Question 12

How is a “single opinion” achieved for multi-site studies?

Austria
Belgium
Bulgaria
Croatia
Cyprus
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece

Hungary
Iceland
Ireland
Italy
Latvia
Lithuania
Luxemburg
Malta
Netherlands
Norway
Poland
Portugal

Romania
Russia
Serbia
Slovakia
Slovenia
Spain
Sweden
Switzerland
Turkey
United Kingdom
Austria

The new Austrian drug law has changed the situation. Since the implementation of the EU Directive a single opinion procedure is possible, but is only required for clinical trials with drugs. Currently there are 7 Ethics Committees (Leitethikkommissionen) entitled to achieve “one single opinion”, nominated by the Health Authorities. They are the three Ethics Committees of the Medical Universities (Vienna, Graz and Innsbruck), the Ethics Committee of the City of Vienna (which is serving the Vienna public hospitals), the Ethics Committee of Lower Austria, the Ethics Committee of Upper Austria and the Ethics Committee of Salzburg.

The procedure for “one single opinion” is as follows:

The sponsor chooses the multi-site Ethics Committee, which has to be competent for one of the sites undertaking the multi-site study; if there is no such committee at any of the sites where the study is to be conducted, the sponsor chooses freely from one of the seven recognised Leitethikkommissionen. The sponsor submits the same application documents to local Ethics Committee as to multi-site Ethics Committees but local Ethics Committees are not included in the review procedure. The local Ethics Committees may provide an opinion regarding the suitability of the site and the qualification of the investigators to the multi-site Ethics Committee.

The Leitethikkommissionen can refuse submission if its current workload is too big.

The multi-site Ethics Committee decides within 35 days, with only one “clockstop” permitted. If the vote is negative, the competent authority issues a legal document prohibiting the clinical trial.

Belgium

The single opinion is given by one of the ethics committees: the choice is that of the investigator, but there are some restrictions (priority for certain ethics committees).

Bulgaria

The Specialized Committee for Authorization of Performance of Clinical Trials achieves a single opinion through the final approval of all trials.

Croatia

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 (that has already received a written positive decision from Central Ethic Committee and Minister of Health for another site) are required to submit a clinical trial application request with all relevant documentation to the Central Ethics Committee and Ministry of Health for approval.
Cyprus

Only one application must be submitted for all research sites in the Republic of Cyprus.

Czech Republic

A single opinion for the Czech Republic is made by an MREC and SUKL provides EMEA this information. In the case of a negative local REC opinion, that is valid only for the relevant site. Currently the sponsor can choose which MREC for multi-site studies.

Denmark

The co-ordinating chief investigator submits an application for a multi-site study to the Regional Committee on Biomedical Research Ethics for the area in which he/she is operating. This regional committee must make up its decision, which forms the basis for the “single opinion”, and then inform other regional committees for the investigators at the other sites involved.

Estonia

In accordance with the Medicinal Products Act the single opinion is mandatory. There is no experience of a situation when applications were submitted to both ECs.

Finland

According to the Medical Research Act each medical research study needs only one opinion of a research ethics committee. In the Medical Research Act it is stated that the study is evaluated in the REC of the region where the person in charge of the research (principal investigator) works or where the majority of the research is performed.

France

The sponsor chooses a national coordinating investigator and then submits the protocol to a CPP of they investigator’s region: the advice of the CPP is valid for all sites.

Germany

The REC of the coordinating investigator becomes the master or coordinating REC is responsible for the assessment of the project. This assessment is achieved in cooperation with all RECs who assess qualification of local sites and investigators and whose assessment regarding their local sites and investigators should be respected by the coordinating REC. The local RECs may also comment on the protocol, but the coordinating REC is exclusively responsible for the decision on the content, i.e. the single opinion.
Greece

From the Greek NEC.

Hungary

There are single opinions exclusively.

Iceland

Art. 5 in Reg. 286/2008, reads: “The National Bioethics Committee shall consider collaborative projects, multi-national research projects, clinical pharmaceutical research projects subject to the provisions of the Regulations on Clinical Pharmaceutical Research on Human Beings no. 443/2004, and other planned scientific studies in the biomedical field, which are not within the mandate of ethics committees under Art. 4”.

