MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
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agencia española de
medicamentos y
productos sanitarios

Memorandum on Collaboration and Exchange of Information between the Spanish Agency of Medicinal Products and Medical Devices and Ethics Committees for investigation with medicinal products

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1. Purpose and framework of application

Regulation (EU) No 536/2014 of the European Parliament and Council, of 16 April 2014, on clinical trials on medicinal products for human use (hereinafter 'the Regulation'), establishes in article 8 the principle of one single decision per Member State, which must be reached in a short period, indicating in article 9 that the assessment should be done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience, leaving each Member State the power to decide who should participate in trial assessment. These aspects include the necessary cooperation between Ethics Committees and the competent national authorities.

Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for research with medicinal products and the Spanish Clinical Studies Registry, allocates the responsibility for authorising clinical trials with medicinal products to the Spanish Agency for Medicinal Products and Medical Devices (hereinafter 'the AEMPS'), determining that assessment of Part I of the trial shall be done jointly by the AEMPS and the Ethics Committee for research with medicinal products (hereinafter 'the CEIm'), and allocating the latter responsibility for assessment of Part II. In addition, it establishes in its article 18, Cooperation and exchange of information between the Spanish Agency for Medicinal Products and Medical Devices and the CEIm, that the AEMPS shall establish the mechanisms and procedures for cooperation and exchange of information on clinical studies with medicinal products and clinical research with medical devices with the CEIm, which shall be made public. This shall be set out in a "collaboration memo" specifying the responsibilities of the CEIm and the AEMPS.

In addition, the Regulation establishes common procedures for clinical trial authorisation throughout Europe setting out a coordinated review procedure directed by the reporting Member State and where both this Member State and the other Member States involved have very tight timelines to share their review and achieve a single European position on Part I. Given the particularities of clinical trials with medicinal products and the processes imposed in the new Regulation, coordination of the single decision for clinical trials with medicinal products, as well as other aspects of supervision related to those Ethics Committees for research with medicinal products which are accredited for assessment of studies with medicinal products, shall correspond to the AEMPS.

This memo summarizes the agreements between the AEMPS, as the competent authority, and the CEIm to comply with article 18 of Royal Decree 1090/2015, of 4 December, and establish an effective collaboration and communication between them. The document should also serve as the framework in which criteria regarding the assessment and authorisation of clinical trials with medicinal products in Spain are standardized.

This memo shall be applicable, unless otherwise specified, to clinical trials with medicinal products. The other clinical studies with medicinal products or research with medical devices shall be governed by their own development regulations.

2. Glossary

The definitions considered of interest in relation to this document are those contained in Regulation (EU) No 536/2014, as well as those stated in article 2 of Royal Decree 1090/2015, of 4 December.

3. Roles and responsibilities in the area of clinical trials

3.1. The **AEMPS** should facilitate the assessment procedure and issuing of an opinion by the CEIm in clinical studies with medicinal products in order to integrate the assessment of both into a single decision per clinical study, valid throughout the Spanish State. The AEMPS shall be the national contact point established by article 83 of Regulation (EU) No 536/2014 of the European Parliament and Council, of 16 April 2014.

3.2. The **Department of Medicinal Products for Human Use** of the AEMPS shall facilitate the exchange of information with the CEIm, it shall coordinate the development and maintenance of a single integrated information system for clinical studies with medicinal products, it shall manage the database of clinical studies with medicinal products of the national network of CEIm, it shall provide technical support to the CEIm on matters of procedure related to clinical studies with medicinal products, and shall perform any other function in relation to the activities of the CEIm that it is attributed by the applicable regulations.

It shall be responsible for assessing the aspects that according to this memo correspond to the AEMPS, to assess the information provided by the sponsor during the conduct of the trial, taking into account the available data on the

efficacy or safety of the investigational medicinal products, and to propose the corresponding corrective measures when required to protect trial subjects.

3.3. **The Department for Inspection and Control of Medicinal Products** of the AEMPS and the Autonomous Communities (ACs), each in the area of its competence, shall verify compliance with good clinical practice guidelines and applicable regulations, performing the required necessary inspections.

3.4. The **Technical Inspection Committee** is the coordinating body for inspection and control services of the Agency and the relevant bodies of the Autonomous Communities, responsible for setting common specific criteria for accreditation, inspection, and renewal of accreditation of the CEIm, according to the procedures and timelines established by it.

3.5. The **Ethics Committee for research with medicinal products (CEIm)** is responsible for aassessing the methodological, ethical and legal aspects of the trial, as set out in Royal Decree 1090/2015, of 4 December, and this memo. It is also responsible for follow-up of the study by assessing the reports received from the sponsor or by other means, from the start of the study to receipt of the final report, and for issuing the corresponding opinions on its actions. The CEIm and the AEMPS may obtain mutual advice on any issue related to clinical trial when appropriate.

