



**The EFGCP Report on  
The Procedure for the Ethical Review of Protocols  
for Clinical Research Projects in Europe**  
(Update: April 2009)

**Croatia**

1. What laws or regulations apply to an application for conducting a clinical trial in Croatia?

The laws or regulations applying to an application for conducting a clinical trial in Croatia are:

The Law 71/07 of 9 July 2007 – Law about drugs (*Zakon o lijekovima* (Official Gazette No. 71/07)), the Law 67/08 of 9 Jun 2008 – Law about medical devices (*Zakon o medicinskim proizvodima* (Official Gazette No.67/08)), and Bylaw (or rule) 121/07 of 26 November 2007 about clinical trials and good clinical practice (*Pravilnik o kliničkim ispitivanjima i dobroj kliničkoj praksi* (Official Gazette No. 121/07)).

The latter by-law sets out the procedure and good clinical practice of clinical trials of drugs and medical devices, including the structure and appointment of the Central Ethics Committee, and translated EU guidelines “Note for Guidance on Good Clinical Practice“ (CPMP/ICH/135/95) and “Clinical Investigation of Medicinal Products in the Paediatric Population“ (CPMP/ICH/2711/99).

2. Which government, legal or authoritative body or bodies is or are responsible for the establishment and/or accreditation of (research) ethics committees for IMPs, and for their supervision and quality? Are there different (research) ethics committees reviewing other projects?

There is a single EC at the national level, the Central Ethics Committee. It is an independent body, whose members are appointed by the Croatian Minister of Health. This is the only EC that is authorized to approve clinical trial protocol for the investigation of drugs and medical devices (industry and non-industry sponsored). A procedure for approval is regulated by the rules approved by the Minister of Health. Local ECs exist in health facilities and medical universities, and review research that is outside the scope of the national Central Ethics Committee.

3. What is the process for achieving clinical trial authorisation from the competent authority in Croatia?

The sponsor submits a clinical trial application request and all required documentations to a) the Ministry of Health, which is the regulatory competent

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authority and b) the Central Ethics Committee. No clinical trial can be started without an approval from the Minister of Health, which is issued after a positive approval from the Central Ethics Committee. The list of requirements for the trial approval is available on the website of the Ministry of Health ([http://www.mzss.hr/hr/zdravstvo\\_i\\_socijalna\\_skrb/zdravstvo/lijekovi/klinicka\\_iskpitiv\\_anja\\_lijekova\\_i\\_medicinskih\\_proizvoda](http://www.mzss.hr/hr/zdravstvo_i_socijalna_skrb/zdravstvo/lijekovi/klinicka_iskpitiv_anja_lijekova_i_medicinskih_proizvoda)), and the Croatian Agency for Medicinal Products and Medical Devices ([http://www.almp.hr/?ln=hr&w=o\\_SEPu](http://www.almp.hr/?ln=hr&w=o_SEPu)).

These requirements are:

- a request form in Croatian language, with the names of investigators and institutions for the conduct of clinical trial
- signed trial protocol(s)/amendment(s)
- investigator's brochure (IB)
- case report form (CRF)
- informed consent form in the Croatian and original language
- investigator's current curriculum vitae
- monitor's current curriculum vitae
- positive opinion of the Paediatric Committee of the Ministry of Health and the National Ombudsman for Children or a positive opinion of the Psychiatry Committee of the Ministry of Health (for clinical investigations of medicinal products in the paediatric or psychiatric patients population, respectively)
- list of states or centres for multicentre trials
- list of states or centres with already achieved positive or negative approval
- recruitment procedures (e.g. advertisements for subject recruitment if used)
- financial aspect of the trial to document the financial agreement between the investigator/institution and the sponsor for the trial
- information about payments and compensation available to subjects
- subject's insurance statement
- proofs of paid fees required for the review process.

4. What is the process for obtaining ethical review of a clinical trial protocol by a competent (research) ethics committee in Croatia?

The sponsor submits a clinical trial application request and all required documentations to the Central Ethics Committee. The procedure for the approval is regulated by rules approved by the Minister of Health and is available at [http://www.almp.hr/?ln=hr&w=o\\_SEPu](http://www.almp.hr/?ln=hr&w=o_SEPu) and <http://narodne-novine.nn.hr/clanci/sluzbeni/329774.html>

For clinical investigations of medicinal products in the paediatric population, the sponsor (the financing body for the trial) is obliged to supply a positive opinion of the Paediatric Committee of the Ministry of Health and the National Ombudsman for Children.

