Instruction document of the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain

Version 16, dated 31st January 2022 (all versions can be reviewed at the end of the document)

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Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for investigation with medicinal products (hereinafter CEIm) and the Spanish Clinical Studies Registry, introduces substantial amendments in national legislation so as to make feasible the application of Regulation (EU) No 536/2014 of the European Parliament and of the Council, of 16 April 2014 (hereinafter the Regulation), and to develop those aspects that the Regulation leaves to national legislation.

This instruction document of the Spanish Agency of Medicines and Medical Devices (hereinafter AEMPS) for conducting clinical trials in Spain provides, in the form of questions and answers, information on the practical aspects involved in the application of the new Royal Decree, highlighting the changes with respect to the previous Royal Decree. This document aims to cover those aspects of Royal Decree 1090/2015, of 4 December, that are left to be developed in instructions by the AEMPS, as well as any others requiring clarification. The document is complementary to the "collaboration memo" between the AEMPS and the CEIm that is referred to in article 18 of Royal Decree 1090/2015, of 4 December, which shall also be public. The subjects requiring greater clarification or rectification based on the experience acquired shall be reviewed in successive versions of this document, which is intended to be dynamic and therefore easily updated.

Any questions or comments regarding the application of the new Royal Decree or this document should be emailed to aecaem@aemps.es, quoting "Questions and Answers" as the reference in the subject field.

Incidents or questions related to submission of an application or communication about a clinical trial via the Portal ECM should be sent to incidensayos@aemps.es.

Incidents, questions, or suggestions related to the Spanish Clinical Studies Registry (REec) should be sent to reec incidencias@aemps.es.

Further information on clinical trials in the European Union and on the

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Clinical Trials Information System (CTIS) can be found in Clinical Trials in the European Union - EMA (euclinicaltrials.eu). Incidents related to the CTIS must be managed through the EMA Service Desk Log in - Service Desk (europa.eu).

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1. When did the new Royal Decree enter into force?

Created in v1

Royal Decree 1090/2015 entered into force on 13th January 2016.

2. What applications must be submitted according to the new Royal Decree?

Created in v1; updated in v2 and v16

Royal Decree 1090/2015, of 4 December, shall apply to all applications for authorisation of a clinical trial and applications for substantial amendments (SAs) or notifications related to authorised clinical trials that are ongoing or for which the summary of the results has not been submitted, as of 13 January 2016.

Applications made as of 13 January 2016 shall be submitted to a single CEIm according to the regulations given in section 6.

The second and third transitional provisions of the Royal Decree indicate the aspects that shall be remain in force only during the transition period for the implementation of the Regulation for applications submitted nationally. These may be summarised in the following points:

- Applications for authorisation of a clinical trial must always be submitted complete (i.e., part I and part II).

- The current requirement for submission via the Clinical Trials with Medicinal Products Portal (hereinafter ECM Portal) and the need for qualification as product under clinical investigation are maintained.

- The periods for validation and assessment are those indicated in the Regulation, but the assessment period shall begin from the date of entry of a valid application.

- The summary of the results must be submitted to the AEMPS and the CEIm (not only to EudraCT).

3. Are there different rules for a low-intervention clinical trial?

Created in v4; updated in v5 and v11

The authorisation process for a low-intervention clinical trial is the same and takes place in the same maximum periods as any other trial. However, the trial documentation and insurance are simpler (see Annex I. Trial

documentation and identification of documents when loaded into the ECM Portal or the CTIS Portal). In addition, monitoring, content of the master file and traceability of the investigational medicinal products may be simplified and, depending on the trial characteristics, may be similar to those in routine clinical practice.

When the sponsor requests qualification of a low-intervention study, the sponsor must indicate the request for qualification of the low-intervention clinical trial in the remarks section of the cover letter (section 2), and provide suitable justification for this qualification, indicating, when appropriate, the additional trial procedures to those that would have been performed on the participants in the context of routine clinical practice In the decision issued by the AEMPS it will be stated whether the qualification was accepted or not, and, where appropriate, the reasons for non-acceptance.

In cases where a clinical trial with low-level intervention in which the medicinal products are used in accordance with the authorised labelling is requested, it should be explicitly shown. Otherwise, a justification must be provided based on published scientific evidence which guarantees the efficacy and safety of the investigational medicinal products used in the conditions of the trial. This evidence may include data published in scientific journals, as well as treatment protocols or relevant national, regional or institutional evaluation reports.

Also, when the diagnostics or monitoring procedures conform with the normal clinical practice, this should be shown explicitly, clarifying the context of normal clinical practice which is referred to (In Spain, or any other EU country, showing which), if applicable, contributing the corresponding evidence. Otherwise, the procedures which do not adjust to the normal clinical practice must be identified and it must be justified that they do not involve more than a minimal additional risk or load for the patient's safety compared with the normal clinical practice.

4.Which CEIm can perform assessment of a clinical trial?

Created in v1; updated in v2, v3, v8 and v16

The sponsor could select the CEIm, by mutual agreement with said Committee, among the Committees included in the list that can be consulted in the Directory of CEIm accredited in Spain, available at the URL Directory of CEIm accredited in Spain – Spanish Agency for Medicine and Medical Devices (aemps.gob.es)

In the event that the sponsor intends to propose that Spain be the Reporting Member State (RMS) in a multinational clinical trial submitted via

the CTIS portal, the sponsor must have obtained confirmation of the availability of said CEIm to participate as an evaluator of the trial, with Spain being the RMS on the dates scheduled to submit the application. For all clinical trial authorization applications submitted via the CTIS Portal, the sponsor must indicate in the cover letter the name of the IRB/IEC that will evaluate the application.

5. What type of Ethics Committee for investigation can assess an observational study with medicinal products (non- interventional study) or a clinical study with medical devices?

Created in v3; updated in v8 and v16

Observational studies with medicinal products and clinical investigations or observational studies with medical devices may be assessed by any of the Committees included in the list that can be consulted in the Directory of CEIm accredited in Spain, available at the URL Directory of CEIm accredited in Spain – Spanish Agency for Medicine and Medical Devices (aemps.gob.es)

When a change of the Committee responsible for the assessment of a non-interventional study or a clinical investigation with medical devices were needed, the new CEIm proposed by the sponsor has had to previously agree on taking over the study assessment. For that purpose, the sponsor must have provided the CEIm with a complete version of the study documents.

6. Submission of applications and communications of a clinical trial

Created in v1; updated in v3, v4, v5, v6, v9, v10, v11, v15 and v16

From 31 January 2022 to 30 January 2023, the sponsor may request the authorisation of a clinical trial through the CTIS Portal or through the ECM Portal for clinical trials with medicinal products Clinical Trials with Medicinal Products (aemps.es).

All applications and communications after authorisation of a clinical trial not uploaded to the CTIS must continue to be made via the ECM portal at the latest up to the date on which the transition of the clinical trial has been requested in the CTIS Portal. This transition will be necessary and must be made in the next three years for clinical trials that will have any sites active in the EU as of 31 January 2025. See section 11 in the Q&A document in EudraLex Volume 10, Chapter V EudraLex - Volume 10 (europa.eu).

Applications must be sent only once and only via the CTIS Portal or the ECM Portal.

For applications submitted through the ECM Portal:

- The applicant shall be the recipient of all communications from the AEMPS on part I and from the CEIm on part II. The applicant for the CEIm may be different from the applicant for the AEMPS.

- The application for authorisation of a clinical trial must be submitted with an electronic signature. In those cases where the applicant does not have an electronic signature, the reception date of the application will be the date of submission via e-mail at aecaem@aemps.es of the proof of electronic submission with his/her handwritten signature. This submission is essential for the validation of the application.

- You can find information about digital signature certificates valid for submission of applications via the ECM Portal at the web address: Digital Headquarters of the Spanish Agency for Medicines and Medical Devices – AEMPS Digital Headquarters

- Applications must be submitted simultaneously to the AEMPS and the CEIm. Given that the ECM Portal does not currently allow this, submission must be consecutive, first to the CEIm and immediately afterwards to the AEMPS. Until the ECM Portal allows submission of documentation in a single step, the date of entry for purposes of processing of the procedure shall be considered as the date of the application that was last submitted.

- To maintain the correct information regarding the sites withat REec [Spanish Register of Clinical Trials], it is important that when it comes to selecting the participating sites within the ECM Portal, using the option “Others - NOT REGISTERED” is avoided as far as possible.

- The sponsor should indicate the date on which the application was sent to CEIm in the free text table of the cover letter.

- Applications must be complete from the date of submission. No submission of additional documentation which has not been requested by the AEMPS or the CEIm shall be accepted after that date. In the event that the documentation is received later than the validation date, the evaluation schedule will be delayed[1].

[1] The instructions on how to report trial dates are given in section 41.

- With the new Royal Decree, it is foreseen that additional information may be requested both in initial applications and in substantial amendments, and both on part I and on part II. This represents a change with respect to the previous situation for which the information systems are still not adapted. Therefore, **submission of *a reply to a request for information on part I in an initial application and all replies to a request for information on a substantial amendment* shall be sent to the CEIm** by email until it is indicated that their submission is feasible via the ECM Portal. In cases in which the clarification of part I refers to documents evaluated solely by the AEMPS (for example, the quality IMPD), the responses will only be sent to the AEMPS.

