Question 4

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

<table>
<thead>
<tr>
<th>Austria</th>
<th>Hungary</th>
<th>Romania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>Iceland</td>
<td>Russia</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Ireland</td>
<td>Serbia</td>
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<td>Croatia</td>
<td>Italy</td>
<td>Slovakia</td>
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<tr>
<td>Cyprus</td>
<td>Latvia</td>
<td>Slovenia</td>
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<tr>
<td>Czech Republic</td>
<td>Lithuania</td>
<td>Spain</td>
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<td>Denmark</td>
<td>Luxemburg</td>
<td>Sweden</td>
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<td>Estonia</td>
<td>Malta</td>
<td>Switzerland</td>
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<td>Netherlands</td>
<td>Turkey</td>
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<td>France</td>
<td>Norway</td>
<td>United Kingdom</td>
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<td>Germany</td>
<td>Poland</td>
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<tr>
<td>Greece</td>
<td>Portugal</td>
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Austria

The sponsor of the Clinical Trial submits the application to the competent ethics committee (EC) and the competent authority (CA).

The CA reviews only the justification for and the relevance of the Clinical Trial.

The EC acts as the “expert reviewer” for the CA and decides within 35 days, with only one “clockstop” possible to obtain supplementary information.

If the EC vote is negative, the CA issues a legal document (“Bescheid”) prohibiting the clinical trial.

The website for the CA is at http://www.ages.at.

Belgium

The investigator submits the application to the ethics committee(s) of the research sites, which has (have) in principle 28 days to respond (with the possibility of one clock-stop for questions), 15 (fifteen) days for phase 1 trials. The ethics committee has to give a written reply.

Bulgaria

The Bulgarian Drug Agency is the responsible body for accreditation and oversight of ethics committees in Bulgaria. All trials are approved by the local ethics committee at the trial site, regardless of the specificity of the trial.

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=en.

For clinical investigations of medicinal products in the paediatric population, the sponsor (the financing body for the trial) is required 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 required to supply a positive opinion of the Psychiatry Committee of the Ministry of Health.

The Central Ethics Committee is required to provide its opinion (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, the Agency for
Medicinal Products and Medical Devices of Croatia (HALMED), plus the Pharmaceutical Inspectorate for clinical trials on drugs.

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 as described here.

**Cyprus**

The website of the Cyprus National Bioethics Committee is: [www.bioethics.gov.cy](http://www.bioethics.gov.cy)

Below is the flowchart for a clinical trial approval by the CNBC.

**Czech Republic**

The opinion of an ethics committee (EC) should be sought for any CT or biomedical research project to be conducted in the Czech Republic.

Single-site trial ethical review is done by the relevant local ethics committee; multi-site clinical trial ethical review is done by an ethics committee for multi-site studies (MEC) (and also by each of the local ECs).
Denmark

An application (in Danish) is made by the investigator to the appropriate regional scientific ethical committee, depending on the location of the principal site for the clinical trial. Detailed guidance on the ethical review process is available in English on the website of the Danish National Committee on Biomedical Research Ethics at http://www.cvk.sum.dk/English/guidelinesaboutnotification.aspx.

Estonia

The application for a clinical trial must be submitted to the secretary of the (research) ethics committee (EC) at least 10 days before the EC meeting, held in every month. The relevant parts of the application are sent to all EC committee members and the research project will be discussed at the next meeting of EC. If there are questions or problems they will be presented to the principal investigator (study coordinator), the answers will be revised and if there are relevant changes they will be discussed on the next meeting. The committee has to give a decision within 60 days after the submission of all documents. Upon application for the clinical trial of a medicinal product, gene therapy, cell therapy or an immunological medicinal product as well as using a genetically modified organism, the Committee shall make a resolution within 90 days.

Finland

The first step in all clinical trials is for the sponsor to apply for a ruling from TUKIJA on whether the ethical admissibility of the proposal is to be reviewed by TUKIJA or by one of the regional ethics committees. Sponsors can apply for a ruling on jurisdiction as soon as it becomes likely that the trial in question will be run in Finland, even if the actual application is not yet complete. Depending on the ruling, the sponsor then applies for an ethics review to be carried out either by TUKIJA or by the relevant regional ethics committee.