For clinical investigations of medicinal products in psychiatric patients, the sponsor is obliged to supply a positive opinion of the Psychiatry Committee of the Ministry of Health.

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The Central Ethics Committee is obliged to provide its decision (positive or negative) in writing to the Minister of Health and the sponsor. After that, the Ministry of Health sends its final decision to the sponsor, the Central Ethics Committee and the Croatian Agency for Medicinal Products and Medical Devices.

This procedure does not apply to scientific, i.e. academic research, which is approved by the ethical committee of the appropriate university or the ministry responsible for the approval of research grants. Academic clinical trials of drugs and medicinal products are subject to the regulatory procedure defined by the Ministry of Health.

5. Is there a single organisation to which to apply for ethical review of a clinical trial for an investigational medicinal product, regardless of whether this is for a single site or multiple sites?

Yes, applications are made to the Croatian Central Ethics Committee.

6. What is the website for the organisation that issues guidelines on the ethical review of a clinical trial for an investigational medicinal product?

The website is <http://www.almp.hr/?ln=hr&w=oSEPu> and <http://narodne-novine.nn.hr/clanci/sluzbeni/329774.html>

7. Is there a procedural interaction between the national or local competent authority and the (research) ethics committee during the approval process?

No. The Central Ethics Committee is obliged to provide its decision (positive or negative) in writing to the Minister of Health and the sponsor. After that, the Ministry of Health sends its final decision to the sponsor, the Central Ethics Committee and the Croatian Agency for Medicinal Products and Medical Devices.

8. Does the application to the EC and to the competent authority have to be submitted in parallel, or, if not, in which order?

This is a two-step procedure because the competent authority (Minister of Health) does not give its authorization before the approval of the Croatian Central Ethics Committee.

9. How many (research) ethics committees are there in Croatia?

The Central Ethics Committee is responsible for clinical trials on investigational medicinal products performed in Croatia, although local ECs have been set up at universities and hospitals but they are only authorized to review local studies that do not fall under the jurisdiction of the national Central Ethics Committee.

10. How are ECs funded in Croatia? Do they charge fees? If yes what is their scale of fees?

Fees for the Central EC review are paid to the Croatian Agency for Medicinal Products and Medical Devices, which gives administrative support to the Central EC. The fees are scaled according to the type of study (e.g., the fee for the review of a new study sponsored by Industry is 25 000 Kunas or ~ Euro 3400). No fees are required for local ECs.

11. Who is responsible for submitting the request for ethical review to the competent ethics committee for single-site and for multi-site clinical trials?

The sponsor, or the contract research organization, or the principal investigator.

12. How is a "single opinion" achieved for multi-site studies?

The same procedure applies for all clinical trials in Croatia, because the Central Ethics Committee always provides a single opinion. For any new centre or site the sponsor or CRO (who already received written positive decision from Central Ethic Committee and Minister of Health for other site) are obliged to submit a clinical trial application request and all required documentation to Central Ethics Committee and Ministry of Health for approval.

13. How many members serve on an EC?

The Central EC is an independent committee of 19 members, comprised of health professionals and other non-medical professions. The current membership of the EC includes clinical pharmacologists, pharmacologists, internists, a neurologist, a psychiatrist, a paediatrician, a surgeon, a theologian, a lawyer, and a representative of patient associations.

14. How many members constitute a quorum?

The absolute majority of members constitute a quorum.

15. How are EC members appointed?

They are appointed by the Minister of Health.

16. How is the independence of members ensured?

All members of the Central EC are independent according to the Drug Law, and there are no specific measures to ensure their independence. Each member of the EC is expected to declare any conflicts of interest.

17. How are conflicts of interest of EC members avoided?

Members of EC are expected to declare any conflicts of interest and should there be any significant conflict of interest, the member must leave the meeting and take no part in that review process.

18. What backgrounds and/or qualifications of members are actively sought?

Professional expertise is the main way of selecting the members. For medical members it is their medical background in a certain specialty, experience in clinical trials, as well as experience in local ECs.

19. How do ECs obtain specialist expertise?

Specialist expertise is available in the Central EC, so that most of the cases are evaluated through the expertise of EC members (rapporteur and co-rapporteur system of analysis). A trial may be evaluated by an appropriate external specialist if such is not already represented on the committee.

20. What are the training requirements for members of ECs?

There are no mandatory requirements for the training of EC members.