- When the response to a rectification or a request for information has the consequence of updating the initial application form (XML and PDF), it must be done as follows:

    1. Update the information on the form by uploading the XML in EudraCT.

    2. Upload that updated XML to the ECM Portal, via the option: New clinical trial

    3. Validate the updated XML in the ECM Portal and save it together with the PDF of the same in order to attach it when sending the rectification/request for information response.

- ***The response to a condition in the authorisation*** of a clinical trial or a substantial amendment must be submitted to the AEMPS via the ECM Portal using “C. Response to a condition in the authorisation (of an initial application or a SA) or response to a request for information (e.g. safety)”.

- When the condition refers to aspects of the trial documentation received by the CEIm, it will be sent a copy of the response via the ECM Portal as a report on the progress of the trial.

- ***The annual safety report*** (DSUR) will be reported to the AEMPS via the ECM Portal using "E. iv) Informe anual de seguridad (DSUR)” (Annual Safety Report (DSUR)” as follows:

    - When a DSUR refers to a medicinal product with the qualification as an investigational medicinal product (IMP)[2], a

[2] Medicinal products not authorised in any country of the European Economic Area containing an active substance or combination of active substances not authorised in Spain require qualification as an IMP .

single application may be submitted simultaneously for all trials related to this IMP. To do so, the XML of the initial application form of all the clinical trials to which the DSUR refers should be loaded, clicking the button "Add Trial" and answering in all cases question "3. Does the application refer to a medicinal product with the qualification as an investigational medicinal product (IMP)?" with a "Yes" and indicating the corresponding IMP number which should have the format "yy-nnn".

- When the clinical trial is linked to more than one IMP, the DSUR corresponding to each IMP should be submitted in a separate application in the way indicated in the previous section.

- When a DSUR linked to various clinical trials refers to medicinal products without the qualification as IMPs, an application should be submitted for each trial.

- **The DSUR shall be sent to the CEIm via the ECM Portal using the option E ii) progress report on the trial**.

Notwithstanding the above, it will not be necessary to send through the ECM Portal the DSUR corresponding to an active ingredient being researched in a clinical trial in which Spain is participating that is authorised in the CTIS. In this case, it will be sufficient to send the DSUR through the CTIS Portal, indicating Spain as one of the Concerned Member States (CMS). See section 7 in the Q&A document of EudraLex Volume 10 EudraLex - Volume 10 (europa.eu).

- **Changes in** the sponsor, applicant or legal representative **contact information** and changes of applicant must be reported using H.- Change in contact information. In this case, the XML and pdf formats of the updated application form must be sent as attached documents. If, at the time of sending this missive, there is a Substantial Amendment (SA) in evaluation for the same trial, it is advisable to indicate this fact in the cover letter, to facilitate sending the decision of the SA to the new contact address which is being communicated. The way in which the **dates of the trial are reported** is indicated in section 41.

- The ***summary of results*** of the trial should be sent to the AEMPS and the CEIm, and also updated in EudraCT no later than one year after the date of the end of the trial globally.

  Submission should be made via the ECM Portal, selecting "Authorised CT" and using the function "E. Informe sobre el ensayo iii) Informe final de resultados" (Trial report iii) Final report of results).

The summary of results should preferably follow the European format required for EudraCT and at least the Spanish version should be submitted, while it is recommended to also submit an English version; however, for trials authorised before 2013, the translation into Spanish is not necessary. You can consult a multimedia tutorial on how to provide the results in EudraCT at https://eudract.ema.europa.eu/whatsnew.html (it is recommended to read the overview on this web page before downloading and viewing the tutorials).

It is advisable to additionally submit a summary of results which is comprehensible to the layperson, taking into account the document "Summaries of Clinical Trial Results for Laypersons" in volume 10 of Eudralex (which can be consulted at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_01_26_summaries_of_ct_results_for_laypersons.pdf)

Applications and communications regarding a clinical trial made through the CTIS Portal must be in compliance with that indicated in the Q&A Document in EudraLex Volume 10, Chapter V EudraLex – Volume 10 (europa.eu)

7. How should early termination of a CT be reported when follow-up of the subjects after the termination date is anticipated?

Created in v5; updated in v16

In cases where the sponsor decides to terminate a clinical trial early, it shall be indicated in the **end of trial notification** that it is an early termination and the appropriate sections shall be completed (see also section 41).

The reasons for early termination must be included in Spanish in section D.2.2.1 of the end of trial form to be published at REec.

In the remarks section of the cover letter (section 2, Comments to take into account with the application), the action plan shall be indicated and whether or not it is planned to carry out additional follow-up of the subjects in the trial and its characteristics.

In those cases, in which follow-up is considered necessary, the date of the end of trial shall continue to be considered the initial date on which the sponsor reported early termination of the trial. It is not required to report the date of the end of the follow-up period.

A summary of the results of the trial should be submitted within a year after the date of early termination. The results of the follow-up period should be considered part of the results of the trial, but they may be submitted at a later date as a supplementary results report.

Notifications of early termination of clinical trials in CTIS shall be reported through CTIS Portal.

8. Should suspected unexpected serious adverse reactions be reported to the CEIm?

Created in v2; updated in v4 and v16

No. Suspected unexpected serious adverse reactions should be reported to the AEMPS but not to the CEIm. In all cases, whether the adverse reaction occurred in Spain or in another country, notification should be made only via the Eudravigilance_CTM.

The narrative of the cases may be written in English or Spanish. In the latter case it should preferably be accompanied by a summary in English.

It is not necessary to send 6-monthly reports on unexpected serious adverse reactions.

9. Should suspected unexpected serious adverse reactions and other necessary communications related to the trial be reported to the Autonomous Communities (hereinafter CCAA)?

Created in v2; updated in v5, v6 and v16

As of 31st January 2022, the reporting of suspected unexpected serious adverse reactions (SUSAR) or of annual safety reports to the health authorities of the Autonomous Communities will not be necessary.

10. Steps to be followed when a change is necessary in the evaluating CEIm of an authorised clinical trial

Created in v4

When a change is necessary in the evaluating CEIm of a clinical trial:

1. The new CEIm proposed by the sponsor must have previously accepted to take over evaluation of the trial.

2. Before sending a request or communication to the new CEIm (e.g. substantial amendment, DSUR submission, etc.), the CEIm must be

changed in both the AEMPS and SIC-CEIC computer system. This should be done as follows:

a) Request a change in the CEIm from the AEMPS via the ECM Portal using the option "E i) Ad Hoc Reports or initial notification of urgent safety measures already taken", indicating in the remarks section of the cover letter that a change in CEIm is requested and the justification for the change, providing as attached documents the XML and PDF of the updated application form where the new CEIm is listed. A separate request should be submitted for each trial.

b) Request the change in the CEIm by sending an email to which is attached the acknowledgement of receipt of having sent the Ad hoc report to incidensayos@aemps.es so that the change takes place in the SIC-CEIC computer system.

3. The request may be made when the applicant has received a message from incidensayos@aemps.es confirming that the new CEIm has been registered in the SIC-CEIC system.

11. Which documents should be submitted when applying for authorisation of a clinical trial?

Created in v1; updated in v3, v4, v5 and v10

The trial documents are essentially the same as the ones currently used, but they have been classified into part I and part II. To facilitate validation and speed up processing, it is necessary that the names of the electronic documents submitted should clearly indicate their content and, if appropriate, the version date and identify the type of document correctly when the documents are uploaded to the ECM Portal, so that the application can be considered valid (see Annex I. Trial documentation and identification of the documents when uploading them to the ECM Portal or the CTIS Portal). Due to a technical problem in SIC-CEIC, when sending something via the ECM Portal which only affects the CEIm, it is necessary for all the documents to be uploaded with the type “Other” (and NOT with the type “Documents to prove changes”) so that the CEIm can see the name assigned by the sponsor to said documents. In requests marking AEMPS or AEMPS and CEIm, when uploading the documents in the ECM Portal, the corresponding type of document must always be selected.

When the sponsor considers that the trial is a low-intervention trial, this should be indicated in the comments section of the cover letter that is completed in the ECM Portal and a suitable justification for that should be provided (see Annex I. Trial documentation and identification of documents when loaded into the ECM Portal or the CTIS Portal).

The documents on suitability of the investigator and suitability of the facilities must conform to the model forms given in Annexes III and IV.

Proof of insurance cover or financial guarantee documents are included in Annexes V to VII.

12. What information should be provided to the potential participant in the clinical trial before obtaining informed consent?

Created in v4; updated in v5 and v6

In Annex VIIIA, a guideline is provided for correct preparation of a model of information sheet for the participant in a clinical trial and the informed consent document. The paragraphs to be included in the informed consent for the collection and use of biological samples in clinical trials are indicated in Annex VIIIB.