The Finnish Ministry of Social Affairs and Health has produced a form to be used in connection with rulings on jurisdiction. The same form is used both by the applicants and by TUKIJA. Applicants are also requested to submit their applications to TUKIJA’s secretary in electronic format (as pdf or rtf files) by e-mail to tukija(at)valvira.fi


Depending on the ruling, the sponsor then applies for an ethics review to be carried out either by TUKIJA or by the relevant regional ethics committee. All applications for ethics reviews of clinical trials must be made using the form issued by the Finnish Ministry of Social Affairs and Health according to the instructions provided. The documents listed on the form must be included in all applications.

All documents pertaining to trials must be submitted to TUKIJA no later than two weeks before the meeting during which the proposal in question is to be reviewed.
France

Clinical trial sponsors have to submit their protocols both to the competent regional ethics committee (CPP), and to the competent authority. These submissions can be either simultaneous or one after the other.

The authorisation to conduct a trial requires both the E.C. (CPP) approval and the competent authority authorization.

No clinical trial will ever start without a CPP approval. This committee evaluates the different parts of the protocol, in line with the requirements set out in the Directive. The CPP sends its written and argued advice within 35 days to the sponsor. This advice is also sent for information to the competent authority.

The CPP has 35 days from the reception of the protocol to give a written argued advice. Lack of advice after the deadline is considered as a refusal. If the CPP needs more information about the research, it can ask the sponsor only on time, the delay for advice sis 60 days.

The competent authority acknowledges receipt of the protocol and informs the sponsor of the date after which in the absence of any remark, the trial can begin (silent approval).

The competent authority is allowed to ask sponsors additional information or to have reservations. These questions are transmitted to the CPP.

The list of CPP is available at http://www.recherche-biomedicale.sante.gouv.fr.

The French licensing authority is the Agence Française de Sécurité Sanitaire des Produits de Santé. Its website is at http://www.afssaps.fr.

Germany

The sponsor must submit a request for a favourable opinion to the competent REC; the request has to contain the elements of the GCP Decree for trials with pharmaceutical drugs and of the MPKP Decree for trials with medical devices:

- In general the REC of the regional Medical Association to which an investigator is attached, is the competent REC, according to States legislation. In few States, RECs are attached to the Local Government. For studies conducted by an investigator attached to a university, in several states the REC of the Faculty of Medicine is the competent REC.
In a multicenter trial, the sponsor nominates one investigator as the lead investigator (Leiter der klinischen Prüfung, LKP). Then the REC of this LKP becomes the master REC which combines the opinions of the local RECs into a single opinion.

There is no central REC for the review of individual biomedical projects.

The members of the “Deutscher Ethikrat”, as established by legislation of the “Deutscher Bundestag” on April 26, 2007, are appointed by the “Deutscher Bundestag”. The “Deutscher Ethikrat” may give general ethical recommendations which are not binding and which only seldom apply to research and the work of the research ethics committees.

There is also the Central Ethics Committee of the German Medical Association (Zentrale Ethikkommission bei der Bundesärztekammer) which gives opinions on general ethical issues and which may give advice to the Ethics Committees of the Medical Associations at their request. Again, the advice is not binding on the research ethics committees.

**Greece**

*NB For Greece these questions 3 and 4 are most appropriately answered together.*

In order to conduct a clinical trial in Greece the application must be submitted to the Competent Authority (EOF) and a separate application must also be submitted to the National Ethics Committee (NEC). EOF issues an authorisation for the conduct of the clinical trial, provided that NEC has given a positive opinion.

The website of the Greek Competent Authority (EOF) is at [http://www.eof.gr](http://www.eof.gr).

**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.

Question 4 - 6
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 EKHP. However, the EKHP’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 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.

