Hungary

Question 1: What laws or regulations apply to an application for conducting a clinical trial in Hungary?

95th Act of 2005 on the medicines for human use and on the modification of other Acts regulating the pharmaceutical market. Articles 3 and 21 (as amended).


140th Act of 2004 on the general rules of public authority procedures and services (as amended).


Decree No 35/2005 (of 26th August 2005) EüM of the Minister of Health on the clinical trial of investigational medicinal products for human use and on the application of the good clinical practice (as amended).

Decree No 23/2002 (of 9th May 2002) EüM of the Minister of Health on biomedical research on human subjects (as amended).

Decree No 33/2009 (of 20 October 2009) EüM of the Minister of Health on clinical trials with medical devices.

Decree No 34/2003 (of 7 June 2003) ESzCsM of the Minister of Health, Social and Family Affairs on the Medical Research Council (as amended).


Decree No 50/1996 (of 27 December 1996) NM of the Minister of Welfare on the fees payable for of administrative and authoritative procedures of the Welfare area.
The EFGCP Report on  
The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe  
(Update: May 2011)

Decree No 1/2009 (of 30 January 2009) on the fees payable for administrative and civil service procedures of the National Public Health Service.

The legislation on clinical trials on investigational medicinal products (CTIMPs) has been almost completely separated from those of other biomedical research. The reason is that, although logically the biomedical research and that with IMPs can be taken as “general” and “specific”, i.e. the latter is subcategory of the former, their regulation is completely different. (E.g. the Ethics Committees approving the trial, the legal/natural persons who may authorise the trial, the special provision applying to the involvement of vulnerable and incapable persons, etc.) Medical devices (with or without IMPs) comprise a third group (with two subgroups). Moreover, non-interventional clinical trials also need authorisation in Hungary as a special subgroup of biomedical research. As for the legislation see above.

**Question 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?

Note: The central ethics committees referred to below are officially appointed by law as public co-authorities (in the meaning of the general rules of public authority procedures). This is a specific Hungarian phenomenon. The opinion of the co-authority (in its field, the ethical approval in the given case) is binding for the decision-making authority. The co-authority opinion must obey the formal requirements required by the 140th Act of 2004 (see in Q1). The co-authority may directly raise questions to the applicant. Moreover, the co-authority, independently from the general flow of the procedure (specified in the law), may also be discussed first, before starting the procedure.

3.1 Clinical trials with investigational medicinal products

There is a single central Ethics Committee named Committee for Clinical Pharmacology and Ethics of the Medical Research Council (the Hungarian abbreviation is KFEB). Its members are appointed by the Minister of Health. Its composition is public; it is on the website of the Medical Research Council. This is the only Ethics Committee authorised to approve clinical trial protocols with IMPs. The KFEB is public co-authority

The role of the local (hospital) ethics committees is to safeguard patients’ interest during the trials.

3.2 Clinical trials with medical devices

The competent Ethics Committee is the Scientific Research Ethic Committee (Hungarian abbreviation: TUKEB) of the Medical Research Council. TUKEB is also public co-authority.
3.3 Other biomedical research involving human subjects

As a rule, the competent Ethics Committee is also the TUKEB except trials connected with human reproduction, when the Human Reproduction Committee (Hungarian abbreviation: HRB) of the Medical Research Council acts, also co-authority. One of these ethics committees acts in case of multicentre trials. In single centre trials the relevant Regional Ethics Committee (which is not co-authorities) gives the approval.

All kinds of Ethics Committees are defined in the Health-care Act as “an independent Committee comprising physician, lawyer, theologian, ethicist and psychologist members, established to give ethical opinion to biomedical research protocols.” KFEB, TUKEB and HRB members are appointed by the Minister of Health while in case of Regional and local committees, according to the 14/1998 MoH Decree, the actual number of the members is determined by the University/hospital administrator, taken the tasks into account.

**Question 3: What is the process for achieving clinical trial authorisation from the competent authority in Hungary?**

The authorisation and approval procedure of clinical trials with IMPs is as follows:

The main rule is that applications should be submitted to the National Institute of Pharmacy (NIP, the competent regulatory authority for human medicinal products). The NIP starts its assessment and, within 8 days, sends the copy of the relevant parts of the application to the KFEB. The KFEB has an independent review and issues an independent decision. The ethical approval/rejection must be sent, within 42 calendar days starting from receiving the documentation from the NIP, back to the NIP. The whole authorisation plus approval procedure may last for 60 calendar days (as required by the Medicines Act). However, in case of a deficiency letter the clock stops. Meeting this deadline, the NIP sends the applicant the authorisation/rejection, the first Annex of that is the KFEB opinion.