Ireland

A single application for ethical review is made to a recognised ethics committee by the chief investigator who, in that single application, will list any other investigator taking part in that clinical trial anywhere in Ireland. No site-specific assessment is carried out by any other body. However, it is still possible for an institution responsible for a site at which a trial is to be conducted, to insist that the trial be reviewed on its behalf before it may be conducted at that site.

Italy

The single opinion is expressed by the Ethics Committee of the facility in which the coordinating investigator works and will either be: a) favourable; or b) not favourable. In the case of b), the sponsor of clinical trial cannot apply to another Ethics Committee. If the sponsor modifies the elements of the clinical trial application in accordance with the reasons of the Ethics Committee for non-approval, he/she may apply again to the same Ethics Committee in order to obtain a new opinion. If the sponsor intends to conduct a multi-centre trial, application has to be made to the Competent Authorities and the Ethics Committees of the sites involved. The Ethics Committees of the collaborating sites have to send their comments, favourable or not favourable, within 30 days to the coordinating Ethics Committee without making any changes regarding the protocol. The Ethics Committees of the participating sites may only change the informed consent form according to the policies of the institution.

Latvia

There are no special provisions for the procedure, but in practice any one of the ethics committees acts as the provider of a single opinion.
**Lithuania**

The Lithuanian Bioethics Committee (LBEC) is the main institution responsible for bioethics policy in Lithuania and it is also responsible (among other functions) for the ethical review of multi-site biomedical research projects (including clinical trials on IMP), issuing the single opinion for the country. The LBEC is established by and is accountable to the Ministry of Health.

According to the Law on Ethics of Biomedical Research, Regional Biomedical Research Ethics Committees are established at the universities where medical studies of three levels take place. Currently there are two Regional Biomedical Research Ethics committees in Lithuania: in Kaunas region (based at Kaunas Medical University) and in Vilnius region (based at Medical faculty of Vilnius University).

The activities of the Regional Biomedical Research Ethics committees are monitored by the LBEC.

**Luxemburg**

The CNER, which is the only REC to which the documents have to be submitted, delivers a single opinion which is valid for all Luxemburgish investigational sites.

**Malta**

There is only one HEC in Malta.

**Netherlands**

In general the accredited METC to which the chief investigator relates is designated the Reviewing METC. But sponsors can in principle choose any accredited METC that meets the requirements. The sponsor is responsible for obtaining the local feasibility declarations from the participating institutes. The directors of the participating centres (and thus not the METC’s in the institutes) are responsible for the local feasibility declaration. It is to the discretion of the hospital director whether he/she asks advice from his METC before signing the local feasibility declaration.

**Norway**

A decision from any of the five Regional Ethics Committees will form that single opinion (only one Committee needs to review any clinical trial for an investigational medicinal product; which one depends on the location of the Chief Investigator).

**Poland**

The Co-ordinating Investigator is identified and the appropriate Bioethics Committee for that investigator provides the “single opinion”. The study sponsor (i.e. the
pharmaceutical company) selects a national coordinator for a multicenter clinical trial. Bioethics committee to which national coordinator is subordinated will review the multi-site clinical trial’s protocol – Art.37s of the Polish Pharmaceutical Act. (According to Polish law, the study sponsor is responsible for selecting a national coordinator for a multi-site clinical trial).

A site specific assessment is sought from the relevant Bioethics Committees for any other investigators and centres in Poland and is required within 14 days of the request for information. However, a passive approval process is in operation and no response is regarded as a favourable response.

**Portugal**

The National Research Ethics Committee (CEIC) is responsible for a single opinion.

**Romania**

Only the NECCT can approve multi-site studies.

**Russia**

The only committee that provides the single opinion for Russia is the Council on Ethics of Ministry of Health and Social Development, responsible for review of Protocols on a national level.

**Serbia**

There is no single opinion facility for multi-site studies. There is no central EC in Serbia.

**Slovakia**

The single opinion is given by one ethics committee which is chosen by the sponsor. This is usually the ethics committee of the institution where the co-ordinating investigator is located. This ethics committee, however, is required by law, before giving its opinion, to consult ECs of all centres involved in the clinical trial.