3.6. The **Clinical Trial Coordination Group (GCEC)** is made up of the Head of the Department of Medicinal Products for Human Use of the AEMPS, the Head of the Clinical Trials Unit of the AEMPS, and a representative from each of the CEIm accredited for assessment of clinical trials with medicinal products. The meetings of GCEC may be attended additionally by other members from both the AEMPS and the CEIm. Its function is to prepare the draft collaboration memo, follow up its application, and prepare proposals for modification.

As a general rule, the GCEC shall meet 11 times a year, either in-person or by teleconference. Until the procedure for re-accreditation of Clinical Research Ethics Committees (CREC) established in the first additional provision of Royal Decree 1090/2015 is implemented, a number of CREC/CEIm which collectively have been committees responsible for giving opinions in at least 85% of the assessed clinical trials shall participate in the GCEC.

4. Trial documentation on Part I and Part II

The clinical trial documentation is divided into two parts, I and II[1].

4.1. Part I documents to be submitted to the AEMPS and the CEIm

4.1.1. Cover letter
4.1.2. Application form
4.1.3. Protocol[2]
4.1.4. Investigator's brochure or summary of product characteristics of the investigational medicinal product
4.1.5. Summary of product characteristics or investigator's brochure of noninvestigational medicinal products (auxiliary medicinal products)[3]
4.1.6. Scientific advice and Paediatric Investigation Plan

4.2. Part I to be submitted only to the AEMPS

4.2.1. Documentation related to compliance with Good Manufacturing Practice of the investigational medicinal product
4.2.2. Investigational medicinal product dossier
4.2.3. Noninvestigational medicinal product dossier (auxiliary medicinal products)[4]
4.2.4. Labeling of investigational medicinal product
4.2.5. Proof of payment of fee to the AEMPS

4.3 Part II documents to be submitted only to the CEIm

4.3.1. Recruitment arrangements
4.3.2. Subject information, informed consent form and informed consent procedure

[1] The documentation for a clinical trial application is specified in greater detail in the document "Instructions of the Spanish Agency for Medicinal Products and Medical Devices for the conduct of clinical trials in Spain", available in http:/www.aemps.gob.es/investigacionClinica/medicinal products/ensayosClinicos.htm
[2] It is recommended to have cross-references to the investigator's brochure instead of reproducing the information in the investigator's brochure.
[3] The summary of product characteristics must be submitted for auxiliary medicinal products not authorised in Spain. In exceptional cases when the auxiliary medicinal product is not authorised in the EU, a rationale for its use and a investigator's brochure must be submitted.
[4] The dossier of the investigational medicinal product and the noninvestigational medicinal product must include with regard to the nonclinical and clinical data only the information that is not included in the investigator's brochure.

4.3.3. Suitability of the investigator
4.3.4. Suitability of the facilities
4.3.5. Proof of insurance cover or financial guarantee
4.3.6. Financial Schedule
4.3.7. Documents on management of biological samples
4.3.8. Proof of payment of fee to the CEIm, if applicable
4.3.9. Statement of compliance with Organic Law 15/1999, of 13 December, on personal data protection and its development regulations

All Part I documents may be submitted in English. However, the application form should contain the information provided in the free text fields in Spanish and English as it supplies the data for the Spanish clinical studies registry. The protocol summary must be submitted in Spanish.

As a rule, the labeling must be in Spanish, though multilingual labelings are acceptable. The availability of labeling in another language may be assessed, provided the sponsor justifies the difficulty of having the labeling in Spanish and the labeling in another language shall not cause confusion in the distribution and administration of the medicinal product.

The Part II documents directed to the trial subjects that are included in point 4.3.2 to be submitted to the CEIm must be written only in Spanish. However, if requested, the sponsor shall be responsible for providing an accurate translation of this information into other languages.

5. Aspects that should be assessed in a clinical trial

The assessment of part I requires assessment of the following aspects according to article 6 of Regulation No 536/2014. The assessment of part II requires assessment of the following aspects according to article 7 of Regulation No 536/2014.

5.1. Assessment on Part I

Part I generally includes the **quality data**, the **non-clinical, pharmacological, and toxicological data**, and the **clinical data**.

As a general rule, the assessment report on Part I on the clinical and non-clinical data shall be prepared according to the following guidelines:

- The AEMPS shall prepare the draft assessment report of phase I clinical trials and clinical trials including phase I, clinical trials with advanced therapy medicinal products and clinical trials with allergens.

- The CEIm shall prepare the draft of the report in all other clinical trials.

