Spain

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

The Spanish legislation concerning clinical trials on investigational medicinal products (CTIMPs) is:

Medicinal Product and Medical Devices Act 29/2006, of July 26th (Official Diary of December 27th, 2006, no. 178), as developed by “Real Decreto 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos”, published in the Official Diary of 7th February 2004, No. 33. Finally, the “Orden SCO/256/2007, de 5 de febrero, por la que se establecen los principios y las directrices detalladas de buena práctica clínica y los requisitos para autorizar la fabricación o importación de medicamentos en investigación de uso humano” (Official Diary of February 13th, 2007, no. 38), addresses GCP, manufacturing and importation of investigational medicinal products for human use.

It is also of interest in the document: “Aclaraciones sobre la aplicación de la normativa de ensayos clínicos desde el 1 de mayo de 2004”. This document has several annexes and gives practical information on the content of a CT application for authorisation submitted to the Spanish Agency for Medicines and Medical devices and on the content of a CT application for an opinion to a Research Ethics Committee (Comité Ético de Investigación Clínica – CEIC) and the processes to obtain them. In this respect, annex 2 clarifies the process to get a single opinion by the CEIC on a CT performed in more than one site in Spain. All CEICs having an accreditation in Spain are shown in annex 4. This document also gives information on how expedited SUSAR reporting should be done.

The above mentioned legislation can be accessed at [www.aemps.gob.es](http://www.aemps.gob.es), then the first link "Investigación clínica", the second link "Investigación clínica con medicamentos" and then the third link "Ensayos clínicos con medicamentos de uso humano". On the same website the legislation on non-interventional trials can be is accessed using the same second link "Investigación clínica con medicamentos", then the different third link "Estudios posautorización de tipo observacional con medicamentos de uso humano". Finally, legislation on clinical trials with medical devices can be accessed
on the first link "Investigación clínica", then the second link "Investigación clínica con productos sanitarios".

**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?

The Chapter III of the Real Decreto 223/2004 states the general composition of the Research Ethics Committees (CEICs), their minimal requirements, and a general definition of their SOPs.

Also in article 9, a Coordinator Centre for CEICs is stated as a contact point to get further information on how the CEIC network operates in Spain. Contact details can be found at the Centro Coordinador de CEIC, Paseo del Prado, 18 – 20; 28071 Madrid (España) [http://www.mspsi.es/profesionales/farmacia/ceic/home.htm](http://www.mspsi.es/profesionales/farmacia/ceic/home.htm).

The Health Authorities in the Autonomous Regions (there are 17 all over the country) have the competence of accreditation of the CEICs. In some regions there is a unique Committee (i.e. Galicia, Navarra, Aragon, Cantabria, I. Baleares, Asturias, La Rioja). In other regions there are many Committees, mainly located in Hospital centres (e.g. Catalunya), and, finally, in other regions (i.e. Madrid, Andalucia, País Vasco) there are both, Regional and Hospital Site Committees.

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

The sponsor submits the application to the competent authority, the Spanish Agency for Medicines and Medical Devices (Subdirección General de Medicamentos de Uso Humano. Área de Ensayos Clínicos. Agencia Española de Medicamentos y Productos Sanitarios - AEMPS). Within 10 days of receiving the CT application, the sponsor gets a letter indicating the validity of it and the assessment schedule, or a letter indicating the reasons why the application is not valid. The maximum assessment periods in the AEMPS are 60 days in general, and 90 days for those clinical trials referring to cell or gene therapy and GMO medicinal products.

The AEMPS needs a favourable opinion from the appropriate CEIC and the letter of conformity by the management board of at least one site stated in the opinion by the CEIC before the authorisation can take place. In addition, the CEIC, but not the AEMPS, has a clock stop in the assessment period starting when clarifications are requested, until the sponsor answer is received. Taking into account all this, it is recommendable that the CT is submitted to the CEIC 2 or 3 weeks in advance of the date of submission to the AEMPS.

Once a CT is authorised, the sponsor must notify the AEMPS that the management board of the site approves starting the trial in that site.
**Question 4:** What is the process for obtaining ethical review of a clinical trial protocol by a competent (research) ethics committee in 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”.

**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?

No.

**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?

http://www.aemps.gob.es (website of the Spanish Medicines Agency)
http://www.msc.es (website of the Spanish Ministry of Health)

The CT register/informatics application for CEIC has a library facility where they share documents. The access is restricted to the CEICs.

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

Currently, the AEMPS gets a copy of the CEIC opinion by e-mail at the same time as the sponsor, when the CT is multi-site. Occasionally, the AEMPS gets into contact with the CEIC where there is a relevant topic for discussion. However, the communication process is expected to be improved in the near future, in order to ensure that the AEMPS receives the CEIC opinion, and the relevant CEICs receive the AEMPS final decision in both cases by a systematic and automatic communication process.
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?

