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Centralized National Ethical Review of Clinical Trials in Croatia

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Aim To present the Croatian system of ethical review of clinical trials and assessment outcomes of the applications reviewed by the Croatian Central Ethics Committee.

Methods Clinical trial applications reviewed by the Croatian Central Ethics Committee, which has the legal mandate to review clinical trials of medicinal products and medical devices, were retrospectively analyzed from May 2004 to the end of 2008 according to the number, research area, and type of opinion issued. Applications from 2008 were analyzed separately according to the study phase, participants (adult trials vs pediatric trials), and sponsor (commercial trials vs academic trials). Data were analyzed by descriptive statistics.

Results Since its establishment in 2004, the Croatian Central Ethics Committee has reviewed 407 trials. The greatest number of clinical trials was in the field of oncology (n=69), mental and behavioral disorders (n=52), and endocrine, nutritional, and metabolic diseases (n=50). In the initial assessment of clinical trials, 60% applications received a conditionally positive opinion. In 28% of applications, the opinion had to be postponed because additional documentation or explanations were required. In 2008, the Croatian Central Ethics Committee reviewed 99 trials, most of which were phase III trials (n=57). Five clinical trials included pediatric population and 3 were academic clinical trials.

Conclusion The model of centralized clinical trial review seems to be appropriate for the current number of clinical trials conducted in Croatia. The efficient and standardized review process of clinical trials by the Central Ethics Committee may positively affect the increasing number of clinical trials conducted in Croatia. Future development includes the transparency of the clinical trials through a publically available database and establishing the basis for conducting academic clinical trials in Croatia.

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With the adoption of the Directive 2001/20/EC in 2001, the implementation of Good Clinical Practice (GCP) in the conduct of clinical trials became obligatory for all member states of the European Union (1). This directive includes the description and enforcement of the responsibilities of Ethics Committees. During the process of clinical trials approval, the Ethics Committee assesses relevant documentation submitted by the applicant, assuring that the rights, safety, and well-being of all clinical trial subjects are safeguarded, based on which either a positive or negative opinion on a clinical trial is issued. After a positive opinion of an ethics committee is issued, a competent authority (drug agency, ministry of health, etc.) may grant the authorization for a clinical trial.

One of the principles set by the Directive 2001/20/EC was the introduction of a single ethics opinion for multi-center trials for each member state of the European Union. This principle was introduced in order to reduce the delay in the commencement of a trial, without jeopardizing the well-being of the people participating in the trial, and excluding the possibility of rejecting it in specific sites (1,2). Although the ICH E6 Guideline on GCP, as the internationally adopted standard, and the Directive 2001/20/EC, as the legal framework for the conduct of clinical trials in the European Union, pose standardized requirements on independent ethics committees concerning their roles and responsibilities (1,3), it is clear that the process of obtaining a single ethics opinion for multi-center trials in Europe is organized differently from country to country. The organization of ethics committees in Europe can be divided into 3 different models (Table 1). In the first model, different local ethics committees are responsible for giving opinions on single-center trials, while for the multi-center trials, one of them is appointed as a single-opinion decision maker. In the second model, different local ethics committees are responsible for giving opinions on single-center trials, while the responsibility for the multi-center trials is on the central ethics committees. In the third model, the responsibility for both single and multi-center trials is on the central ethics committees (4).

Until the beginning of 2004, all opinions on clinical trials in Croatia were issued on a local level by the ethics committees of the institutions in which the clinical trial was conducted. With the first harmonization of the Croatian law with the Directive 2001/20/EC, the Croatian Central Ethics Committee was established and the second model of the review process of clinical trials by the ethics committees was accepted (Table 1). This model was changed very soon (the end of 2004) and since then, all clinical trials in Croatia, both single-center and multi-center, have to be reviewed by the Central Ethics Committee (5-8). Since December 2007, the Central Ethics Committee has also been responsible for issuing opinions on non-interventional trials (9). It is important to emphasize that the Central Ethics Committee has the mandate, according to Croatian law, to review clinical trials of medicinal products and medical devices but not medical procedures (7-9).