13. How should authorisation for a substantial amendment of a clinical trial be applied for?

Created in v2; updated in v3, v5, v8, v9, v14 and v16

In the remarks section of the cover letter (section 2, Comments to take into account with the application), it shall be indicated if the amendment refers only to part I, only to part II, or to both parts. It must also be shown if the updated form attached includes a variation in any data from the information visible in REec (for example, inclusion criteria) in order to keep the Register updated.

The amendments that only affect part II must only be sent to the CEIm and those that affect the manufacture of the medicinal products or fulfilment of regulations regarding good manufacturing practices, must only be sent to AEMPS.

Given that a single substantial amendment can refer to many changes of different importance within the authorised clinical trial, it is very important with regard to its assessment that changes are shown in a simple and summarised manner to the assessor.

The structure of the current section F of the application form (which generates the table with the previous text, the current text and its justification), as well as the use that is made of it, does not facilitate a rapid assessment of its content. For this reason, sponsors are requested to submit an additional document called “Summary and justification of changes”.

The “Summary and justification of changes” document should be a summary of the changes introduced and the reasons for these in no more than 1,200 words that allows the assessor to access this information in a summarised manner in order to be able to make decisions. Therefore, the changes that are made should be adequately explained in this document, and not be a mere reference to the sections of the document that change, and the changes should be accompanied by a clear explanation or justification of the reasons for them and an assessment of the consequences of the changes for the trial participants and for the robustness and reliability of the trial results. This summary is complemented with the corresponding documents showing the old and new text and their justification or the table of changes.

When the information required in “Summary and justification of changes” is included in another document, this shall be indicated in the cover letter.

It is usual to include merely the change itself as the justification of an amendment (e.g., in the justification of a modification of a selection criterion to specify “change in selection criteria”). This justification is not considered acceptable, and the reasons why the change was made should be briefly stated. In the case of an update of different points of the investigator’s brochure, reference should be made to what is relevant in the information that is updated [e.g. The results of 4 new clinical trial are added and the evaluation of all adverse events shows an increase (4% vs. 2%) in the number of cancers in the experimental versus the placebo group]. It must be emphasised this document should not be the “table of changes” in section F of the application form of a relevant modification, or in a separate document where a comprehensive list of “previous text versus new text” in the different sections or documents listing each change indicated in the Summary of Changes, or the document changed with track changes activated, which does not replace them.

Applications not including the “Summary and justification of changes” document that clearly explains the changes and reasons for the amendment and the consequences of the amendment, or applications that are lacking modified documents with change tracking and justification for the changes, or failing this, a table of changes, shall not be accepted as valid for processing.

The authorisation and opinion of the CEIm regarding part II shall refer only to the changes specified in the table of changes and in the modified documents with change tracking and justification of the changes that were explained in the “Summary and justification of changes” document. The sponsor is responsible for all changes specified in the summary and justification of changes that correspond to the changes included in the table of changes and in the modified documents with change tracking.

When a substantial amendment is to affect various clinical trials, it is important to submit the application simultaneously for all the trials, identifying in the cover letter the clinical trials that are to be affected. This is of special interest in Amendments that refer to a change in the manufacture or in the investigator's brochure of the medicinal product.

When a substantial amendment refers to previously authorised changes for another clinical trial or is to document changes already adopted as previously reported urgent safety measures, this should be indicated in the cover letter.

The documents that should be submitted with a substantial amendment are listed in Annex I.

See also sections 30 to 36.

The Q&A document of EudraLex Volume 10 must be taken into account with regard to the submission of modifications through the CTIS Portal EudraLex - Volume 10 (europa.eu).

14. Suppressed

15. What should the financial budget include?

Created in v2; updated in v3

A single financial budget should be submitted to the CEIm per trial. This should include all aspects of the contract of all participating sites. No additional amounts to those foreseen in the financial budget submitted to the CEIm may be required by the sites, unless they correspond to fees published by the competent national or autonomous community health authority in their respective official journals.

A single document may be submitted, the single financial budget of the trial, which includes variable amounts in some items whenever necessary (e.g., indirect costs applicable to the site, costs of additional tests, administrative costs of the site, etc.). Alternatively, the set of financial budgets of each of the participating sites may be submitted.

In any event, the single financial budget per trial must contain the following information:

- Costs of additional tests and cost per visit and recruited patient, with the commitment of the sponsor that the amount to be paid covers the expenses generated by the study in each site, specifying that these amounts may vary depending on the site.

- A brief text indicating that the specific amounts and other items (indirect costs and administrative costs) shall be specified in the contract of each site.

- A note indicating that the sponsor agrees to provide the investigational medicinal products at no cost and ensure that the participation of a subject in the trial shall involve no additional cost other than that which the subject would have had to incur in the context of routine clinical practice, or otherwise, justification for the additional cost.

- Planned compensations for the participants, both the nature and amount of the compensation as well as the procedure to be followed by the sponsor to deliver the foreseen compensations, this being an especially important aspect of the financial budget to be reviewed by the CEIm.

The CEIm, if it is considered necessary for the ethical assessment of the study, may request the information it considers relevant regarding the individual financial agreements for each site.

Assessment by the CEIm is considered necessary only for those modifications that imply changes in the compensations for the participants and the investigators submitted in the initial financial budget.

The AEMPS is evaluating the possibility of including a model financial budget for the CEIm in future editions of these instructions.

16. Which contract model should be used?

Created in v2

A single contract model is still not available, so the currently available models should continue to be used.

17. What is the minimum documentation to start contract negotiation with a research site?

Created in v4; updated in v5

The agreement reached on 6 October 2016 between the AEMPS and representatives of the Autonomous Communities involved in aspects of clinical trial management on the minimum documentation necessary for requesting management of the contract to conduct clinical trials between the sponsor and the research sites and for requesting the document on the suitability of the facilities is included in Annex IX.

18. Contact persons to obtain information about the requirements for managing a contract with a research site

Created in v5; updated in v6

The contact points where the sponsor can obtain information about the requirements for managing a contract with a research site are indicated in **Annex X**.

19. When can a clinical trial be started in Spain?

Created in v1

Clinical trials with medicinal products shall be subject to prior authorisation by the AEMPS after a scientific and ethical assessment of parts I and II.

Furthermore, in the case of a clinical trial with a medicinal product that includes a genetically modified organism, the sponsor shall be required to have the relevant authorisation as provided by Act 9/2003, of 25 April, on the legal regime of the confined use, voluntary release and placing on the market of genetically modified organisms (see section 25).

To be able to start a clinical trial in a participating site, the sponsor must have the favourable opinion for conducting the clinical trial at that site issued by the CEIm, the decision for authorisation from the AEMPS, and the contract signed with the site management. In addition, the sponsor must have activated the site for the trial in the Spanish Clinical Studies Registry (hereinafter REec).

If the sponsor had technical problems to activate the site at REec, he or she may start the trial in the site after having reported the problem to incidensayos@aemps.es.

With the aim of ensuring that the information at REec is updated with regard to the participating sites and is useful for the patients, in substantial amendments involving the addition of a site the sponsor must send to the AEMPS, once the substantial amendment has been authorised, the **notification of site extension** using option D i) of the ECM Portal for an authorised trial (see also section 35).

20. Should agreement of the management of the participating sites be submitted to obtain authorisation for the trial?

Created in v1; updated in v2

No. There should be an agreement between the site and the sponsor for the conduct of a clinical trial which is expressed in the contract. Only in clinical trials in which the sponsor is an investigator who belongs to the site and signing of the contract is not required shall express agreement of the management of the participating site be required. However, this document is only for the sponsor.

The agreement of the site management should no longer be notified to the AEMPS in the case of clinical trials authorised before 13 January 2016. In these cases, activation of the site at REec shall be sufficient.

21. What fee is to be paid for the assessment of a clinical trial?

Created in v1; updated in v2, v4 and v14

The Regulation provides for a single fee payment per country but this is still not in force. Therefore, the fees to be paid to the AEMPS and to the CEIm shall be those established as up to now, and they should continue to be paid separately.

Current fees for the AEMPS are specified in article 123, Group V of Legislative Royal Decree 1/2015, of 24 July, approving the Consolidated Text of Law on Guarantees and Rational Use of Medicinal Products and Medical Devices, and may be paid electronically at https://tasas.aemps.es/tasas/gestion/inicio

On the other hand, the exemption of current fees is that provided in article 121 section 3 of the previously mentioned Legislative Royal Decree, and it is only applicable to clinical trials investigating advanced therapy medicinal products.

See section 28 on the options for reuse of a fee previously paid to the AEMPS.

The AEMPS shall inform in a timely manner of any change.

22. What has changed with respect to the procedure for authorisation of a clinical trial?

Created in v1; updated in v3, v10 and v16

A single CEIm shall evaluate the trial. This CEIm shall be the one who reports to the sponsor if part II of the application is valid and the opinion on part II.

The AEMPS shall be the one who reports to the sponsor if part I of the application is valid and the schedule for assessment. The AEMPS shall also report the result of the assessment of part I, which shall reflect the assessment of both the AEMPS and the CEIm integrated into a single position. However, the sponsor must send his or her response to a request for information on part I to both the AEMPS and the CEIm (see section 6 on how this information should be sent to the CEIm).