Legislation allows the submission in parallel. However, it is recommended to submit the application to the Spanish Agency AEMPS at least two or three weeks after the CT is submitted to the CEIC. This is in order to ensure that the AEMPS has the CEIC opinion before the deadline for the CT authorisation.

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

There are one hundred and thirty six EC. They are periodically updated in the previously mentioned annex 4 of “Aclaraciones…”.

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

Institutions responsible for the CEICs provide funding (i.e. Regional Governments and Public Hospitals) at different levels. Most of the CEICs charge fees for reviewing protocols. Fees vary, ranging from 300 € to 1200€ per protocol.

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 person responsible is the sponsor or someone specifically designated to make the submission.

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

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.

Question 13: How many members serve on a REC?

By law, the minimum number of members of a CEIC is nine. The mean is around fourteen.

Question 14: How many members constitute a quorum?

A quorum is constituted when 50% plus one of the appointed members is present.
**Question 15:** How are REC members appointed?

By the Regional (Autonomous) Government.

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

There is a declaration of conflict of interests, signed by each member.

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

Members are obliged to declare any conflict of interest.

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

Legislation has established that the CEIC shall consist of at least nine members to guarantee the independence of its decisions and ensure that it has the qualifications and experience to review the methodological, ethical and legal aspects of research, pharmacology and clinical care practice in both hospital and community medicine. Its members shall include physicians, one of whom shall be a clinical pharmacologist; a hospital pharmacist and a registered nurse.

At least one member should be independent of the sites where research projects requiring ethical evaluation by the committee are to be conducted.

At least two members must be professionals outside the field of health care, one of whom should have a degree in law.

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

Specialist expertise is obtained by agreeing on suitable experts.

**Question 20:** What are the training requirements for members of RECs?

None are laid down.

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

Nowadays training programmes are not standardized. Currently, the CC-CEIC and the Health Authorities responsible for the CEICs accreditation are working together to improve the situation.

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

Timelines are 60 days in general, according to the regulations; 90 days for CT on cell or gene therapy or with GMO medicinal products. When a CEIC requests additional
information, a clock stop is allowed. Conversely, there is no clock stop for the AEMPS.

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

Substantial amendments are validated in 10 days and assessed within 35 days, in accordance with the regulations.

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

Currently there is no uniformity on this. Some CEIC request the sponsor to summarize the procedures local in the CT which are not common in the clinical practice (e.g. extra diagnostic tests) and how they are going to be done during the CT. Others, request a document from the sponsor where suitability of investigator and site is certified, others…? It is an objective for harmonization in Spain.

**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?

There is a requirement for the budget for each study, and for each site, to be submitted to the CEIC.

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

Payment to volunteer subjects in Phase I studies is included in the study budget. Patient subjects are not expected to be paid more than a small compensation for expenses (e.g. transport ticket), except when no clinical benefit is foreseen.

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

Yes, there are internal SOPs and inspections from Regional Governments.

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

No.

**Question 29**: How do RECs deal with SUSAR reports and Annual Safety Reports?

SUSARS are routinely received and Annual Safety Reports are required. However, SUSARS reception overburdens CEICs activities.
**Question 30:** How are ‘substantial amendments’ defined?

The definition in the European “detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities in the European Union, notification of substantial amendments and the declaration of the end of a clinical trial” applies.

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

The indemnity insurance is €250,000/subject, or €25,000 €/subject/year. €2,5 K/trial/year.

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

This is not clear.

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

This is specifically covered in the legislation in some detail (see art. 7 on Real Decreto 223/2004).

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

Annual reports and a final report are required. Beyond these reports no systematic assessment is performed.

**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?

This is not yet known.

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

There are no provisions regarding participation of healthy volunteer children in Spanish regulations.

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

There are no provisions regarding payment to children taking part in clinical research.
**Question 38:** Do RECs invite or allow a) applicants or b) observers to attend committee meetings?

Spanish REC are allowed to invite applicants and observers to their meetings under REC request.

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

Usually the minutes of REC meetings are not made public.

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

In Spanish regulations, there are no provisions regarding the role of the REC Chairman in between meetings.

**Question 41:** Do (research) ethics committees ever appoint subcommittees for any specific purpose?

There is no general rule regarding subcommittees. It depends on each REC SOPs.

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

Currently, there is no national policy on this.

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

N/A

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

N/A

**Question 45:** With regard to Clinical Trial Insurance, do research ethics committees in Spain work to a set template of requirements?

No

**Question 46:** If the answer to Q45 is ‘yes’, how are these requirements decided upon?

a) Decided upon?
b) Cross referenced to statutory requirements?
c) Updated?

N/A

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