Before the Directive 2001/20/EC came into force, delays and diversities in the practice of local ethics committees' assessment of multi-center clinical trials in Europe were frequent. The diversities mostly concerned the type of information required by the committees, committees' time to respond and, what was most important, the final opinion on the same trial (10-13). This unsatisfactory situation demanded that some improvements are made in the process, and was legally finally overcome by the Directive. However, even though the Directive ensures that the ethical review of a multi-center trial occurs only once and within a maximum of 60 days from the application, if different local ethics committees act as single-opinion decision makers, variations in their work are still inevitable (14,15). The aim of our study was to present the Croatian system of ethical review of clinical trials and the data on the assessment outcomes of applications reviewed by the Croatian Central Ethics Committee.

METHODS

Croatian Central Ethics Committee: organization and principles

The Croatian Central Ethics Committee is an independent committee of 19 members appointed by the Minister of

TABLE 1. Organization of review process of clinical trials by the ethics committees in different countries in Europe

	Review of single-center clinical trial	Review of multi-center clinical trial	Example
Model 1	Local ethics committee	Local ethics committee acting as single-opinion decision maker	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Ireland, Italy, Latvia, Netherlands, Norway, Poland, Slovak Republic, Spain, Sweden, UK
Model 2	Local ethics committee	Central ethics committee	Lithuania, Portugal
Model 3	Central ethics committee	Central ethics committee	Croatia, Cyprus, Greece, Hungary, Malta, Slovenia

Health and Social Welfare – medical doctors from various fields of expertise, a representative of patients, a theologian, and a lawyer. It is important to emphasize that the Central Ethics Committee assesses both the scientific and ethical aspects of clinical trials, assuring that the anticipated benefits and risks for the participants are satisfactory and justified. In preparing its opinion it considers the trial protocol, the investigator's brochure, the suitability of investigators and monitors, the adequacy of facilities, the insurance, the methods and amounts of payments, and the methods and documents to be used to inform trial subjects and obtain their informed consent (9,16). The complete documentation on a clinical trial is reviewed by two independent expert assessors, who prepare their recommendations in a written form. Every Informed Consent Form is additionally assessed by the representative of patients and the theologian, while the details of insurance and contract between the applicant, institution, and principal investigator are also verified by the lawyer. The members of the Central Ethics Committee, following the interdisciplinary discussion, vote for the opinion which is afterwards sent to the applicant. There is also a possibility to obtain an external expert opinion when needed. The meetings are held regularly every 2 to 3 weeks, depending on the number of applications. The review process of a clinical trial application by the Croatian Central Ethics Committee is presented in Figure 1.

According to the Internal Rules of the Central Ethics Committee, 4 types of opinions on clinical trials may be issued: 1) positive opinion; 2) conditionally positive opinion (minor objections); 3) postponed opinion (major objections which ask for additional documentation and explanations); and 4) negative opinion.

Data extraction

Clinical trials applications reviewed by the Croatian Central Ethics Committee were analyzed retrospectively from May 2004 to the end of 2008. The gathered data included the number of analyzed clinical trials per year, research area, and type of opinions issued. Because the new Ordinance on Clinical Trials and Good Clinical Practice, which regulates the administrative support of Croatian Agency for Medicinal Products and Medical Devices was introduced at the end of 2007, clinical trial applications in 2008 were analyzed separately according to study phase, participants (adult trials vs pediatric trials), and sponsor (commercial trials vs academic trials). Diseases most commonly addressed in clinical trials were also classified according to the 10th revision of the International Classification of Diseases of the World Health Organization (17).

RESULTS

Since its establishment in May 2004 until the end of 2008, the Central Ethics Committee reviewed 407 trials: 28 in May-December 2004, 92 in each 2005 and 2006, 96 in 2007, and 99 in 2008. The median number of trials assessed per meeting was 7 (range 1-13).