In practice, to save time, it is recommended that the sponsor should submit the protocol and related materials to all the (research) ethics committees concerned. Local ECs should focus on solely local aspects of the clinical trial; however, they may make comments or suggestions concerning any scientific or ethical aspect of a CT protocol. A negative opinion from a local EC means that the clinical trial cannot be conducted at that facility/institution. Whenever a single opinion is positive, the clinical trial may be conducted in any centres whose local ECs have also given a positive opinion.

For CTs conducted in outpatient physicians’ offices, an opinion of a “regional” EC should be sought (located at the regional state authority).
The EFGCP Report on
The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe
(Update: April 2012)

Slovenia

As there is only one ethics committee for the approval of IMPs, the NMEC, it always provides the single opinion.

Spain

For multi-site trials, the application must be submitted to all the CEICs where the trial will be performed at the same time (from the 1st to the 5th day of the month). One CEIC is the “lead Committee”, and the rest are the so-called “local Committees”. There is an informatics application through Internet where all local Committees must provide their comments to the Protocol. The “lead CEIC” provides its final “single opinion”, after assessing the comments from all the local Committees.

Sweden

A decision from any Regional Boards for Research Ethics Review will form that single opinion (only one Board needs to review any clinical trial for an investigational medicinal product; which one depends on the location of the Chief Investigator).

Switzerland

The Lead Ethic Commission makes the ethical decision on the study. The secondary REC’s can accept or refuse this decision or eventually add locally determined minor supplements.

Turkey

First step: EC approval
Application is made to the related Ethics Committee for the purpose of receiving approval scientifically and ethically for clinical trials.
According to kind of clinical trial, application is made to the related Ethics Committee with the application form and cover letter samples prepared considering the appropriate application form and application cover letter samples published at the website of General Directorate for Pharmaceuticals and Pharmacy (www.iegm.gov.tr).

Second step: MoH permission
Permission of the Ministry is required to commence a clinical trial that has been approved by an ethics committee. The study sponsor will make an application to the General Directorate of Pharmaceuticals and Pharmacy to obtain permission of the Ministry.

In order to receive Ministry permission after the received scientific and ethical approval application is made to General Directorate for Pharmaceuticals and Pharmacy for clinical trials to be conducted with medical devices, for bioavailability/bioequivalence (BA/BE) studies, for comparability studies of bio-similar products, for Phase I, Phase II, Phase III, and Phase IV drug clinical trials, for clinical trials to be conducted with advanced treatment medicinal products, for observational drug studies, for
observational medical device studies, for efficacy and safety studies to be conducted with cosmetic raw materials or products, and for clinical trials to be conducted with traditional herbal medicinal products.  
In order to receive Ministry permission following scientific and ethical approval, for clinical trials to be conducted with non-industrial advanced medicinal products application is made to General Directorate of Treatment Services for clinical trials to be conducted with industrial advanced medicinal products, for gene treatment clinical trials, for stem-cell transplantation trials, for organ and tissue transplantation trials, and for new surgery method trials.

**United Kingdom**

A single application for ethical review is made to an appropriate REC by the Chief (or co-ordinating) Investigator (CI). This REC is known as the “main REC” for the study.

Each site and local Principal Investigator (PI) in a clinical trial requires a Site-Specific Assessment (SSA). The local Principal Investigator is required to submit a Site-Specific Information Form with their CV for review by an appropriate local assessor.

For sites within the NHS, arrangements the SSA is carried out by the local NHS R&D office for the care organisation, as part of standard R&D review, prior to giving local management permission for the research. A standard condition of any favourable opinion from the main REC is that permission must be given by the NHS R&D office before the site is initiated. There is no requirement for the outcome of the R&D review to be notified to the main REC or for the REC to confirm the favourable opinion for the site. The favourable opinion will be in place once permission is given by the R&D office. R&D review may take place in parallel with the ethical review by the main REC.

For sites outside the NHS, the SSA is undertaken by a local REC, which will advise the main REC for the trial within 25 days (or 14 days for a Phase 1 trial) whether there are any concerns about the suitability of the site or investigator. The main REC will then confirm that the favourable opinion is extended to the site. The SSA can take place in parallel with the main ethical review.

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