However, for each clinical trial, except for phase IV and low-intervention clinical trials which shall be assessed only by the CEIm, the distribution of responsibilities between the AEMPS and the CEIm in assessment of the different aspects that should be considered in clinical trials shall be as specified in the table below:

Distribution of responsibilities in the assessment on Part I	**CEIm**	**AEMPS**
QUALITY DATA		**X[(a)]**
NONCLINICAL, PHARMACOLOGICAL, AND TOXICOLOGICAL DATA		**X**
CLINICAL DATA		
Classification as low-intervention clinical trial	**X**	**(b)**
Rationale and relevance of the clinical trial	**X**	**(c)**
Design of the clinical trial	**X**	**(d)**
Treatment	**X**	**(e)**
Characteristics of the trial population	**X**	
Contraceptive measures and pregnancy control adjusted to reproductive toxicity profile and embryonic and fetal development	**X**	**(e)**
Identification of risks and measures to minimize damage	**X**	**(f)**
Criteria for treatment discontinuation and subject withdrawal	**X**	
Blinding and unblinding	**X**	
Safety data monitoring committee		**X**
Definition of end of the trial		**X**
Criteria for early termination of the clinical trial	**X**	
Statistical aspects		**X**
Compliance with good clinical practice (GCP)		**X**
Overall assessment of the burdens for trial subjects	**X**	
Access to treatment after trial has concluded	**X**	
Overall risk/benefit assessment	**X**	**X**

(a) The AEMPS shall assess the quality of medicinal products and medical devices without CE marking that may be used in the trial.
(b) The AEMPS shall contribute to consistency of classification.
(c) The AEMPS shall assess whether the CT has been recommended or imposed by scientific advice or by previous regulatory decisions, or if it is part of a Paediatric Investigation Plan (PIP) and has the opinion of the Paediatric Committee (PDCO).
(d) The AEMPS shall assess the trial category and phase.
(e) The AEMPS shall assess whether there is consistency with nonclinical data.
(f) The AEMPS shall assess the risks of the medicinal products, adverse events of special interest and reference safety information.

Assessment of the different aspects included in Part I, as well as of Part II detailed below, **shall always be proportional to the risk**. Guidelines for assessment of some of these points, which provide orientation and give clarity and predictability to the assessment and also to assist in the distribution of responsibilities, are detailed below. This memo shall incorporate in the future those elements which, as a result of practical use, are considered necessary for the proper functioning of the system.

5.1.1. LOW-INTERVENTION CLINICAL TRIAL

A low-intervention clinical trial means a clinical trial which fulfills all of the following conditions:

a) The investigational medicinal products, excluding placebos, are authorised;

b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation, or use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and

c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

Assessment of point b) of the above conditions, essentially when use outside the indication is evidence-based and supported by published scientific data on the safety and efficacy of those medicinal products in any of the Member States concerned, shall take as a reference recital 11 of Regulation (EU) No 536/2014 of the European Parliament and of the Council, of 16 April 2014.

Assessment of the risk posed by the additional diagnostic or monitoring procedures indicated in point c) shall take as a reference Annex 4 of the guideline *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*.[5]

[5] http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf

5.1.2. RATIONALE

Assessment of the rationale for the trial generally includes analysis of whether the trial population reflects any potential target population for treatment (for instance, children, the elderly, women) or, otherwise, if it is duly justified, the reasons to conduct the trial in subjects unable to give informed consent, when applicable, and the state of scientific knowledge.

The sponsor shall also provide information on whether the clinical trial has been recommended or imposed by scientific advice or by previous regulatory decisions or if it is part of a Paediatric Investigation Plan (PIP) and has the opinion of the Paediatric Committee (PDCO). This information may sometimes assist in assessment of the clinical trial and, if required or not be adequately provided by the sponsor, may be obtained through the Agency.

5.1.3. DESIGN

Assessment of the design includes, among other things, its rationale (single group, parallel, crossover or factorial; randomized or not, blinding and who is blinded), objectives, the primary endpoint(s) and the method of measurement and time of assessment, secondary endpoints and for each the method of measurement and time of assessment, and the category of the trial.

For assessment of the trial category and phase, the criteria specified in the document Appendix, on disclosure rules to the "Functional specifications for EU portal and EU database to be audited - EMA/42176/2014[6], setting out the transparency criteria, shall be used.

5.1.4. CONTRACEPTIVE MEASURES AND PREGNANCY CONTROL

For assessment of contraceptive measures and pregnancy control adjusted to the reproductive toxicity profile and embryonic and fetal development, the *Recommendations related to contraception and pregnancy testing in clinical trials*[7] prepared by the European Clinical Trial Improving Group (CTFG) shall be used as the reference document.

[6] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500195084.pdf
[7] http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

5.1.5. UNBLINDING

The assessment of the protocol requires checking that the investigator appears as the person responsible for unblinding in emergency situations. In general, the sponsor should not be involved in this decision.[8]

5.1.6. END DATE OF THE CLINICAL TRIAL

The definition of what date shall be considered the end date of the trial has a direct implication on when the summary of results shall be available for public. This data should normally be the date of the last patient visit, unless another criterion is justified.