In 2008, the Croatian Central Ethics Committee reviewed 99 trial applications (Figure 2), most of which were for

Figure 1.

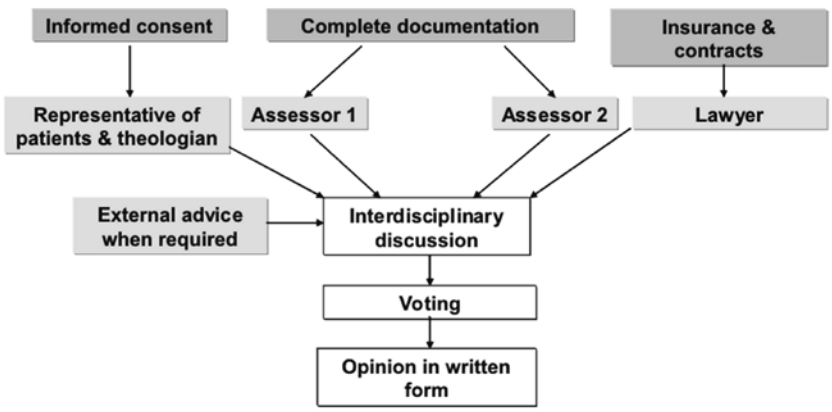
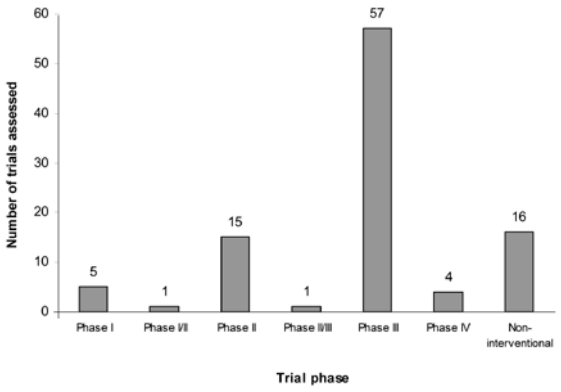


Diagram of review process of clinical trials application by the Croatian Central Ethics Committee.

Figure 2.

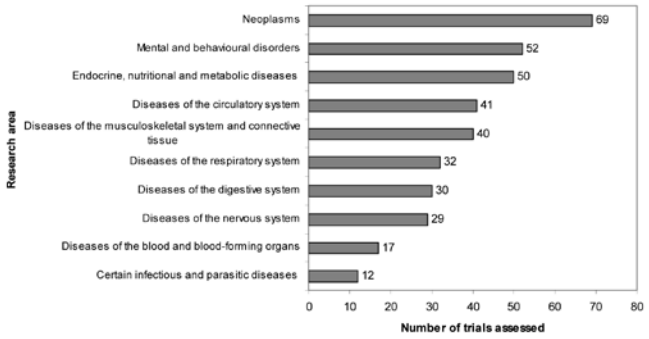


Number of clinical trials assessed by the Croatian Central Ethics Committee in 2008 according to phase.

phase III trials (n = 57). 5 applications for clinical trials which included paediatric population and 3 applications for academic clinical trials were reviewed.The greatest number of trial applications for the whole period was in the field of oncology (n = 69), followed by mental and behavioral disorders (n = 52), and endocrine, nutritional, and metabolic diseases (n = 50). The first 10 research areas of clinical trials assessed by the Central Ethics Committee are presented in Figure 3.

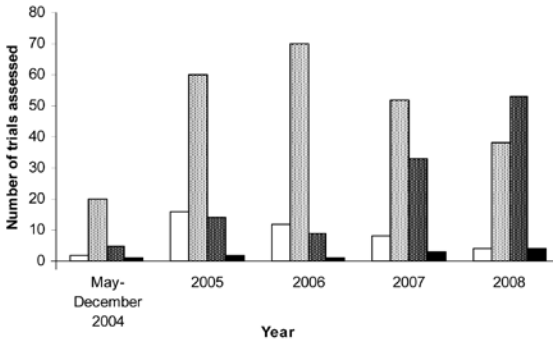
The most common initial recommendation by the Central Ethics Committee was conditionally positive opinion (60%), followed by postponed opinion (28%) (Figure 4). The number of postponed opinions increased from 10 in 2006

Figure 3.