**Iceland**


**Ireland**

The chief investigator must apply for an ethics committee opinion to a single ethics committee recognised by the Ethics Committees Supervisory Board, in writing, accompanied by the details set out in Article 8 of the Directive 2001/20/EC, and the appropriate fee.

The list of recognised ethics committees in Ireland is available on:
Italy

For all the trials, even for those authorised by a central Competent Authority, the sponsor needs to obtain:

1. The single opinion released, within 30 days from the receipt of the clinical trial application, by the Ethics Committee of the clinical site of the coordinating investigator and then, the acceptance or refusal of the single opinion released by the Ethics Committees of the satellite clinical sites, within 30 days from the receipt of the single opinion.

2. The financial agreement between the Legal Officer of each clinical site, or a person appointed by him, and the sponsor.

In order to start a clinical trial, a sponsor must enter the data into the web-based database of the "Osservatorio Nazionale per la Sperimentazione Clinica" (National Monitoring Centre for Clinical Trials) [http://oss-sper-clin.agenziafarmaco.it/normative_ingl.htm] established at the Italian Medicines Agency. At the end of the electronic procedure it is possible to print the data entered into the OsSC and the result will be a Clinical Trial Application (CTA) form, in Italian, to submit to the Competent Authority and the Ethics Committee, respectively, for authorization and opinion.

Latvia

The sponsor should submit an application both to the ethics committee and to competent authority (State Agency of Medicines). A clinical trial cannot be started without a positive decision from an ethics committee and without authorization from the State Agency of Medicines.

The website for the State Agency of Medicines is at http://www.zaale.vza.gov.lv.

Lithuania

The sponsor or the principal investigator must apply to the LBEC for obtaining ethical review of a clinical trial protocol. In this case, the LBEC shall get the opinion of the regional biomedical research ethics committee(s) of the region(s) where research will be carried out. The examination of the clinical trial shall be undertaken by Kaunas Regional Biomedical Research Ethics Committee if it is planned to be conducted in Alytus, Kaunas, Klaipeda, Marijampole, Taurage and Telsiai district regions and/or by Vilnius Regional Biomedical Research Ethics Committee if it is planned to be conducted in Vilnius, Utena, Panevezys and Siauliai district regions.

Luxemburg

- Synthetic descriptive sheet, downloadable on the CNER website.
The EFGCP Report on
The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe
(Update: April 2012)

- Study protocol as well as all amendments with their respective dates.
- Patient information sheet and informed consent form in French and German. If the study involves genetic material analysis, the informed consent form must be divided in two parts, so that the participants can sign once to consent to the main study and a second time if they want to partake in the genetic study. In the case where patients' personal data would need to be stored, the storage length would need to be given in the informed consent form / information sheet.
- Subject recruitment procedures.
- Investigator brochure with all information concerning the safety and pharmaceutical quality of the product.
- Information concerning the financial aspects of the study, as well as the financial contract signed by the sponsor and the principal investigator.
- Insurance certificate.
- A recent curriculum vitae of the principal investigator.
- Patient questionnaires.
- Other documents specifically demanded for a study by the CNER.
- Electronic version of the documents (on CD-Rom, by email or on a USB key).

Malta

In order to conduct a clinical trial in Malta the application must be submitted to the Medicines Authority and a separate application must also be submitted to the HEC (clarifications may be sought by the sponsor before an application is formally submitted). Following successful validation, each body generally has a 60 day period to assess the application (excluding clock-stops). A clinical trial may start if both the Health Ethics Committee and the Medicines Authority have separately issued an authorisation.

The Regulations can be accessed on http://www.doi.gov.mt.

The website of the Maltese Medicines Authority is at: http://www.medicinesauthority.gov.mt/.


Netherlands

Only accredited research ethics committees (METCs or the CCMO) can review biomedical research with human subjects. The criteria for accreditation are laid down in the WMO. In short a research ethics committee has to fulfil the minimal composition, has to have standing orders and SOPs in which their operations are described and has to review on average 10 research protocols per year or more. The Central Committee (CCMO) is responsible for the accreditation and oversight of the accredited research ethics committees. If an METC no longer fulfils the criteria, the accreditation can be withdrawn by the Central Committee.
Norway

Application is made to the relevant Regional Ethics Committee using a form that is available on the following website: http://www.etikkom.no/Engelsk/NEM/REK. An English translation is available.