The AEMPS shall also issue the decision on the trial, which may be expressed as authorisation of the clinical trial, authorisation subject to conditions, or refusal of authorisation. For the decision on the trial to be authorisation or authorisation subject to conditions, this must be the conclusion on part I and also be the opinion of the CEIm on part II.

The responsibilities of the AEMPS and the CEIm with regard to the trial and the exchange of information between both bodies are set out in the collaboration memo that shall be published on the web page of the AEMPS.

Temporarily, until a common information system for the AEMPS and the CEIm is available, the sponsor must send the opinion of the CEIm to the AEMPS as soon as it is obtained, both in the case of an initial application and that of a substantial amendment affecting parts I and II. Authorisation of the trial shall always be subsequent to receipt of this document.

To send the part II opinion to the AEMPS, the sponsor can resend the email from the CEIm (sent via SIC-CEIC) to aecaem@aemps.es maintaining the subject line of the email.

In the case of applications sent through CTIS Portal, the timing and coordinated evaluation process for Part I established in Regulation 536/2014 will apply (see Q&A document in EudraLex Volume 10). In the event the application is not complete, in general, only a single request for information will be viable. The sponsor is expected to present the response together with the updated versions of the corresponding documents. The request for information (RFI) to the sponsor shall only include questions that, if not satisfactorily answered, will lead to the denial of the request or a condition in the authorization.

It is considered of interest that Spain may appear on the initial application for clinical trial authorization, receiving both Part I and Part II.

Trial authorization will expire in the CMS where no subject has been enrolled within 2 years.

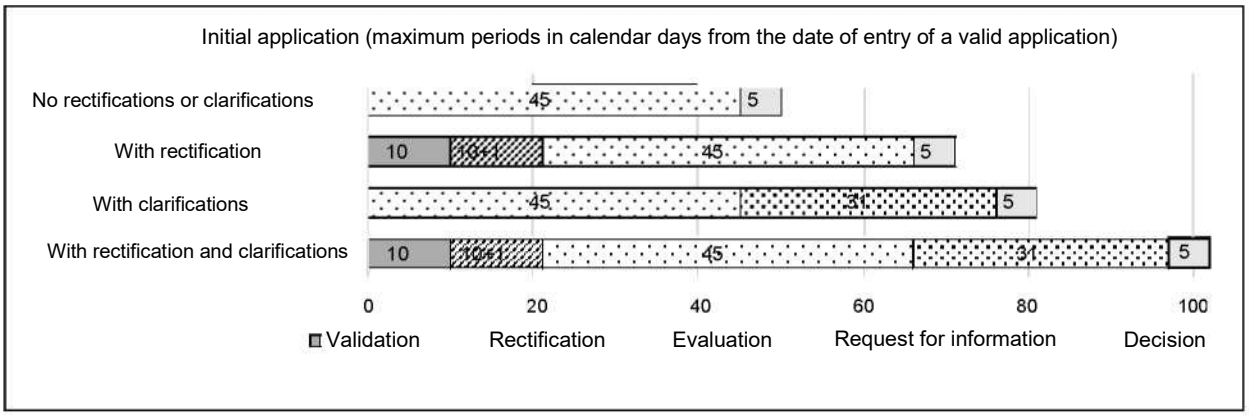
23. What is the schedule followed by an application for authorisation of a clinical trial?

Created in v1; updated in v2, v3, v10 and v16

The evaluation calendar of an application submitted via CTIS portal is as set out in Regulation 536/2014.

For an application submitted via the ECM Portal, the timing is the same, but the evaluation starts from the entry date of a valid application.

The process followed by an application from the date of entry is summarised in the following figure. In section 6 an explanation is given of what shall be considered the date of entry in the case of non-simultaneous applications to the AEMPS and the CEIm, and in the case of sending an application without an electronic signature.



The CEIm shall validate part II and the AEMPS shall validate part I in a maximum period of 10 calendar days. If rectification of the application is required, the sponsor shall have 10 calendar days to submit the requested information[3] and the AEMPS (part I) and the CEIm (part II) shall have 5 calendar days to notify the sponsor if the application is valid or not.

If part I or part II are not considered valid, the complete application shall not be considered valid.

[3] In the case of non-commercial clinical trials, the maximum period for the sponsor to reply to a request for rectification of an application shall be 30 calendar days.

If the sponsor fails to respond to a request for rectification of the application with regard to part I or part II within the requested period, the sponsor shall be considered to have withdrawn the complete trial application.

The maximum period for assessment shall be 45 calendar days as from the valid application date.

The valid application date is the next calendar day after the last effective entry date of an application that contains all the necessary documents for the AEMPS and the CEIm, taking into account that the entry date in the case of an application without an electronic signature shall be the entry date of the signed proof of electronic submission.

If there is a request for rectification, this date shall be the next calendar day after the date of the response of the sponsor to the request for rectification by the AEMPS or the CEIm. The last date if the response is with regard to part I and to part II.

However, it is currently not feasible for the AEMPS to know whether the CEIm has requested a rectification with regard to part II. Therefore, on a transitional basis, the period for assessment of part II shall start from the day after the date on which the response to said request for rectification was sent.

Both for part I and for part II, supplementary information may be requested once only, in this case the above period being extended by 31 calendar days (12 days for the sponsor to respond and 19 days to assess the response).

In the event of the sponsor failing to respond to a request for supplementary information during the assessment with regard to part I or part II within the requested period, the sponsor shall be considered to have withdrawn from the complete trial application.

If the sponsor decides to withdraw from part I or part II, the withdrawal shall apply to the complete trial application and the sponsor shall receive a decision notifying that said withdrawal has been accepted.

The AEMPS shall send the decision on the application to the sponsor and the CEIm within 5 calendar days of the date on which the assessment period for part I has expired[4] and the sponsor has sent to the AEMPS the opinion of the CEIm on part II. When the conclusion on part I is that the trial is authorised or authorised subject to conditions, the conclusions on part I shall be notified to the sponsor in the decision on authorisation of the trial. Only in the case that the conclusion of part I is to refuse authorisation of the trial shall the reasons be notified to the sponsor 5 days before receiving the decision.

The trial shall be considered to be authorised if the applicant indicated by the sponsor has not received the decision on authorisation within 5 calendar days of sending the opinion of the CEIm on part II to the AEMPS and the deadline for receipt of the conclusions on part I (whichever is later).

As an exception to the above paragraph, a written *decision* shall be required in the following cases:

- When the clinical trial refers to a medicinal product that requires or has the qualification as an investigational medicinal product (IMP), to an advanced therapy medicinal product, or to a medicinal product containing a genetically modified organism.

- When the AEMPS has notified the sponsor of a request for clarifications on part I within 45 days from the valid application date or the opinion of the CEIm is unfavourable.

- In the CTs evaluated by voluntary harmonisation procedure (VHP).

Therefore, a CT not linked to any product in the clinical research phase (IMP), neither with advanced therapy medicinal products nor with advanced therapeutic medicinal products containing genetically modified organisms, when an application for information on part I has not been made on time, can be understood to be authorised as shown in the following example: * [4]

In the case of an initial application with CEIM opinion communicated to the AEMPS on the 60th day, the CT can be understood to be authorised on the 66th day (day 60+5+1) if the decision has not been received beforehand.

24. Is the application to be considered refused in the case of clinical trials submitted through the ECM Portal requiring a written decision, if the AEMPS has not sent the decision on authorisation within the stipulated period of 5 days?

Created in v2; updated in v16

The application shall not be refused in the case of clinical trials requiring a written decision if, within 5 days of having received the favourable opinion on part II and once the deadline for notification of the conclusions on part I has expired, the sponsor has not received the authorisation. The AEMPS shall make a decision in all these cases.

[4] In the event of supplementary information on part I but not on part II being requested, the assessment period for part I may be extended up to 31 calendar days with respect to the assessment period for part II.

25. How should authorisation be applied for, according to Act 9/2003, of 25 April[5], in the case of clinical trials with medicinal products containing a genetically modified organism?

Created in v1; updated in v4, v8, v10 and v11

Further information can be found on the web page of the Ministry for the Ecological Transition Authorization procedures for voluntary release of GMOs

26. Suppressed

27. What happens if the sponsor withdraws from one of the parts of the trial or fails to respond to a request for information?

Created in v2

Any withdrawal of the application before the AEMPS or the CEIm implies withdrawal of the complete trial application. This is also applicable when the sponsor fails to respond to a request for information during validation of the application or a request for supplementary information during assessment by the AEMPS or the CEIm.

During validation, the sponsor shall be informed of the schedule for assessment and be provided with a contact point for any questions.

28. Can the application for authorisation of a clinical trial be resubmitted after withdrawal or refusal of a previous application?

Created in v1; updated in v4

Yes. In this case, the sponsor must maintain the same EudraCT number for the clinical trial and the same CEIm as in the previous application. In section A.6 of the application form, the appropriate letter for the resubmission number of the application should be indicated, A for the first, B for the second, etc.