In case when the KFEB (as co-authority) is consulted first, its (positive) opinion is appended to the application to the NIP. However, the NIP’s approval time is still 60 calendar days in this case.

In case of clinical trials with immunological medicinal products, there is a second co-authority: the National Centre of Epidemiology. It has 10 work days to express its opinion.

It should be noted that non-interventional trials with IMPs also need authorisation in Hungary. The authority (also acting as ethics committee) is the TUKEB. The procedure may last 45 working days.
Clinical trials with medical devices

Applications should be sent to the Office for Health Administration and Authorisation (Hungarian abbreviation is EEKH) that sends its relevant parts to the TUKEB. TUKEB has 35 working days, the whole procedure should last for 45 working days.

In case when the TUKEB (as co-authority) is consulted first, its (positive) opinion is appended to the application to the EEKHP. However, the EEKH’s approval time is still 45 working days in this case.

When the medical device contains also IMP, there is also a second co-authority: the NIP. It has 10 working days to express its opinion. (Please note that this 10 working days interval starts when NIP receives the application and EEKH re-starts its procedure when the co-authority opinion arrives).

General biomedical research

The authorisation is given by the Regional Office of the National Public Health Service, on the basis of the ethics committee (indicated above) opinion. The whole procedure is 45 work days within which the ethical approval may last for 35 work days.

In case when the trial is not directly the subject’s interest (but may serve the interest of similar group of patients), the authorisation is given by the Minister of Health (the same ethics committees apply as indicated above). The time-frame is also the same.

**Question 4:** What is the process for obtaining ethical review of a clinical trial protocol by a competent (research) ethics committee in Hungary?

See question 3.

**Question 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?

See question 3.

**Question 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 National Institute of Pharmacy, in agreement with the KFEB, is authorised to issue guidelines (“methodological letters”) on clinical trials with investigational medicinal products. (E.g. describing when the use of placebo is ethical). Its website is [http://www.ogyi.hu](http://www.ogyi.hu).
**Question 7:** Is there a procedural interaction between the national or local competent authority and the (research) ethics committee during the approval process?

Only as indicated in Question 3.

**Question 8:** Does the application to the REC and to the competent authority have to be submitted in parallel, or, if not, in which order?

See question 3.

The general rule is one single submission to the authority that sends the relevant documents to the ethics committee for opinion. However, co-authority ethics committees may be consulted before the procedure has been started officially.

**Question 9:** How many (research) ethics committees are there in Hungary?

Only one single, See question 3.

**Question 10:** How are RECs funded in Hungary? Do they charge fees? If yes, what is their scale of fees?

There are civil service procedure fees.

**Clinical trials with IMPs**

The fee to be paid in connection with clinical trials with IMPs has been determined by the 95th Act of 2005 (see in Q1). At present (April 2010) the fee for an application is 450,000 Hungarian Forints (HUF), while for protocol variations 90,000 HUF (in April 2010, 265 HUF was worth €1).

This fee is distributed between the authority (the NIP) and its co-authorities (including the KFEB). The exact amounts will be specified by law that is expected to be issued in the first half of 2010.

For the authorisation of non-commercial trials, no fee should be paid.

**Non-interventional clinical trials with IMPs**

The fee is 200,000 HUF.

**Clinical trials with medical devices**

The fee is 374,000 HUF. It will be distributed among the EEKH and the co-authorities. The exact amounts will be specified by law that what is expected to be issued in the first half of 2010.
Other biomedical research

Both the original authorisation and its variation cost the same fees.

<table>
<thead>
<tr>
<th>Ethics Committee</th>
<th>Authority</th>
<th>EC fee (HUF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUKEB</td>
<td>114,000</td>
<td>320,000</td>
</tr>
<tr>
<td>HRB</td>
<td>114,000</td>
<td>315,000</td>
</tr>
<tr>
<td>Regional EC</td>
<td>98,700</td>
<td>15,300</td>
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</tbody>
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Authorisation of special trials by the Minister of Health (see Q3) is free of charge.

The local committees may not charge fees, if necessary; their remuneration should be part of the contract between the sponsor and the trial site.

**Question 11:** Who is responsible for submitting the request for ethical review to the competent (research) ethics committee for single-site and for multi-site clinical trials?

The sponsor.

As a rule (e.g. in case of clinical trials with investigational medicinal products), all the documentation must be submitted to the authority that sends the relevant part to the ethics committee.

**Question 12:** How is a “single opinion” achieved for multi-site studies?

See question 3, there are single opinions exclusively.

**Question 13:** How many members serve on a REC?

In the central KFEB: twenty.