Poland

The Chief Investigator, or the Co-ordinating Investigator, must apply for a Bioethics Committee opinion to the appropriate committee depending on his or her place of work and the site at which the trial is to be conducted. The process for obtaining ethical review of a clinical trial protocol contains of the following steps:

1. An expert (or experts if necessary) chosen by the Chairman of the REC is (are) obliged to prepare a preliminary opinion about clinical trial.
2. All REC members are notified about the preliminary opinion (usually the preliminary opinion is red during the REC session).
3. There is a discussion about main topics (risks, rationale, scientific value, quality of documents) of the clinical trial.
4. Main investigator is invited for interview.
5. Main investigator leaves the session and discussion keeps going.
6. Main investigator is invited again and informed about conditions and amendments which should be implemented into the project (if it is necessary). The main investigator has the right to accept proposed changes or to reject them.
7. Than main investigator leaves the session again and members ballot for or against the project (positive opinion means majority of positive votes).
8. Main investigator is invited again and the final opinion about the project is announced.
9. Negative opinion of the REC might be appealed to the Appeal REC in the Ministry of Health.
10. The Appeal REC repeats the whole process of evaluation and its decision (opinion) is final.

Portugal

The sponsor requests an opinion from the National Research Ethics Committee – CEIC according to the guideline available on the website http://www.ceic.pt.

Romania

According to detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use - NMA SCD No. 50/2006.
Russia

The sponsor should submit an application both to the Competent Authority (Scientific Centre for the Evaluation of Products for Medical Use) and the Council on Ethics of Ministry of Health and Social Development. A clinical trial cannot be started without a positive decision from both of these bodies.

The sponsor is responsible for submitting the request to the Council on Ethics of Ministry of Health and Social Development and the principal investigator is responsible for submitting the request to the local research ethics committee.

Serbia

The sponsor/CRO or principal investigator of the clinical trial submits the application to the relevant LEC. The LEC acts and decides, usually within 35 days.

Slovakia

An opinion of the ethics committee (EC) should be sought for any CT or biomedical research project, to be conducted in Slovakia, and the necessary authorization is granted only after positive opinion from EC has been obtained. It should be asked for and the necessary documents sent by the sponsor to:

a) For a single-site clinical trial: the EC of the health care facility or research institution, where the trial is to be conducted.

b) For a multi-site trial:

   ba) Conducted solely in the inpatient institutions: the EC of one of the involved institutions, chosen and specifically asked by the sponsor to issue “a single opinion” as required by Dir. 2001/20/EC (usually this is the EC of the institution of the country coordinator of the trial).

   bb) Conducted in the outpatient facilities: the regional EC, chosen and specifically asked by the sponsor to issue “a single opinion” as required by Dir. 2001/20/EC (as described in 12).

   bc) Conducted both in the inpatient and outpatient facilities: the regional EC, chosen and specifically asked by the sponsor to issue “a single opinion” as required by Dir. 2001/20/EC (as described in 12).

However, to help the consultation process of the chosen EC with the ECs responsible for all sites involved, it is advisable to the sponsor to submit the necessary documents for ethics review to all ECs responsible for the sites involved.

Slovenia

The project proposal should be submitted to the NMEC. Guidelines (also in English) for preparation of the application are available at the NMEC web-site http://www.mf.uni-lj.si/kme-nmec. Ethical review is done by the NMEC. The proposal is reviewed by at least one rapporteur (see SN, paragraph 5). Decisions are taken at
monthly meetings. Their decisions are sent to the applicants by post well within 60 days of the receipt of application. The decision of NMEC should be sent by the applicant to the CA when available.