5.2. Aspects that require assessment in Part II

The CEIm acting for each clinical trial shall assess, for the whole Spanish territory, the following aspects:

5.2.1. COMPLIANCE WITH INFORMED CONSENT REQUIREMENTS

The CEIm shall review the process for obtaining consent from the participants (or, if applicable, from their legally authorised representative), and shall approve participant information documents that shall be used in all the Spanish sites. In the different sites, the investigator and the sponsor may agree on specific local information to be included, such as identification of the investigator at the site or the contact point for the participant, but should not make changes to information approved by the CEIm. Linguistic versions may also be made into other languages, where the sponsor shall be responsible for ensuring that it is a faithful translation of the original. These translations shall not be part of the Part II documents that the CEIm should assess.

5.2.2. COMPENSATION TO SUBJECTS FOR THEIR PARTICIPATION

The CEIm shall review the payments or compensation provided to participants are adequate for the burden and the discomfort caused by the research, but not to the point that they may pose an incentive to assume a risk that the participant would not accept under other conditions. It shall also review the suitability of compensations for loss of income directly related to participation in the clinical trial.

[8] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000016.jsp&mid=WC0b01ac05800296c5

5.2.3. COMPENSATION TO INVESTIGATORS

The CEIm must know the trial budget and the financial compensations to investigators and sites and take this information into account when assessing its acceptance of the project. However, it is not the function of the CEIm to assess the details of these compensations or relevant aspects of the contracts such as extraordinary costs in the different sites, as these are the responsibility of the site within the framework of the contract with the sponsor.

5.2.4. ARRANGEMENTS FOR RECRUITMENT OF SUBJECTS

The CEIm shall review the subject recruitment process and the materials and procedures used for this purpose. Unless described in the protocol, the procedures for inclusion of the trial subjects shall be described in detail in a separate document and shall provide a clear indication of what is the first action in the recruitment process. If the subject recruitment is done through advertising, copies of the advertising material, whether in print form, audio or video recordings or website material, shall be submitted. The proposed procedures for handling responses to advertisements, including copies of communications used to invite subjects to participate in the clinical trial and arrangements for information or advice to the respondents found not to be suitable for inclusion in the clinical trial, shall be outlined.

Sites may adapt the approved material to specific local characteristics (such as indication of a local contact or a linguistic version) and may limit the use of some materials in their facilities.

5.2.5. PERSONAL DATA PROTECTION

The CEIm shall review that personal data handling is adequate and complies with the legislation on personal data protection.

5.2.6. SUITABILITY OF THE PERSONS INVOLVED IN CONDUCTING THE CLINICAL TRIAL

The CEIm shall review that the trial is planned so that the principal investigator at each participating site is a medical doctor (or a professional considered qualified to be an investigator because of the necessary scientific knowledge and experience in care of the patient involved) with the suitable professional profile for the responsibilities that this trial requires. The CEIm shall also assess the need for other professionals to participate in the investigator's team who by their education, training and experience are needed to conduct the trial or to provide medical care to the participants.

For this assessment, the CEIm shall assess the CV of the principal investigators as well as their declarations of economic interests and institutional affiliations and shall take into account the responsible declaration of the sponsor stating that the selected investigators are suitable for the conduct of the trial (see document on suitability of the investigator in "Instruction document of the Spanish Agency of Medicinal Products and Medical Devices for conducting clinical trials in Spain"[1]). In case of a change in a principal investigator at a site after the study has been approved, the new documentation shall be sent to the CEIm and shall be treated as a substantial modification.

For the assessment of the need to declare conflicts of interest in the CV of the investigators, taking into account that the Regulation states "Any conditions, such as economic interests and institutional affiliations, that might influence the impartiality of the investigators shall be presented.", in cases where a CV does not contain any declaration of conflict of interest it will be understood that there is no need to declare conflict of interest.

The sponsor is responsible for having informed to the investigator of the type of conflict of interest that he/she has to take into account and indicate in the CV, when applicable (see also annex III in the "Instruction document of the Spanish Agency of Medicinal Products and Medical Devices for conducting clinical trials in Spain").

In case of coexistence at the same time of studies with the same selection criteria, acceptability of participation in more than one CT in the same pathology and with the same population (similar selection criteria) can generate a conflict in respect to which study will a particular patient be invited to participate. The CEIm could ask the investigator how the decision will be made in this situation and/or ask for a commitment of consecutive and not simultaneous participation in those studies, in spite of being active all of them.

5.2.7. SUITABILITY OF THE FACILITIES

The CEIm shall review that the general characteristics of the sites where it is proposed to conduct he clinical trial are suitable for the conduct of the trial. For this assessment, the CEIm shall consider the declaration of the director of the healthcare center or institution (or other delegated responsible person) where the clinical trial site is located, on the suitability of the clinical trial site, taking into account the nature and use of investigational medicinal product, and including a description of the suitability of the facilities, equipment, human resources and a description of specialized knowledge (see

annex IV on suitability of facilities in the “Instruction document of the Spanish Agency of Medicinal Products and Medical Devices for conducting clinical trials in Spain”[1]).

If new sites are included after the study has been approved, the new documentation referring to the new sites and investigators shall be sent to the CEIm and shall be treated as a substantial modification.