First ten clinical trials research areas by number of clinical trials assessed by the Croatian Central Ethics Committee (May 2004-2008) – classified according to the chapters of WHO International Statistical Classification of Diseases and Related Health Problems (10th Revision, Version for 2007)

Figure 4



Types of opinions issued by the Croatian Central Ethics Committee after the initial assessment of a clinical trial . Open bars – positive opinion; light gray bars – conditionally positive opinion; dark gray bars – postponed opinion; closed bars – negative opinion.

to more than 50 in 2008, paralleled by a decrease in the number of conditionally positive opinions (Figure 4). The number of negative opinions also increased, although their numbers remained generally low, less than 5 each year.

DISCUSSION

The greatest number of trials assessed by the Croatian Central Ethics Committee was conducted in the most challenging fields of medicine today (oncology, mental and behavioral disorders, and endocrine, nutritional and metabolic diseases). These 3 research areas are identical to those in the study published by the German drug regulatory agency (The Federal Institute for Drugs and Medical Devices) for the same period (18).

According to our analysis, phase I, II, and IV clinical trials, especially academic trials and trials on pediatric population, are rarely conducted in Croatia. Small number of phase I and II trials in Croatia, compared with Germany (30% phase I; 27% phase II trial applications) (18), may be explained by the absence of innovative pharmaceutical industry in Croatia. However, even with a long history of generic pharmaceutical industry in Croatia, the Central Ethics Committee did not assess any bioequivalence/bioavailability studies. This is probably the result of the type of generic drugs production in Croatia, which includes only the final steps in the process, and specific requirements in this field, ie, bioequivalence/bioavailability studies are performed by the Croatian industry only in internationally recognized laboratories with accreditation.

The number of phase IV trials was very low compared with European countries, where they constitute up to 20% of all trials in Germany (18) and up to 25% in the United Kingdom (19), but it is expected to increase with an increase in the number of academic trials. The small number of academic clinical trials is probably the result of a lack of financial and institutional support, but also the consequence of the growing complexity of the requirements for clinical trials, which include the demands of GCP (Directive 2001/20/EC). An investigation at the university hospital in Austria found 66% decrease in academic research after the introduction of the Directive, while the number of industry-sponsored clinical trials remained constant (20). On the other hand, there has been no decline in the number of academic clinical trials in Denmark, and the explanation is in the established system of GCP units, ie, university and university hospital GCP units provide free assistance to academic clinical researchers (21).

Although the number of clinical trials with pediatric population in 2008 was small (n = 5), it can be expected that it will increase in near future because of the Pediatric Regulation, which came to force in the European Union in January 2007 (22).

A considerable increase in the number of opinions which had to be postponed due to major objections in 2007, and even greater in 2008, may be attributed to the changes in the legislation at the end of 2007, which introduced specific requirements for investigators, monitors, contracts, and insurance (9). This legislative change introduced the need for the Central Ethics Committee approval of non-interventional trials, and is aimed at preventing trials conducted primarily for marketing purposes (9).

The advantages of the centralized review process of clinical trials by the ethics committee, based on the experience of the Croatian Central Ethics Committee, are the following: single application form, standardized requirements, standardized assessment, no variations in time-to-respond, single point of contact, and a single database of clinical trials. If sufficiently equipped and funded to take the responsibility, this model allows efficient and standardized assessment of clinical trials suitable for countries similar to Croatia according to the number of inhabitants and clinical trials per year. The efficient review process of clinical trials by the Central Ethics Committee may increase the number of clinical trials conducted in Croatia. There is certainly a room for future development, which includes increasing the transparency of the clinical trials through a publically available database, according to the EU guidelines (23). Further, there is a possibility and a need for specific GCP education units which would promote academic clinical trials.

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