When the previous application was not considered valid or if the previous application was withdrawn during the validation phase, the sponsor may reuse the fee previously paid to the AEMPS, provided it is the same as that

[5] Act 9/2003, of 25 April, on the legal regime of the confined use, voluntary release and placing on the market of genetically modified organisms.

corresponding to resubmission of the application, without having to pay it again.

The sponsor should indicate in the free text space of the cover letter that is completed in the Portal ECM what changes have been made relative to the previous application and must only attach the new versions of the documents that have changed. In this case, the document should include a section summarising all the changes in the document, or otherwise this summary of changes should be provided in a separate document. The application form should not be sent as an attached document. See also Annex I.

29. Is it required to send an annual report on the progress of the trial?

Created in v2; updated in v5, v6, v10 and v11

Yes, this is required, unless the trial lasts for less than a year. The annual report has the purpose of facilitating the tasks of follow-up of the trial as specified in Section 4.10 of the ICH Good Clinical Practice guidelines and should conform to the format and content indicated in Annex XI.

The annual report should be submitted annually from the date of trial **start** in Spain and until the date of the end of the trial in Spain. The data on the number of participants in the trial shall be cumulative and annual data on serious breaches, withdrawals and discontinuations and corrective measures taken shall be indicated.

The annual report shall be submitted on the appropriate date and can be sent throughout the 12 months following its beginning to facilitate the sending of all the annual reports of open studies in a shared period of one year. It shall be submitted to the AEMPS via the Portal ECM using the option “E ii) Report on trial progress” in “Authorised CT” and to the CEIm by email.

30. What is considered a substantial amendment of the trial?

Created in v1; updated in v16

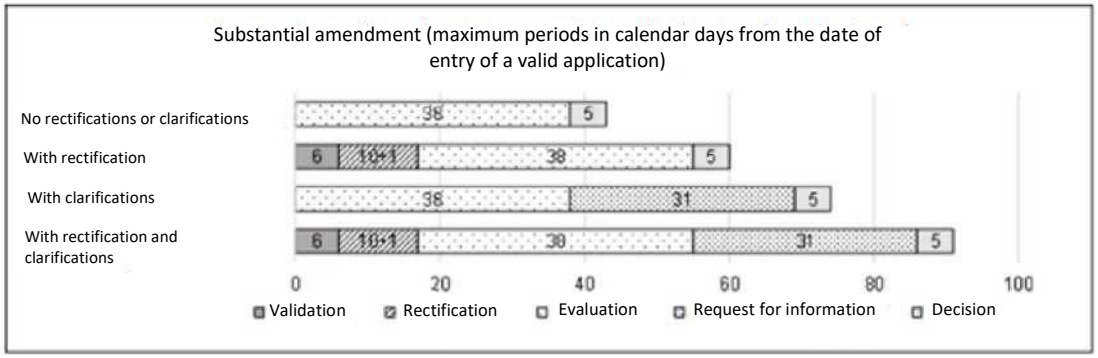
You can find examples of substantial amendments in the Q&A Document of EudraLex, Volume 10 EudraLex - Volume 10 (europa.eu)

31. What is the schedule followed by an application for authorisation of a substantial amendment?

Created in v1; updated in v3, v10 and v16

The process followed by an application complies with that indicated in Regulation 546/2014, though in applications submitted through the ECM Portal, the start date is the date of receipt of a valid application and is summarised in the following figure. In section 6 it is explained what shall be considered the date of entry in the case of applications to the AEMPS and the CEIm and in the event of sending an application without an electronic signature.

The same conditions as for validation of the initial application for authorisation of a clinical trial shall be applicable, but the validation period shall be 6 calendar days.



The assessment procedure for a substantial amendment shall be the same as for the initial application, but the assessment period shall be 38 calendar days from the valid application date.

The reply to a request for information on part I must be submitted simultaneously to both the CEIm and the AEMPS.

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

Substantial amendments implying changes in part I and part II shall be considered authorised if the applicant indicated by the sponsor has not received the decision on authorisation within 5 calendar days of the notification to the AEMPS of the favourable opinion of the CEIm on part II, once the assessment period for part I has ended (whichever is later).

Substantial amendments that only imply changes in part I shall be considered authorised if the applicant indicated by the sponsor has not

received the decision on authorisation within 5 calendar days of the assessment period end date.

Notwithstanding what is indicated in the above paragraph, written authorisation shall be required in the following cases:

- When the clinical trial refers to a medicinal product that requires or has the qualification as an investigational medicinal product (IMP), to an advanced therapy medicinal product, or to a medicinal product containing a genetically modified organism.

- When the AEMPS has notified the sponsor of a request for information (clarifications) on part I within 38 days from the valid application date or the opinion of the CEIm is unfavourable.

- When the clinical trial has been authorised by VHP.

- When the SA refers to a re-start after a temporary suspension of discontinuation of the trial for safety reasons (including lack of efficacy and lack of medicinal product quality).

Therefore, SAs of a CT not linked to any product in the clinical research phase (IMP), neither with advanced therapy medicinal products nor with advanced therapeutic medicinal products containing genetically modified organisms, which does not refer to a re-start of the trial, when an application for information on part I has not been made on time, can be understood to be authorised as shown in the following example:

✓ A SA part I and II application with CEIM opinion communicated to the AEMPS on the 69th day can be understood to be authorised on the 75th day (day 69+5+1) if the decision has not been received beforehand.

✓ A SA part I and II with CEIM opinion on the 35th day is considered authorised on day 44 (day 38+5+1) if the decision has not been received beforehand.

32. How should a substantial amendment which involves changes in parts I and II be submitted to the AEMPS and the CEIm?

Created in v2; updated in v4 and v16

The application should be submitted via the Portal ECM and at the same time to both bodies (first to the CEIm and immediately afterwards to the AEMPS), providing the documentation specified in section 13.

For applications sent via CTIS portal, see the Q&A document in EudraLex Volume 10, Chapter V.

33. Is it possible to submit a substantial amendment only implying changes in part II to the CEIm before the trial has been authorised by the AEMPS?

Created in v2

No, this is not possible.

34. Can several substantial amendments be submitted simultaneously for the same trial?

Created in v2; updated in v16

As a general rule, this is not acceptable. The submission of several simultaneous applications shall be acceptable when one of them affects changes only in part I and another affects only changes in part II, which are not related to the changes in part I, and when the modification refers to taking an urgent safety measure for safety reasons.

For applications sent via the CTIS portal, see the Q&A document in EudraLex Volume 10, Chapter V.

35. How should substantial amendments referring to changes in part II not related to a change in part I be notified?

Created in v1; updated in v16

In order to simplify assessment, the sponsor is recommended to submit substantial amendments referring to a change in the principal investigator or site extension as substantial amendments only referring to part II and hence only to the CEIm.

When the amendment refers to a site extension, the sponsor should send a notification of site extension to the AEMPS so that the new sites can be seen at REec. Said notification shall include the favourable opinion of the CEIm for the amendment and the XML of the substantial amendment form with the sites included in the opinion. In section 19, the necessary steps are indicated for starting the trial in a site, maintaining the trial information up to date at REec.

For applications sent via the CTIS portal, see the Q&A document in EudraLex Volume 10, Chapter V.

36. How should urgent safety measures including temporary halts of a clinical trial be submitted?

Created in v4; updated in v5, v10 and v16

Should there be any circumstances that might affect the safety of the subjects, the sponsor and the investigator shall take the appropriate urgent safety measures to protect the subjects against any immediate risk. The sponsor shall inform both the AEMPS and the CEIm of these circumstances and the measures taken to minimise the risks and discomforts for the participants as soon as possible. This notification should indicate the date on which the trial was halted (if it involves a partial or total halt of the trial), the justification for taking this measure, the effect of the measure (countries or sites affected when not all of them, recruitment halted, treatment interruption, complete halt of the trial, number of patients affected, etc.) and a report on the current status of the trial, at least in Spain.

This notification will be made via Portal ECM as one of the following:

- "Ad hoc report or initial notification of urgent safety measures already adopted"

- "Substantial amendment"

"Ad hoc report or initial notification of urgent safety measures already taken" will be used for notification when these measures do not imply a substantial change affecting any of the trial documents (e.g. protocol, investigator's brochure, etc.) and when the measures taken imply substantial changes but at the time of making the notification the documents required for requesting the substantial amendment are still not available.

The "Ad hoc report or initial notification of urgent safety measures already adopted" will also be used to notify of temporary discontinuations of the CT in all member States involved for reasons that do not affect the benefit-risk ratio.

When authorisation is requested for a "Substantial Amendment" in the substantial amendment form, the checkbox "E.2.5 Esta modificacion se refiere a medidas de seguridad ya adoptadas" (This modification refers to urgent safety measures already taken) should be marked "yes". When the urgent safety measure also implies a temporary halt to the trial, in the modification form the checkbox "E.2.6 Esta modificacion es para notificar una paralizacion urgente del EC" (This modification is to notify an urgent halt of a CT) will also be marked "yes" and section E.4 will be completed. In addition, as with any other substantial amendments, the "Summary and justification of changes" document and the table of changes, or failing this,

the corresponding modified documents with change tracking, shall be provided.