5.2.8. DAMAGE COMPENSATION

The CEIm shall review compliance with the requirements of the compensation for damage that could be suffered by a trial subject as a result of their participation in a clinical trial. The damage to trial subjects as a result of a low-intervention clinical trial shall not need to be covered by an insurance contract if it is covered by the individual or collective professional civil liability insurance or equivalent financial guarantee of the site where the clinical trial is conducted.

5.2.9. COMPLIANCE WITH STANDARDS FOR COLLECTION, STORAGE AND FUTURE USE OF BIOLOGICAL SAMPLES OF TRIAL SUBJECTS

Law 14/2007, of 3 July, on biomedical research, states in its article 1.3 that the biomedical research to which this Law refers includes basic and clinical research, except in this latter case of clinical trials with medicinal products and medical devices, which shall be governed by their own specific regulations.

Royal Decree 1716/2011, developing Law 14/2007, states in its explanatory memorandum that human biological samples that were obtained in clinical trials with medicinal products and medical devices fall within its scope, provided they are to be used for the purposes of biomedical research. Subsequently, in its article 3(2)(d), it specifies that this scope covers from termination of the corresponding clinical trial and provided that those samples are to be incorporated into a collection or a biobank.

If clinical trial samples are stored after completing the trial for subsequent use in research, the ethical and legal requirements provided in national (Royal Decree 1716/2011, article 3d) and international rules (including the Council of Europe Oviedo Convention (1997) and Recommendation R (2006) on research on biological materials of human origin) must be complied with, depending on the case.

6. Substantial modifications

As a general rule, the CEIm and the Spanish Agency for Medicinal Products and Medical Devices shall assess those aspects on which they had already reached a decision in the initial assessment report.

The AEMPS shall coordinate the assessment in cases where a relevant modification of the protocol or investigator's brochure affects various trials.

7. Content and language of assessment report and decision

The assessment report on Part I in relation to the preclinical and clinical parts shall include comments that the AEMPS or CEIm consider relevant regarding the aspects mentioned in section 5.1, as well as an overall assessment section including the final conclusion and if applicable the possible list of clarifications (requests for information) for the sponsor regarding each part.

The report on Part I shall express the position of both the AEMPS and the CEIm.

The assessment report on Part II shall include comments that CEIm considers relevant regarding the aspects mentioned in section 5.2, as well as an overall assessment section including the final conclusion and if applicable the possible list of clarifications (requests for information) for the sponsor.

The conclusion in both cases may be that the clinical trial is considered acceptable, that it is considered acceptable subject to compliance with specific conditions, or that it is considered unacceptable, in which case the reasons shall be explained. The report on Part II shall include the sites that the CEIm considers acceptable to conduct the trial, indicating in each case the name of the principal investigator.

For the trial to be authorised, the conclusions of the assessment reports on Part I and Part II should be that the trial is acceptable or acceptable subject to compliance with specific conditions, and both the AEMPS and CEIm must agree on these conclusions.

The language of the assessment report shall be Spanish, except when the trial assessment is performed using an assessment procedure coordinated in the European Union, in which case, it must be in English and according to the format used in this regard.

8. Exchange of information between the AEMPS and the CEIm

Regulation (EU) No 536/2014 of the European Parliament and Council, of 16 April 2014, establishes a single portal and database for clinical trial authorisation in the European Union. The initial situation in Spain is a single portal and two systems of databases for managing the trials in the AEMPS and CEIm, respectively. On the other hand, the new clinical trial authorisation system requires frequent communication and exchange of information between the AEMPS and CEIm.

Once the single EU portal and database is operational, the AEMPS shall determine the need for adding national functionalities to the European system to ensure its operation in our country. Meanwhile, as a general rule, the AEMPS, and CEIm shall report and shall share information and documents that are considered necessary through the SIC-CEIC application. This does not preclude the use of other channels of communication to facilitate the implementation of the process.

Since the established process for clinical trial authorisation and substantial modifications to the trial has tight timelines, it is necessary that the exchange of information between the AEMPS and the CEIm allows for the possibility of working within these periods. It is necessary to point out that these are maximum periods and that the assessment and decision procedure does not necessarily require exhausting them in any of its phases.

The table below shows the schedule for **initial applications** of clinical trials expressed in calendar days:

<table>
<tr><td colspan="6">ASSESSMENT</td><td rowspan="8">AEMPS SENDS DECISION ON PART I AND PART II (5 days)[b]</td></tr>
<tr><td colspan="6">PART I: Phase II, III and IV</td></tr>
<tr><td>DRAFT ASSESSMENT SENT TO AEMPS[a]</td><td colspan="2">INTEGRATION AND SUBMISSION OF CONCLUSIONS TO SPONSOR</td><td>SPONSOR RESPONSE</td><td>SUBMISSION OF CONCLUSIONS ON RESPONSE TO AEMPS</td><td>INTEGRATION AND SUBMISSION OF FINAL CONCLUSIONS TO SPONSOR</td></tr>
<tr><td>35</td><td colspan="2">10</td><td>12</td><td>10</td><td>9</td></tr>
<tr><td colspan="6">PART I: Phase I, allergens and advanced therapies</td></tr>
<tr><td>DRAFT ASSESSMENT SENT TO CEIm[a]</td><td>CEIm SENDS COMMENTS TO AEMPS</td><td>INTEGRATION AND SUBMISSION OF CONCLUSIONS TO SPONSOR</td><td>SPONSOR RESPONSE</td><td>SUBMISSION OF CONCLUSIONS ON RESPONSE TO AEMPS</td><td>INTEGRATION AND SUBMISSION OF FINAL CONCLUSIONS TO SPONSOR</td></tr>
<tr><td>30</td><td>7</td><td>8</td><td>12</td><td>10</td><td>9</td></tr>
<tr><td colspan="6">PART II:</td></tr>
<tr><td colspan="3">ASSESSMENT AND SUBMISSION OF OPINION TO SPONSOR</td><td>SPONSOR RESPONSE</td><td colspan="2">ASSESSMENT AND SUBMISSION OF OPINION TO SPONSOR AND AEMPS</td></tr>
<tr><td colspan="3">45</td><td>12</td><td colspan="2">19</td></tr>
<tr><td colspan="3">ASSESSMENT</td><td colspan="3">CLARIFICATIONS</td></tr>
</table>

(a) The assessment period starts from the first day following the date of entry of a valid application in both the AEMPS and the CEIm.
(b) The AEMPS shall send the decision on the CT integrating the conclusions on part I and II within 5 days of the date of submission of the opinion of the CEIm on Part II, provided the assessment period on Part I has been completed.

AEMPS
CEIm
Sponsor

Assessment of an initial application must have been completed a maximum of 45 to 96 days **from the date of entry of the application**[9]. If no rectification or request for clarifications were required, this maximum period shall be 45 days. If a rectification and request for clarifications were required, the period shall be 96 days. If a rectification but no a request for clarifications was required, the period shall be 65 days. If no rectification but a request for clarifications was required, the period shall be 76 days.

[9] It should be taken into account that the periods indicated below are counted from the date of entry of the application and therefore include the maximum periods to validate the application (10 calendar days in the case of an initial application and 6 calendar days in the case of a substantial modification) and, if applicable, to receive the response from the sponsor (10 days in both cases).

The table below shows the schedule for **substantial modifications** of Part I in clinical trials expressed in calendar days:

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<tr><td colspan="3">ASSESSMENT</td><td colspan="3">CLARIFICATIONS</td></tr>
</table>

(c) The assessment period starts from the first day following the date of entry of a valid application in both the AEMPS and the CEIm.
(d) The AEMPS shall send the decision on the CT integrating the conclusions on part I and II within 5 days of the date of submission of the opinion of the CEIm on Part II, provided the assessment period on Part I has been completed.

