. According to the regulation, LECs had to consist of at least seven members including, but not limited to: three medical doctors, a clinical or medical pharmacologist, a pharmacist, a biochemist and a pathologist.

One of the responsibilities imposed on LECs was the review of protocols and documents related to clinical trials, and the notification of all trials to the MoH. Updates on the trial's status were also required every six months. LECs were also empowered to halt a clinical trial if deemed necessary. In addition, LECs were given the responsibil-

ity for evaluating and supervising compliance with Article 11 of the Medical Deontology Ordinance, which prohibits any medical interventions not proven to be safe (although novel interventions that are untested but likely to be of benefit are permitted), and for budget control of Phase IV studies.

Unfortunately, LECs were not always constituted in strict compliance with the 1993 regulation. For example, the absence of a pharmacist or a medical pharmacologist was not always considered to be an important procedural issue. Furthermore, some LECs did not have standard operating procedures for reviewing and evaluating clinical trials. As a result,

some LEC decisions might not have been signed off by the majority of the committee. Consequently, the CEC review process was made more difficult and some trials were delayed, or were even conducted without fulfilling all the regulation's requirements.

The 1993 clinical trials regulation was supplemented in 1995 by the Good Clinical Practice Guideline (GCPG),<sup>3</sup> which covered such matters as the ethical principles of clinical drug trials applied to human beings, the constitution and activities of ethics committees, and the procedures for obtaining informed consent.

Its primary aim was to protect all aspects of participants' wellbeing and to guarantee the accuracy and robustness of the data obtained. It was also intended to ensure that data were collected in compliance with ethical standards. In the case of clinical research carried out to foster scientific understanding in medicine or to find answers to specific scientific questions, the GCPG established rules to avoid the abuse of societies and/or individuals' rights and welfare. The GCPG tried to strike a balance between the interests of science and those of the individual.

In 1998, another regulation was introduced to protect patients' rights.<sup>4</sup> It requires everyone involved in providing healthcare to behave in accordance with the principles that protect patients' rights and it effectively enforces legal protection of patients.

**Latest clinical trial regulations**

The new regulation introduces a number of new requirements. It obliges sponsors to conduct clinical trials in training hospitals and medical faculties. This is to ensure that only experienced investigators, who are familiar with clinical research and publication procedures in an academic environment, conduct studies. Trials may also be permissible in some private hospitals provided they have investigator profiles appropriate for the type of clinical research planned. This should foster rapid patient recruitment and motivate more qualified investigators to participate in international clinical trials.

Another effect of the new legislation is that, before an LEC can even begin to consider an application to conduct a clinical trial, it must apply for recognition by the MoH. There are now 76 LECs which have done so (most are based in hospitals and universities in Istanbul (n=25) and Ankara (n=17). If the MoH finds the committee meets the requirements outlined in the EU Directive 2001/20/EC, the committee is approved as a selected ethics committee (SEC).

At the same time, the CEC has been replaced by the Competent Authority for Clinical Trials (CA), aided by a clinical advisory committee appointed by the MoH. The CA is responsible for approving the composition of SECs and auditing their performance, and it is the only institution that can give final approval for a clinical trial to go ahead. In order to make its decision the CA can draw on advice from its clinical advisory committee. The SECs provide

**Turkey: Factfile on clinical trial applications**

Some 1,264 applications for clinical trial approval were made to the Central Ethics Committee between 1997 and February 2005.

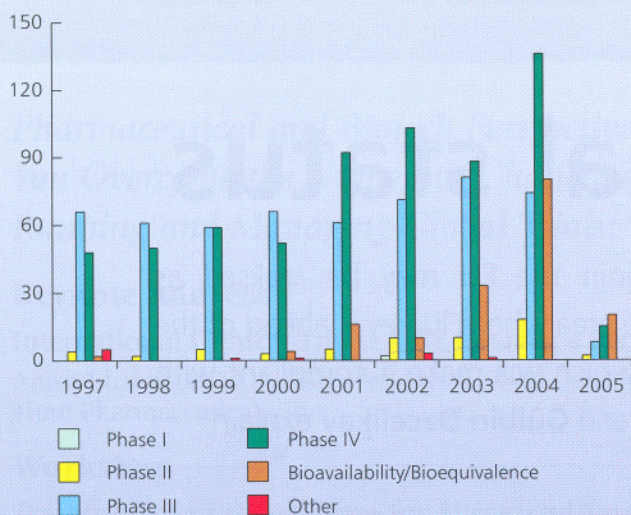


Figure 1: Number of applications from some LECs to the CEC between 1997 and February 2005. Source: Turkish MoH.

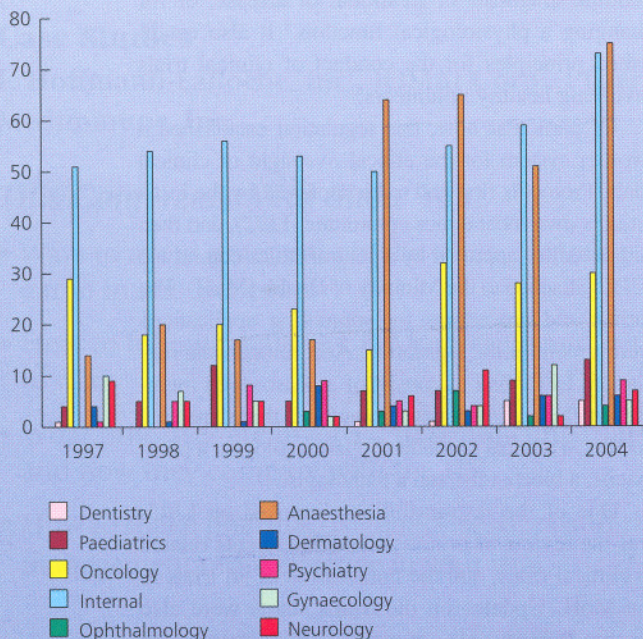


Figure 2: Clinical trial applications by therapeutic area between 1997 and 2004. Source: Turkish MoH.

## Conducting clinical studies on children in Turkey

There has been some confusion over the legality of paediatric research in Turkey since October last year when the Turkish Penal Code was published. It included the provision: 'under no circumstances may scientific experiments be conducted on children' (Paragraph 3 to Article 90).

However, the position was clarified when the provision was amended, from 1 June, to read: 'For any scientific experiments conducted on children to involve no penal liability, and aside from the conditions required in Paragraph 2, it is required that:

- scientific data intended to be gathered with the experiments being conducted make it necessary that they are to be conducted on children as well for the sake of accomplishing the intended targets;
- written consent of the parents or of the guardian has been received in addition to that of the child capable of making a declaration of consent;
- a specialist in child healthcare and diseases is available at the competent bodies, which should grant authorisation for the experiment.'

the CA with information on the site's capability to conduct the study. Now that the application process is centralised, the timeline outlined by the new regulation is 60 days in total. This is the same timescale as set out in EU Clinical Trials Directive. A parallel application procedure has also been proposed which means that submissions can be made simultaneously to SECs and the CA, so the 60-day timeline covers the entire approval process. This new approach will significantly shorten the application process.

The MoH is also determined to organise GCP training courses and to audit the courses provided by other accredited institutions in Turkey in order to increase the number of qualified investigators. This programme is part of the MoH's attempt to increase the level of awareness of investigators and the public about international clinical trials. **GCPJ**

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