21. What training programmes are available for EC members in Croatia?

There is no regular, formal training programme specified in the regulation, both for the Central EC and ECs at institutions.

22. What are the timelines for the assessment of single- and multi-site studies?

The Central EC is obliged to provide an opinion within 30 days. The exceptions are the drugs for gene therapy, treatment with somatic cells, including genetically modified organisms, for which the opinion has to be given within 90 days. This deadline can be extended for another 90 days if there is a need for consultations with experts or other committees. Time restrictions do not apply for xenogeneic drugs.

23. How are substantial amendments submitted during the review process dealt with?

Substantial amendments are subject to the same principles of review as a new study.

24. How does an EC assess the suitability of investigators and of sites?

This is judged according to their professional expertise (from CV), with data about their experience in the conduct of clinical trials, proficiency in good clinical practice,

and a list of clinical trials in the patient recruitment phase (it should be no more than five such clinical trials).

25. How are the requirements for (research) ethics committees to review the contractual or financial arrangements in clinical trials for both investigators and hospitals handled?

In principle, financial arrangements should be transparently disclosed to the Central EC.

The total expenses for conducting a clinical trial (including sponsor expenses with expenses of medical and other services, information about payments to institution, investigators and subjects, and sponsor obligation for all expenses for diagnostics and laboratory procedure or tests) must all be stated in written, dated, and signed financial arrangements between the investigator/institution and the sponsor of the trial.

26. How are the requirements for ethics committees to review the compensation arrangements for study subjects handled?

The compensation arrangements for the study subject should be transparently disclosed to the Central EC.

Written, dated, and signed financial arrangements between the investigator/institution and the sponsor of the trial must state any fees or remuneration or payments or compensation to study subjects.

27. Is there an ongoing quality assurance process (e.g. audits, inspections, internal SOP) for (research) ethics committees in Croatia?

No because there is only a single Central EC.

28. Is there an appeal mechanism?

An appeal on the final decision of the Minister is not possible, but it is possible to initiate a court petition to the Administrative Court of the Republic of Croatia.

29. How do ECs deal with SUSAR reports and Annual Safety Reports?

The Central EC closely collaborates with the Croatian Agency for Medicinal Products and Medical Devices. According to Croatian law and by-laws, the sponsor or investigator should expedite the reporting to the Croatian Agency for Medicinal Products and Medical Devices and Central Ethics Committee of all adverse drug reactions (ADRs) that are both serious and unexpected. Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

The Croatian Agency for Medicinal Products and Medical Devices must monitor all AE of clinical trials, and send a report to Central Ethics Committee and the Minister of Health as the regulatory authority.

30. How are 'substantial amendments' defined?

As in the European guidance documents in accordance with the Directive 2001/20/EC.

31. What are the indemnity insurance requirements for research projects?

A copy of a valid insurance policy (documentation about compensation for trial-related injury) is required as a part of application for a clinical trial.

32. What are the indemnity insurance requirements for ethics committee members themselves?

None.

33. How is informed consent obtained from vulnerable subjects who are potentially to be involved in a clinical trial?

Informed consent is obtained according to the Declaration of Helsinki and the Council for International Organizations and Medical Sciences (CIOMS) Guidelines on Ethics of Clinical Trials. When the subjects are either incompetent or otherwise substantially unable to give informed consent, their agreement will be supplemented by the permission of their legal representatives.

34. How do ECs assess the progress and outcome of research projects that they have approved?

By interim and final reports (for any clinical trial that is prematurely terminated, reports should be prepared within 15 days after the termination of the trial, with detailed explanation for this decision; information about regularly completed clinical trial, within the period of 90 days; and summary of final report within the period of 1 year), which are required by law.

35. How does the EC ensure reception of the Annual Safety Report and the Summary of the Final Report of a research project that it has approved?

It is the responsibility of the sponsor to ensure that Annual Safety Reports (ASRs) and the Summary of the Final Report are submitted. These are required by law. The Central EC discusses the ASR and the Final Report at the official, regular meetings and that is confirmed in written form. According to the By-law 29/05 about monitoring adverse drug and medical devices reaction and adverse event, if the report of serious AE is not expedited, responsible person should be fined with an assigned penalty of EUR 4000-7000.

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36. Do national regulations in Croatia allow research on healthy volunteer children (subjects under 16)?

No.

37. Do national regulations in Croatia allow payment, (other than expenses), to children taking part in research?

No.

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