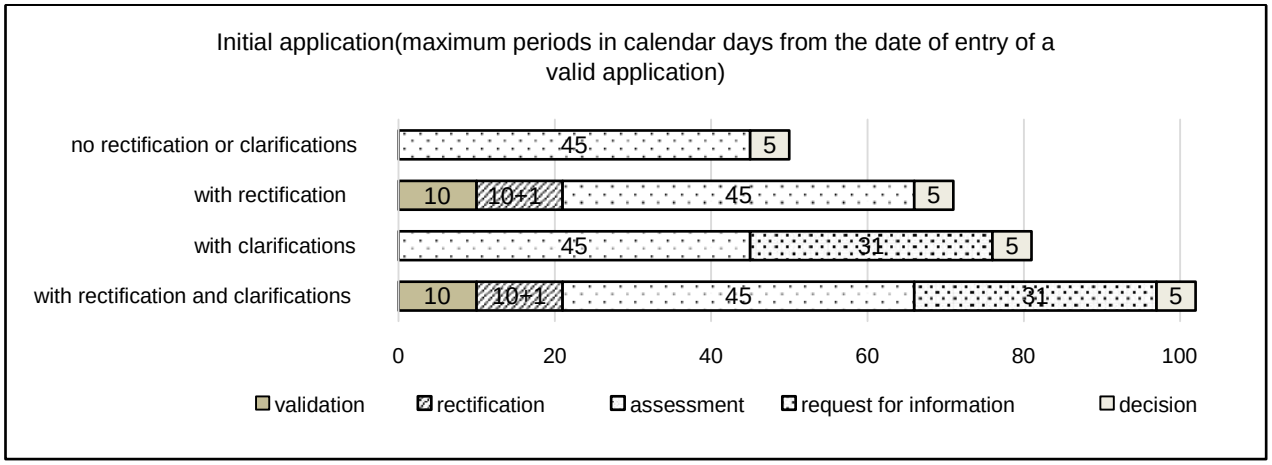
AEMPS
CEIm
Sponsor

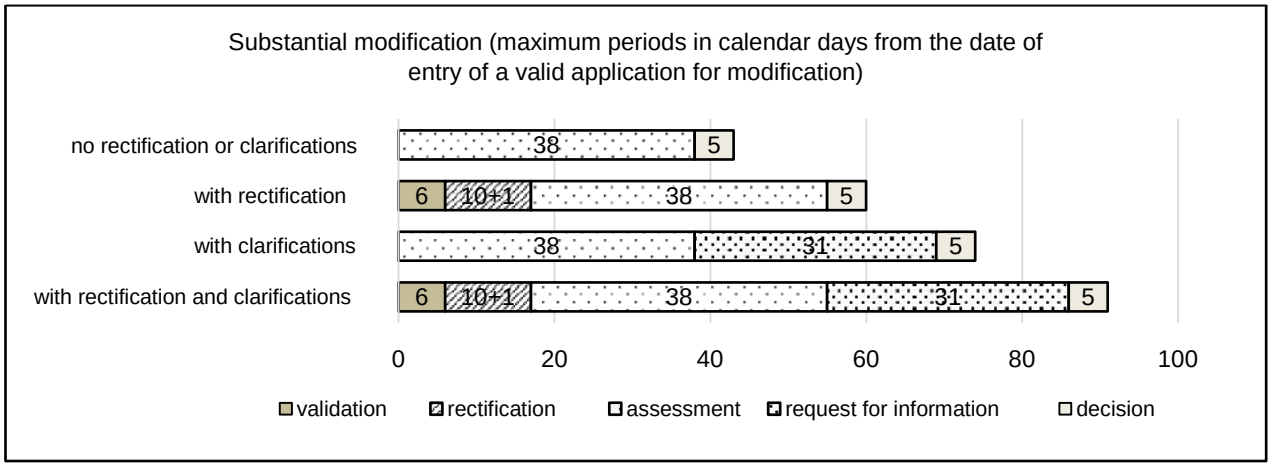
Assessment of an application for a substantial modification must have been completed a maximum of 38 to 85 calendar days **from the date of entry of the application**. If no rectification or request for clarifications were required, this period shall be 38 days. If a rectification and request for clarifications were required, the period shall be 85 days. If a rectification but no a request for clarifications was required, the period shall be 54 days. If no rectification but a request for clarifications was required, the period shall be 69 days.

Assessment on Part I and Part II shall be implemented in parallel, and the CEIm shall submit its conclusions on the two parts to the AEMPS simultaneously. The AEMPS shall send the sponsor the conclusions on Part I integrated in the decision.

MINISTERIO DE SANIDAD,
SERVICIOS SOCIALES
E IGUALDAD
Agencia Española de
Medicamentos y
Productos Sanitarios

The CEIm shall send the sponsor the opinion on Part II according to the sample forms given in Annex I (for the initial application) and Annex II (for a substantial modification).





In the case of a substantial modification that only affects Part II, the modification shall be considered approved or denied on the date on which the CEIm informs the sponsor of its opinion with the conclusions on Part II of the assessment report.

As currently accepted in the voluntary process of harmonization and as indicated in the functional specifications for the EU portal and database which shall be auditable, between December 23 and January 7 there shall be a clock stop in all applicable periods during that period, unless prior to the application it has been agreed with the AEMPS and the CEIm that the assessment may be performed without that clock stop.

9. Safety monitoring

The AEMPS and the CEIm shall perform follow-up of the trial based on the information provided by the sponsor for the conduct of the trial, and the information obtained from other data sources that are available and may be relevant.

In order to be as effective as possible in this follow-up, the AEMPS shall inform the CEIm of any relevant information on the safety of the investigational medicinal products that might not be known by the CEIm.

In turn, the CEIm shall notify the AEMPS of any assessment or proposal deemed relevant regarding aspects related to the safety of the subjects in the trial, and shall assess the changes that may be considered necessary for the informed consent of subjects or any other issue related to Part II.

When it is necessary to take possible corrective measures related to the trial, the AEMPS shall be responsible for requesting information to the sponsor with regard to Part I, and for suspension or revocation of the authorisation, or for requesting from the sponsor the modification of any aspect of the trial.

10. Complaints

The CEIm may send to the AEMPS or ACs, to each according to their area of competence, any complaints referring to clinical trials considered of interest.

11. Approval process and planned review

This collaboration memo must be published by the AEMPS once it has been accepted by the Clinical Trial Coordination Group (GCEC). It may be modified at any time by agreement of all parties. The memo shall be formally reviewed at least annually.