**Spain**

As already mentioned the process to get a single opinion when the CT is intended to be performed in several sites under the area of influence of more than one CEIC is detailed in annex 2 of the document “Aclaraciones….”. In these cases, the CT application must be submitted at the same time to all the CEICs in the area of influence of the sites where the trial will be performed (from the 1st to the 5th day of the month). It is recommended to submit the application to the AEMPS at least two or three weeks after the CT is submitted to the CEIC. One CEIC is the “lead Committee”, and the rest are the so-called “local Committees”. There is a common CT register for CEICs where all local Committees must provide their comments on the protocol. Finally, after assessing the comments from all the local Committees, the “lead CEIC” provides the final “single opinion”.

**Sweden**

Application is made to the relevant EC (Board for Ethics Review) using a form that is available on the website [http://www.epn.se](http://www.epn.se). An English translation is available.

**Switzerland**

Projects are submitted for review to the authorized REC of the investigator.

**Turkey**

1) The application dossier for a clinical trial will be prepared according to the Guideline for Good Clinical Practice and other applicable guidelines, using the application form and its relevant annexes posted on the Ministry’s website, and will be reviewed for Ministry permission and ethics committee approval according to this Regulation and the guidelines to be issued by the Ministry.

2) In multi-center clinical trials, the scientific and ethical approval will be obtained of the ethics committee in the locality where the coordinating center is located. Notifications will be made to ethics committees in places where the other sites are located.

3) The application for a clinical trial will be made to the relevant ethics committee or general directorate 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.

4) Applications to obtain Ministry approval for conducting a clinical trial that have been granted ethical and scientific approval with any substances or products which and which may involve investigation in human beings, including clinical trials with medical devices, BA/BE trials, comparability studies for biosimilar products, Phase I, Phase II, Phase III and Phase IV drug clinical trials, clinical trials with advanced therapy medicinal products, observational studies with drugs, observational studies
with medical devices, clinical trials with traditional herbal medicinal products and cosmetic products or raw materials, will be made to the General Directorate of Pharmaceuticals and Pharmacy. a) For clinical trials with Class III medical devices or with implants or long-term invasive devices in Class IIa or Class IIb, the study sponsor or a contract research organization delegated by the sponsor will, upon the approval of the ethics committee concerned, make an application to the General Directorate of Pharmaceuticals and Pharmacy, and the application will be evaluated within sixty days after the notification date. b) For all clinical trials with medical devices, excluding the ones mentioned in subparagraph (a), and all other drug clinical trials will be evaluated within not more than thirty days by the relevant general directorate.

5) Applications to obtain Ministry approval for conducting clinical trials with industrial advanced medicinal products or non-industrial advanced medicinal products, gene therapy clinical trials, stem cell transplantation trials, organ or tissue transplantation trials and clinical trials with a novel surgical procedure which have been given scientific and ethical approval will be made to the General Directorate of Health Services. These applications will be evaluated within not more than sixty days.

6) If the general directorate concerned adopts an unfavorable decision regarding the request for conducting the clinical trial, this decision will be notified to the applicant, together with the rationale for the decision. The sponsor will be granted a single opportunity to resubmit the application after making amendments to address the issues raised in the decision, or to file a reasoned objection against the decision. If the requested changes are not fulfilled or an acceptable justification cannot be offered, the general directorate concerned may reject the clinical trial.

7) In the case of clinical trials with cellular therapies using products containing genetically modified organisms or products involving gene therapy, the thirty days specified for Ministry approval may be extended for an additional thirty days. However, in cases where it becomes necessary to hold detailed deliberations or to consult non-Ministerial third party experts, the timeline may be extended further by an additional ninety days, depending on the subject matter of the study.

United Kingdom

The Chief Investigator must apply for ethics committee opinion to a recognised ethics committee, depending on the type of trial. Application must be made via the on-line Integrated Research Application System (IRAS) provided on behalf of all partner organisations by the Health Research Authority. IRAS captures all information a researcher needs to submit for the relevant permissions and approvals to enable the conduct of health and social care research:
https://www.myresearchproject.org.uk/Help/UsingIRAS.aspx

MoDREC has its own application procedures at present but consideration is being given to adopting IRAS. For all other RECs in the UK, application is made using IRAS.

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