It is recommended to indicate in the free text box of the cover letter (carta de acompanamiento) to be filled in Portal ECM if the urgent safety measure was previously notified as an ad hoc report.

If the trial is terminated as a result of the reason that led to a temporary halt, the relevant notification of termination of a clinical trial should be made.

For applications sent via CTIS portal, see the Q&A document in EudraLex Volume 10, Chapter V.

37. Particularities in the time schedules during the Christmas period

Created in v1; updated in v4 and v16

Between December 23rd and January 7th there shall be a clock stop in all applicable time frames 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.

38. Suppressed

39. What is considered to be an auxiliary medicinal product in a clinical trial?

Created in v1; updated in v11

The term 'auxiliary medicinal product' is equivalent to the term 'non investigational medicinal product'. Auxiliary medicinal products are described in the specific guideline in EudraLex Volume 10, Chapter III.

40. Should the sponsor of a clinical trial provide the investigational medicinal products and auxiliary medicinal products in the trial?

Created in v1

The sponsor is responsible for providing the investigational medicinal products at no cost. In clinical trials sponsored by an investigator of a site or a non-profit scientific entity, or in those where there is mutual agreement with the site management where the clinical trial is to be conducted, other means of supply may be agreed with the site, particularly when treatment of the patients in the trial, or part of it, were the one they would receive if

they decided not to participate in the trial. In any case, the sponsor must ensure that participation of a subject in the clinical trial shall involve no additional cost other than that which the subject would have had to incur in the context of normal clinical practice.

41. Publication of the dates of trial start, of first visit of the first subject, of the end of recruitment, of the end of the trial, of reasons for early termination and of date of the final Summary of results report at REec

Created in v1; updated in v4, v5 v6 and v9

The sponsor must notify the AEMPS and the CEIm of the following trial dates:

1. *Trial start date in Spain.*

In general, the first act of selection of **potential subjects** for a clinical trial This could be understood as the start date of the trial in the first site, that is, the date on which it is considered that the first site is ready to begin to recruit.

2. *Date of first visit of the first subject included in Spain.*

This should be understood as the date on which the first subject selected in Spain or his/her legally designated representative signs informed consent to participate in the trial.

3. *Recruitment end date in Spain.*

This is considered as the date on which subject selection is Spain is concluded.

4. *Trial end date in Spain and trial end globally.*

In general, the trial end date will be considered as the date of the last visit of the last patient. If the trial ends without having recruited any patients, the end of the trial shall be considered an early termination.

In the case of early termination of the trial, it will be considered as the end date of the trial.

The maximum period for notification in all cases shall be 15 calendar days from the date of occurrence of the circumstance, specifying the reasons in the case of an early termination (see also section 7). The reasons for early termination must be included in Spanish in section D.2.2.1 of the end of trial form to be published at REec.

All dates related to the trial shall be reported via the ECM Portal using the applications for an authorised clinical trial. The trial start date shall be indicated using section "A. Notification of trial start date". The date of the first patient visit and the recruitment end date in Spain and the end date globally shall be indicated in the cover letter of section “E) i) Informes Ad Hoc o notificacion inicial de medidas urgentes de seguridad ya adoptadas” (Ad Hoc Reports or initial notification of urgent safety measures already taken). The trial end date in Spain shall be notified using "F. Notificacion de fin del ensayo” (Notification of trial end date). If the end date in Spain and the global end date coincide or are less than 15 days apart, a single notification using “F. Notificacion de fin del ensayo (Notification of trial end date) can be made, indicating this situation in the cover letter and specifying the global end date when this is different to the end date in Spain.

In addition, the sponsor shall send a copy of the summary of results published in EudraCT to the AEMPS and the CEIm no later than one year after the date of the end of the trial. The only time when sending results shall not be applicable is when the trial has been carried out only in Spain and has ended early without recruiting any patients.

The trial results should be sent via the ECM Portal using the section “E. Informe sobre el ensayo iii) Informe final de resultados” (Trial report iii) Final report of results).

When the analysis of the results of a substudy of a clinical trial ends on a later date than the rest of the trial, it shall be necessary to submit the summary of the results to the AEMPS and the CEIm during the year following the end of the trial, without this involving a delay in submitting the results of the rest of the trial.

All the information mentioned above shall be published without delay at REec.

It is important that the sponsor report to the AEMPS all dates and information that should be published at REec, even if there is a delay with regard to the periods established for this communication.

42. Update of participating sites in a clinical trial at REec

Created in v4; updated in v5, v6 and v9

When the AEMPS authorises a clinical trial or processes a notification of site extension, the sites accepted by the CEIm in the opinion on part II will be visible at REec and listed as “no iniciado” (not started).

In order to facilitate participation in the trial and follow-up of the activity of the sites participating in the trial, the person designated by the sponsor as responsible for updating the information at REec must keep the status of the sites updated as follows:

- ***No iniciado*** (Not started): the trial is authorised and the site has the favourable opinion of the CEIm to participate in the trial, but the trial has not started in the site (red). If the site finally decides not to participate in the clinical trial, the state "**Not initiated**" and not "**Closed**" must be left, because it could cause confusion by looking as if it has been open at some point.

- ***Activo*** (Active): from the time the site begins to accept new subjects to participate in the trial until the last visit of the last treated subject takes place and the site is closed (green).

- ***Cerrado*** (Closed): The trial has ended in that site (white).

43. Sponsor contact at REec

Created in v4

The contact that is shown to request more information about the trial at REec corresponds to the information in section: "B.5 Contact point designated by the sponsor to obtain additional information about the clinical trial" from the initial application form.

Since this is a contact of interest for investigators and potential participants in the trial, the sponsor needs to select a mailbox (preferably institutional), where it is possible to answer in Spanish the queries made in Spanish and it is also of great interest and highly recommendable that the telephone is in Spanish.

44. Person or entity designated by the sponsor as responsible for the study at REec

Created in v4; updated in v8

The person or entity designated by the sponsor as responsible for the study at REec is responsible for updating the trial information at REec. When submitting the application for authorisation of the trial, the applicant will indicate in the cover letter the email of the one designated by the sponsor as responsible for the REec as follows: next to the text: "Responsable de la informacion del estudio en REec" (responsible for study information at REec), "Usuario responsable en REec" (User responsible in REec) should be selected and where it is indicated "Especifique el Correo electronico del Usuario responsible de la informacion en REec" (Specify the email of the user responsible for information in REec) it is very important to include an

email address. This responsible person or entity will receive in the specified email a message to active his/her account in REec when the trial is published due to being authorised. If this information is not correct, the access codes will be automatically sent to the email specified in point C.1.4.6 of the initial application form: Solicitante a la AEMPS (Applicant to the AEMPS).

The responsible for the study on REec will keep track of the information at REec. He/she may create new users (without limit) and assign e them to their clinical trials or delete them. He/she must also add the study rationale and manage activation and closing of the sites.

In case of difficulty, please, indicate which is the problem in an e-mail and send it to reec incidencias@aemps.es

45. What information can the responsible person for the clinical trial at REec manage?

Created in v4; updated in v5 and v8

After entering the REec web page with his/her username and password, the responsible person for the clinical trial may:

- Edit the study rationale.
- Change the states of the trial sites (not started, active, and closed).
- Assign or delete users to their study. These users can be registered by the responsible for the study at REec.
- A phase I clinical trial not including paediatric population, will be published with reduced information at REec. The responsible for the study at REec can expand publication to all the clinical data by pressing the green button F1 “publicar datos de fase I” (Publish phase I data). As a result, the trial will show the same amount of information as all other trials.

46. How can I change the user responsible for the clinical trial at REec?

Created in v4; updated in v8

The responsible for the trial on REec can create a new responsible user and cease to be so. In order to do that, he/she has to enter at REec with his/her access codes, open the study and press the blue button “reasignacion de studios” (re-assignation of studies).

47. What information is published at REec?

Created in v4; updated in v5 and v8

The data published at REec are from the application form, trial dates and results provided by the sponsor via the Portal ECM. The only information that must be included directly on REec is the trial rationale and management of the status of the sites.

Management of the status of the sites

This is done by clicking directly on the site in the study detail and modifying the value from "no iniciado (not started)" to "activo (active)" when the trial is started in the site or to "cerrado (closed)" when the trial has ended (see also section 42).

Rationale

The responsible for the clinical trial on REec must include this information within 14 days of publication of the trial and it is then validated by the AEMPS. The information will be made public when it has been validated by the AEMPS.

The rational for the CT has to meet the following characteristics:

1. Language should be appropriate for lay persons, avoiding as much as possible, abbreviations and signs.
2. It should be in both Spanish and English.
3. No more than 2000 characters.

In case the validation is not passed due to non-compliance with some of the required characteristics, this will be notified to the responsible for the study at REec asking for an amend of such information.

Publication of studies

As soon as the clinical trial is authorised, it is published at REec. Then, the responsible for the study on REec will receive an e-mail with the confirmation of publication of the study.