The composition of the KFEB is as follows:

- 2 general pharmacologists (one in the chair).
- 12 clinicians (cardiologist – vice chair, psychiatrist, internist, internist and clinical pharmacologist, paediatrician, dermatologist, endocrinologist, gastro-enterologist, gynaecologist, haematologist, oncologist, orthopaedic surgeon).
- 1 microbiologist.
- 2 lawyers.
- 1 head nurse.
- 1 nursing-ethicist.
- 1 patient organisation representative (Hungarian League Against Cancer).
However, there has been an important change in the procedure, introduced in 2010: bioequivalence, Phase IV clinical trials, protocol variations and other urgent cases decided by the Chairperson are not discussed by the whole KFEB. A “quorum” of a five members (healthcare professionals and laymen) acts in these cases.

As said before, membership of local ethics committees varies widely.

The TUKEB and HRB have similar memberships.

**Question 14: How many members constitute a quorum?**

As for the KFEB, the only committee that approves IMP protocols, minimum 11 members must be present (at least one of the laypersons) and the quorum is 50% of those who are present plus one vote (including at least one layperson’s).

As for its small subcommittees indicated above, all but one person must vote.

**Question 15: How are REC members appointed?**

As said above, the Minister of Health appoints the members for the central KFEB, TUKEB and HRB while the hospital administrator is responsible for the establishment of the local ethics committees. National Medical Boards advise the Minister whom to appoint.

The central committees supervise the operation of the local committees, although no concrete legal requirement is specified.

**Question 16: How is the independence of members ensured?**

The KFEB, TUKEB and HRB members are esteemed scientists. According to their internal rules, if a member’s institution participates in a given trial, that members may not vote.

**Question 17: How are conflicts of interest of REC members avoided?**

They have conflict of interest declaration.

**Question 18: What backgrounds and/or qualifications of members are actively sought?**

See above in §13.

**Question 19: How do RECs obtain specialist expertise?**

The KFEB may consult any leading specialist in the country (that actually is the case, e.g. to approve protocols concerning vaccination).
**Question 20:** What are the training requirements for members of RECs?

Only well esteemed specialists are appointed by the Minister. Moreover, the physician members possess also a certificate of a GCP course, attended not later than 5 years, organised by a University.

**Question 21:** What training programmes are available for REC members in Hungary?

University-organised courses on GCP.

**Question 22:** What are the timelines for the assessment of single- and multi-site studies?

See above. No difference between multi and single site study assessment.

As for gene therapy, somatic cell therapy and GMO IMPs, the NIP’s process may last for 90 days, within which the KFEB has 72 days. In case of xenogenic cell therapy protocols, the deadline is 12 months (11 for the ethical approval).

**Question 23:** How are substantial amendments submitted during the review process dealt with?

The same procedure applies to all protocol amendments. Their submission follows the route of the original submission.

**Question 24:** How does a REC assess the suitability of investigators and of sites?

An MoH Decree (35/2005, see above) specifies the minimum requirements for CT sites. For example, in Phase I sites, both the Head of the site and the chief investigator must possess special postgraduate degree in clinical pharmacology. Moreover, Phase I sites must have a prior “accreditation” (based on pre-inspection) by the National Institute of Pharmacy.

Other sites should have a certificate from the National Public Health Service proving they meet the minimal requirements. The professional CV of the investigator is also part of the application.

For instance, the objective and subjective minimum requirements are specified as follows:

**Objective ones:** University Clinic or hospital or out-patient ward or Physician (M.A.) consulting room, all with Emergency Room background and adequate diagnostic facilities. The premises and equipments should meet the minimum requirements specified in another MoH Decree on the in- and out-patient wards.

**Subjective ones:** The chief investigator should have an M.A. degree in the medical discipline suitable for the intended clinical trial. Moreover, he/she should
possess M.A. degree in clinical pharmacology or a certificate of a GCP course, issued not earlier than 5 years, by a University.

Moreover, the ethics committee assesses the investigator’s CV.

**Question 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?

These data are to be submitted to and decided by the research ethics committee case by case.

**Question 26:** How are the requirements for (research) ethics committees to review the compensation arrangements for study subjects handled?

No specific requirements have been issued. The insurance contracts are subjected to both ethical (ethics committee) and professional (made by the authority) review.

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

Uniquely, KFEB must be subjected to a formal GCP inspection annually. The GCP inspectors are identical to those of the NIP, inspecting also clinical trials with IMPs. The requirement is GCP with emphasis to existing guidelines governing the activities of ethics committees (e.g. EFGCP).