Sample Form:

Annex I: OPINION OF THE ETHICS COMMITTEE FOR RESEARCH WITH MEDICINAL PRODUCTS

Annex II: OPINION OF THE ETHICS COMMITTEE FOR RESEARCH WITH MEDICINAL PRODUCTS ON A SUBSTANTIAL MODIFICATION

ANNEX I. CEIm Opinion Model

LOGO OF INSTITUTION TO WHICH THE CEIm IS ATTACHED

OPINION OF THE ETHICS COMMITTEE FOR RESEARCH WITH MEDICINAL PRODUCTS

Mr/Ms._____, Chairman/Secretary

Ethics Committee for research with medicinal products _____

_____

CERTIFIES

That this Committee assessed the following proposed clinical trial

CODE: _____ EUDRACT NUMBER: _____
TITLE: _____

_____
SPONSOR: _____
PROTOCOL: Version _____Date: DD/MM/YYYY
GENERAL PIS/IC: Version _____ Date: DD/MM/YYYY
Other PIS/IC (substudies, for future use of biological samples, etc.).
Version _____ Date: DD/MM/YYYY
Procedures and materials used for subject recruitment (advertisements, website information, information brochures, etc.).
Version _____ Date: DD/MM/YYYY

That this Committee assessed Part I of the application for authorisation of the trial, as well as the sponsor's responses to the clarifications requested (if any), and transmitted to the Spanish Agency for Medicinal Products its final opinion on Part I.

That this Committee assessed Part II of the application for authorisation of the trial in accordance with Royal Decree 1090/2015 and article 7 of Regulation (EU) 536/2014 and considers that:

- The procedure for obtaining informed consent (including the trial subject information sheets and informed consent forms mentioned above) and the planned subject recruitment are suitable and meet the requirements for obtaining the informed consent foreseen in Chapter II of Royal Decree 1090/2015.
- The planned compensation for participants is adequate, as well as the planned arrangements for compensation for damages that could be experienced by the subject.
- The planned procedure for personal data handling is adequate.
- The future use of biological samples obtained during the trial is adapted to Royal Decree 1716/2011.
- The sites and investigators specified in Annex II are considered adequate for the conduct of the trial, considering the suitability statements issued by the sponsor and the persons responsible for the relevant institutions.

That this Committee decided to issue a **FAVOURABLE OPINION** at the meeting held on DD/MM/YYYY (minutes number____).

That in this meeting the requirements set down in current legislation (Royal Decree 1090/2015) were met in order for the decision of the aforementioned CEIm to be valid.

That the CEIm_____,
both in its membership and its procedures, complies with GCP guidelines (CPMP/ICH/135/95) and with current legislation governing its functioning and that the membership of the CEIm _____is that specified in Annex I, taking into account that any member participating in the trial or declaring a conflict of interest shall not have participated in the assessment or the opinion on the application for authorisation of the clinical trial.

Signed in_____, on DD/MM/YYYY

Signed _____

Annex I Initial Opinion on Part II

CEIm MEMBERSHIP

Chairman	
Vice-chairman	
Technical Secretary	
Members	

Annex II Initial Opinion on Part II

SITES AND PRINCIPAL INVESTIGATORS PARTICIPATING IN SPAIN

CODE: _____ EUDRACT NUMBER: _____
TITLE: _____

_____

SPONSOR: _____

Principal investigator	Study site

ANNEX II. CEIm Opinion Model (Substantial Amendments)

LOGO OF INSTITUTION TO WHICH THE CEIm IS ATTACHED

OPINION OF THE ETHICS COMMITTEE FOR RESEARCH WITH MEDICINAL PRODUCTS

Mr/Ms._____, Chairman/Secretary

Ethics Committee for research with medicinal products _____

_____

CERTIFIES

That this Committee assessed the proposal of the sponsor_____, _____ for a substantial modification number _____ dated DD/MM/YYYY, corresponding to the clinical trial with protocol code _____ and EudraCT no _____entitled: _____
_____
_____

And considers that:

The CEIm _____,
at its meeting of DD/MM/YYYY, after assessment of the following substantial modification:

Substantial modification: _____
Modified documents: _____
_____
_____
_____
_____

issues a **FAVOURABLE OPINION**.

That this Committee assessed the substantial modification of the application for authorisation of the trial, in accordance with Royal Decree 1090/2015 and Chapter III of Regulation (EU) 536/2014.

That the CEIm_____,
both in its membership and its procedures, complies with GCP guidelines (CPMP/ICH/135/95) and with current legislation governing its functioning and that the membership of the CEIm _____
is that specified in Annex I, taking into account that any member participating in the trial or declaring a conflict of interest shall not have participated in the assessment or the opinion on the application for authorisation of the clinical trial.

Signed in_____, on DD/MM/YYYY

Signed _____

Annex I

CEIm MEMBERSHIP

Chairman	
Vice-chairman	
Technical Secretary	
Members	

Annex II

(In case of a substantial amendment by addition of a site and/or a change in a principal investigator)

SITES AND PRINCIPAL INVESTIGATORS PARTICIPATING IN SPAIN

CODE: _____ EUDRACT NUMBER: _____

TITLE: _____

_____

SPONSOR: _____

DATE OF UPDATING OF ANNEX II: DD/MM/YYYY (same date as opinion)

Principal investigator	Study site