If the responsible for the study on REec does not have any study assigned previously at REec (i.e., he/she is not a registered user at REec), he/she will receive an email at the time of publication of the clinical trial with the user and password to do the management of his/her trial at REec.

If he/she is listed as a registered user at reec, an email will be sent indicating that a new study has been published associated with his/her username.

Publication of phase I studies not including the paediatric population

Publication at REec is automatic for all authorised clinical trials. However, when they are phase I and do not include the paediatric population, only reduced information of the trial is published (EudraCT No, sponsor, phase, type of study population and number of subjects, study scope, participating sites, trial dates). The responsible for the REec can expand the publication to the standard information available for all trials.

Publication of the trial dates and reasons for early termination

See section 41.

Publication of clinical trial results summary

The summary report of results sent to the AEMPS (see section 6) will be automatically published at REec as soon as it is received. The sponsor will be solely responsible for the accuracy of the data provided.

48. Summary of intermediate report of results and summary of the final report of results

Created in v5; updated in v8 and v9

It can be foreseen in a clinical trial that there may be several analyses of results that are performed at different times (e.g. efficacy and safety after all patients have followed 1 year of treatment and after 3 years of treatment). In these cases, as required in Article 37.8 of Regulation 536/2014, a summary of these results should be reported to the Member States. On the other hand, a publication of the analysis of intermediate results is commonly made.

When it is planned to perform intermediate results analysis in a trial, the sponsor must indicate if it is planned to make public these analyses before the final analysis of results is available. If in the authorised protocol it is planned to publish intermediate results before the end of the trial, the sponsor must send a summary of the intermediate results using option “E. i) Informes Ad Hoc o notificacion inicial de medidas urgentes de seguridad ya adoptadas” (Ad Hoc Reports or initial notification of urgent safety measures already taken) within one year of analysis of the intermediate data.

The summary of intermediate results and the summary of final results should not be a preliminary or draft analysis but contain the final data of the analysis.

49. Aspects that should be taken into account by the sponsor so that data collection in the Case Report Form (CRF) complies with legislation on data protection

Created in v5; updated in v9

The CRF (Case Report Form) of a clinical trial is not a document to be included in the application for authorisation of a clinical trial and therefore should not be submitted to the AEMPS or the CEIm. The key aspects so that the sponsor can comply with current regulations are highlighted in this section.

Regulation (EU) No. 536/2014 requires that the data of trial subjects be processed in accordance with EU legislation on data protection. In Spain, application legislation is the Organic Law 3/2018, of 5 December, on the protection of personal data regarding Protection of Personal Data and Guarantee of Digital Rights, complementary to Regulation (EU) 2016/679 of the European Parliament and of the Council, of 27 of April 2016, relating to the protection of natural persons with regard to the processing of their personal data and the free circulation of these data repealing Directive 95/46/EC. This legislation requires the application of high-level security measures in the management of health data, so that the distribution of the supports is done encoding these data or using another mechanism that guarantees that this information is not accessible or manipulated during transport.

Health-related data are considered by the LOPD to be specially protected data that warrant a stricter regimen of protection, which is a wider concept including information regarding the past, present and future physical or mental health of an individual, as well as the level of disability and genetic information of the person. For this reason, the case report form should only include a code not allowing identification of the subject. In addition, identifying data of the subjects participating in the study cannot be collected: the medical history number or similar assigned by the Administration, name, surname, or initials of the subject, postal or email address, telephone number, tax identification number, digital fingerprint, DNA, a photograph, social security number[6].

[6] Farmaindustria's "codigo tipo" for personal data protection in clinical research and pharmacovigilance

In some clinical trials in which the sponsor may require access to personal data of the subjects participating in a clinical investigation study, this situation must be justified in the protocol and specified in the informed consent of the participating subject. In this case, the sponsor is required to notify previously the creation of a file of Case Report Forms (FCRD) in the Register of the Spanish Data Protection Agency (AEPD).

50. How long should the master file of a trial authorised with Royal Decree 223/2004, of 6 February 2004, regulating clinical trials with medicinal products, be retained?

Created in v3; updated in v16

The legislation applicable to the archiving period of the master file from the entry into force of Royal Decree 1090/2015, of 4 December, is its article 43, according to which "1. The clinical trial master file shall comply with the provisions laid down in articles 57 and 58 of Regulation (EU) No. 536/2014 of the European Parliament and of the Council, of 16 April 2014. The content must take into account the supplementary guidelines in this regard published by the European Commission. 2. The sponsor and investigator shall keep the contents of the master file in paper or digital format of each clinical trial **during at least twenty-five years after the end of the trial**, or for a longer period if this is set down in other applicable requirements, such as in the case of the study being submitted as a basis for the authorisation of a medicinal product which must comply with Annex I of Royal Decree 1345/2007, of 11 October, or an agreement between the sponsor, the investigator and the site(...)".

51. When should observational studies be loaded into the REec?

Created in v2; updated in v4 and v16

You can find more information at this link

52. How should the serious breaches referred to in article 29 be reported?

Created in v2; updated in v5, v6 and v16

The sponsor of a clinical trial should report to the AEMPS and the CEIm a serious breach of current clinical trial legislation or of the version of the protocol authorised at the time of the breach that has occurred in Spain without delay and not later than seven calendar days from becoming aware of the breach.

For this purpose, a serious breach shall be understood to be a breach that may significantly compromise the safety and rights of the trial subjects or the reliability and robustness of the data obtained in the clinical trial.

Until submission via the Portal ECM is feasible, serious breaches should be reported to the Department of Inspection and Control of Medicinal Products of the AEMPS via the email incumplimientosgraves@aemps.es. The report shall be made using the form and according to the instructions in section "4. Notificacion de Incumplimientos graves de un ensayo clinico" (Notification of serious breaches of a clinical trial) in http://www.aemps.gob.es/industria/inspeccionBPC/home.htm.

Serious breaches shall be reported to the CEIm via email.

From publication of these instructions, only deviations considered a serious breach should be reported to the AEMPS and the CEIm. Deviations which are not considered a serious breach do not need to be reported to the AEMPS; however, it is important to note that a deviation that is repeated several times could be considered a serious breach.

For clinical trials authorized on CTIS, the information on serious breaches shall be submitted to the CTIS as indicated in the Q&A document in EudraLex Volume 10, Chapter V.

Queries about this subject should be sent to the email area_bpc_bpfv@aemps.es

53. Clarification on application in Spain of Annex VI of Regulation (EU) No. 536/2014 on labelling of investigational medicinal products and auxiliary medicinal products

Created in v4

Until the above Regulation is fully applicable, Annex 13 "Manufacture of Investigational Medicinal Products" from Good Manufacturing Practice will continue to be applicable in Spain.

54. In which cases shall it be required to request authorisation of compliance with good manufacturing practice by the AEMPS for the manufacture or distribution of medicinal products by the hospital pharmacy department?

Created in v7; updated in v15

54.1 This authorisation shall be required for total or partial manufacture of investigational medicinal products, as well as for some processes of dividing up and packaging, whereas the following processes shall be exempt:

a) Relabelling.

b) Repackaging, when it consists of:

- modification of the secondary packaging of all dosage forms.
- modification of the primary packaging only for solid oral dosage forms (tablets and capsules).

  Although authorisation is not required in these cases, the application for clinical trial authorisation must be accompanied by the following documentation:

  • Standard operating procedure (SOP) describing in detail the modifications of both the primary and secondary packaging occurring in the investigational medicinal products.

  • In cases of modification of the primary packaging, an evaluation of the impact that this modification may have on the final quality of the product should be provided. This is to provide justification for the suitability of the new primary packaging of the investigational medicinal product and the expiry date and stability of the modified medicinal product in its new packaging.

c) Reconstitution. Reconstitution shall be understood as the simple process of:

- dissolving or dispersing the investigational medicinal product for administration of the product to the trial subject, or
- diluting or mixing the investigational medicinal product with some other substance used as a vehicle for the purpose of administering the product (without being repackaged in a new packaging).

Reconstitution is not the mixing of different components of the formulation, including the active ingredient, to produce an investigational medicinal product.

The investigational medicinal product has to exist previously so that a process can be defined as reconstitution.

The reconstitution process should be immediately before administration.

This process has to be defined in the clinical trial application/investigational medicinal product dossier and in the clinical trial protocol or related document available in the site.

54.2 When the investigational medicinal product(s) are distributed from a hospital pharmacy department to the other sites participating in the trial, authorisation of compliance with good manufacturing practice should also be requested for those sections applicable to distribution.

In any case, when the hospital pharmacy department is to be involved in tasks other than the dispensing of investigational medicinal products, the sponsor must inform the pharmacy department of the procedures that are intended to be carried out in said department prior to the authorisation of the clinical trial.

55. Is authorisation by the AEMPS required to prepare a magistral formula intended for a clinical trial?

Created in v7

Magistral formulas and officinal preparations are medicinal products for human use that are defined in Article 8, paragraph 1b and 1c of Royal Legislative Decree 1/2015, of 24 July, approving the consolidated text of the Law on guarantees and rational use of medicinal products and medical devices.