**Question 28:** Is there an appeal mechanism?

The decision of the National Institute of Pharmacy on authorisation/rejection of a clinical trial application may be challenged on the Court. For the KFEB ethical review is annexed to the decision, it applies also to it (i.e., formally the NIP decision is challenged).

Note: it applies to clinical trials with IMPs exclusively. In case of other clinical trials the following rules apply:

- Non-interventional trials with IMPs: an appeal to the Medical Research Council is possible.
- Trials with medical devices: an appeal to the Minister of Health is possible, who consults also the Medical Research Council.
- Biomedical research trials: the appeal should be sent to the National Chief Medical Officer’s Office that consults as the ethics committee for appeal.
  - The Medical Research Council, if the ethics committee in the preceding procedure was the TUKEB.
  - The TUKEB is the preceding ethics committee was a regional one.
**Question 29**: How do RECs deal with SUSAR reports and Annual Safety Reports?

The above mentioned 35/2005 MoH Decree requires that they must be sent both to the NIP and KFEB. The research ethics committee procedure is not specified, they evaluated case by case.

**Question 30**: How are ‘substantial amendments’ defined?

It is specified in the above mentioned 35/2005 MoH Decree:

Article 18 para (2): “The amendment of the clinical trial protocol is classified as substantial when:

a) It may affect the safety of the trial subjects.
b) It may alter the assessment of the scientific documents supporting the trial.
c) The sponsor intends to amend the assessment results of the Investigators’ Brochure.
d) Previous trial results make the amendment of the written patient information necessary”.

**Question 31**: What are the indemnity insurance requirements for research projects?

It is specified in the 95th (human medicines) Act of 2005. The sponsor must possess an indemnity insurance to cover any health or other injury in connection with the trial. The insurance company must be within the European Economic Area.

**Question 32**: What are the indemnity insurance requirements for (research) ethics committee members themselves?

None. No responsibility of the ethics committee for its opinion to clinical trials is specified in the law.

It may be noted, the 95th (human medicines) Act of 2005 defines the regulatory authority’s indemnity if “an authoritative decision on the amendment of the original trial protocol causes health damage for the trial subject”. However, it is such a remote, theoretical possibility that the authority has no insurance for these cases.

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

It is described in the Health Care Act (see 1) in a very detail. Professional/legal representatives (in a very detailed sequence specified by the Act) give the consent on behalf of the vulnerable patient. The latter may be involved into the trial only if there is a direct benefit for them. This is the same for trials both with investigational medicinal products and other biomedical ones.
In very special urgent cases (oxiology), when the research, to all possibilities, will serve the interest of the subject, it may be done without consent.

**Question 34:** How do RECs assess the progress and outcome of research projects that they have approved?

In case of lengthy trial the committees must receive a report annually.

**Question 35:** How does the REC ensure reception of the Annual Safety Report and the Summary of the Final Report of a research project that it has approved?

It is required by law.

**Question 36:** Do national regulations in Hungary allow research on healthy volunteer children (subjects under 16)?

Yes. The prerequisites are that the research can not be conducted on adults, the legal representatives (parents) gave their consent, the child him/herself (as expectable) gave his/her consent.

**Question 37:** Do national regulations in Hungary allow payment, (other than expenses), to children taking part in research?

Payment is not possible.

Clinical trial subjects may receive payment in bioequivalence, Phase I, non-therapeutic interaction and pharmacokinetic trials, not applicable to children.

**Question 38:** Do RECs invite or allow a) applicants or b) observers to attend committee meetings?

No. Until the end of 2009 the KFEB invited the representative of the authority (the NIP) as observer (who answered also questions, if any). However, the recent legislative changes that have given KFEB co-authority status excluded that (the authority may not be present when the co-authority makes its assessment).

**Question 39:** Are the minutes of (research) ethics committee meetings made public?

No.

**Question 40:** Is there any scope for Chairman’s actions in between meetings?

See question 13: Bioequivalence, Phase IV clinical trials, protocol variations and any other urgent cases decided by the Chairperson are not discussed by the whole KFEB. A “quorum” of a five members (healthcare professionals and laymen) acts in these cases.
**Question 41:** Do (research) ethics committees ever appoint sub-committees for any specific purpose?

Yes, see question 13.

**Question 42:** Is there a national policy on the registration of clinical trials before they start?

Not national. All clinical trials (with IMPs) should be registered in EudraCT.

**Question 43:** If the answer to Question 42 is ‘yes’, do (research) ethics committees have any role to play in reviewing such registration?

No.

**Question 44:** If the answer to Question 42 is ‘yes’, is this register of clinical trials made available to the public?

Not at present. After the decision of the public part of EudraCT will this issue be addressed nationally.

*EFGCP May 2011*