In the event that the investigational medicinal product meets the definition of a magistral formula or officinal preparation prepared in an authorised pharmacy department (as defined in RD 175/2001), the following shall be taken into account:

A) If the investigational medicinal products are classified magistral formulas or officinal preparations, as they are formulas known and described in the National Formulary manufactured in an authorised pharmacy department, it shall not be required to request authorisation of manufacturing from the AEMPS. In this case, the following should be done:

- Attach, along with the other trial documentation, a document with the reference to the magistral formula in the National Formulary. A copy of the relevant page of the National Formulary containing this formulation is acceptable.

- Indicate this in the cover letter filled in in the Portal ECM: in the section “Descripcion de los procesos realizados por la Oficina de farmacia” (Description of processes performed by the pharmacy department), choose the option “Otras” (Other) and specify “Classified magistral formula”.

B) If the investigational products are unclassified magistral formulas (i.e., not described in the National Formulary), the relevant authorisation must be requested from the AEMPS. The procedure detailed in the next point of these instructions shall be followed.

In the event that this unclassified magistral formula is prepared regularly in the Pharmacy Department, this should be stated in the “comments” section of the cover letter and the available data on efficacy and safety of this treatment be provided.

56. What is the procedure for requesting authorisation of manufacturing/distribution by the hospital pharmacy department?

Created in v7

At the same time as submitting the application for clinical trial authorisation, the request for authorisation of manufacturing by the pharmacy department should be included providing the following documentation:

1. APPLICATION FORM for authorisation of manufacturing specifying the following:

- Title of trial and EudraCT No.

- The investigational medicinal product it is desired to manufacture and its dosage form (this includes any placebo).

- Pharmacy department where the manufacturing process will be performed.

- If the investigational medicinal product will be delivered from a pharmacy department to the other participating sites.

The application must be signed by the SPONSOR and by the person responsible for the PHARMACY DEPARTMENT.

2. PROTOCOL (or protocol summary): It shall include complete information about the manufacturing operations to be performed in the pharmacy department.

3. DOCUMENT EQUIVALENT TO THE INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER QUALITY PART, where the following is specified:

- The manufacturing operations involved; types of placebo and blinding that are planned to be performed, indicating the medicinal products and pharmaceutical forms to which they refer.

- The manufacturing and control process, with the relevant documentation.

- Identification of the manufacturing site, specifying the premises, technical team and control processes.

4. AGREEMENT AND ACCEPTANCE of the Director of the site where the manufacturing operations are to be performed. This agreement is different from the agreement of site management to conduct the clinical trial.

5. SOP for distribution of investigational medicinal products when the pharmacy department will send the medicinal products of other trial sites.

57. Suppressed

58. Suppressed

59. Clinical research with cells and/or tissues that are not considered medicinal products.

Created in v11

The CEIm/CEI can receive for their evaluation clinical studies or trials in the field of clinical research with cells and/or tissues.

The human cells and/or tissues are considered advanced therapy medicinal products when they undergo substantial manipulation and/or are used with a different function to their original one. In case of doubt regarding the classification of a product of this type, it is the AEMPS who must proceed to classify it, for which the study sponsor must send the classification

application for advanced therapy medicinal product via the following form: https://www.aemps.gob.es/medicamentos-de-uso-humano/investigacionclinica_medicamentos/form_solicitudasesora_terapiavanzada/

The authorisation of clinical research studies with human cells and/or tissues which are not considered medicinal products is regulated by that specified in article 29 of Royal Decree 9/2014, of 4 July, by which are established the quality and safety standards for the donation, obtaining, evaluation, processing, preservation, storage and distribution of human cells and tissues and the regulations of coordination and functioning for use in humans are approved.

The sponsor must send the study for evaluation to the CEIm/CEI and for its authorisation to the competent authority in each Autonomous Community (usually, the Autonomic Coordination of Transplants) who will require it to be evaluated by the committee of experts of the Inter-Territorial Transplant and Regenerative Medicine Organisation of the National Health System.

If in doubt regarding the administrative procedure to follow in said studies, you can process your consultations via ont@mscbs.es indicating CLINICAL STUDY WITH CELLS and/or TISSUES.

60. Exceptional measures applicable to clinical trials to manage problems arising from the COVID-19 emergency

This section of version 12 of 29 June 2020 updates the informative note of 04/2020 of 5th May 2020. This section is updated in v. 13 of 30 November 2020. Paragraph 7 has been updated in v. 14 of 30 April 2021. Section 7 has been updated in v.15, 16th September 2021.

The Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) [Spanish Agency for Medicines and Medical Devices], as competent national authority in the authorisation of clinical trials, underlines the importance of the measures approved in the EU Council of Health Ministers on 27 April 2020[7] of exceptional application during the period which the COVID-19 crisis lasts in Spain, and indicates the specific aspects of its implementation in our country. These measures are intended to preserve the trial activities as far as possible, guaranteeing healthcare to the patients, protecting their safety and well-being and preserving the traceability of actions implemented in this health emergency situation.

This section aims to clarify the aspects of its application specific to Spain, in particular with regard to the form of obtaining the informed consent, the

[7] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

distribution of study drugs to the home of the patient, the remote monitoring of source data and form of communication of these measures to the AEMPS and the Drug Research Ethics Committee (CEIm).

It is essential to maintain as much as possible the capacity of the health system, reducing the risk of infection for the population. Also, the measures taken in the different autonomous communities following the declaration of the state of alarm by the Government must be taken into account.

In this context, the scheduled follow-up visits and the access of non-site staff and in situ monitoring could be affected. In some cases, it might be necessary to transfer a patient from one site to another to facilitate their healthcare or send the trial drugs to their home. Meanwhile, there could be a reduction in sponsor's staff entrusted with trial follow-up.

It is important that the sponsor, together with the investigator, carries out a risk analysis and prioritises critical activities and the way they must be carried out. Both of them must also evaluate the application of these measures proportionately to each clinical trial considering its particularities, the organisation of each site and the epidemiological characteristics of COVID-19 at each site. These measures could be updated to adapt to epidemiological evolution according to the decisions of the Ministry of Health and will be valid until they are expressly revoked.

1. Scheduled in-person visits for clinical trial patients

The sponsor, together with the investigator, must consider the advisability of postponing said visits, or turning them into telephone visits, re-scheduling them on the clinical trial schedule of visits. It must be guaranteed that the critical scheduled in situ visits are carried out. In the case of rescheduling visits, these protocol deviations will not be considered serious non-compliance unless they put the patient's safety at risk.

2. Recruitment of new patients

Expected prospective protocol deviations are unacceptable and it is to be expected that all subjects included in a clinical trial comply with all selection criteria. The sponsor together with the investigator, based on a risk/benefit assessment which takes into consideration the characteristics of the trial and circumstances of the participating sites shall be able to cease recruitment and even discontinue the treatment of trial patients with the aim of avoiding unnecessary risks and guaranteeing the best possible healthcare for the patients. This analysis is especially pertinent in clinical trials which involve treatment with immunosuppressants and therefore a greater risk of infection, without any expectation of benefit for the participants.

3. Access to trial treatment

Patients' access to the trial drug must be guaranteed in the same conditions in which it was being given. It is recommended that the investigator assesses the possibility and advisability that, when the patient attends a scheduled visit, he/she receives an amount of the drug to cover a longer period of treatment.

The Pharmacy Departments of hospitals will be able to take the measures they consider necessary, for example, the dispensing to a person authorised by the trial patient of a treatment which must be taken at home or the sending from the Pharmacy Department of the treatment to the patient's home when their circumstances make it advisable. With regard to the latter, preservation of the treatment must be ensured during transport, and communication with the patient, allowing treatment reception and appropriate administration of the same must be maintained.

In the exceptional case that, being necessary, the Pharmacy Department cannot send the trial treatment to the patient's home, said Department might consider other alternatives and entrust the sponsor to organise dispatch via an authorised drug distributor.

The situation must be assessed in each particular case by the sponsor, the principal investigator and the Pharmacy Department following the instructions and directives of the UE1 and section four of order SND/293/2020[8].

In the case of a discontinuation of the trial due to lack of supplies of some drug, the sponsor must adopt the necessary measures to guarantee the alternative treatment of the patients. This discontinuation and the measures adopted will be communicated by sending an ad hoc report to both the AEMPS and the CEIm in the 15 days following the discontinuation.

4. Informed Consent

Obtaining consent in COVID-19 studies

Consent must be obtained preferably in writing. However, to guarantee that the process of obtaining the informed consent is carried out avoiding the risk of contagion, allowing the recording of the patient's willingness, and in line with that included in the current ethical and legal recommendations, the consent can be obtained orally and preferably before a witness[9], documenting it in the patient's medical records and ratifying it later in writing by means of the patient's signature and that of

[8] Order SND/293/2020, of 25 March.

[9] Providing the epidemiological situation of the pandemic allows it.

the investigator, as far as possible and making a reasonable effort to obtain it.

In the case of a patient without the capacity to consent or a minor, the consent must be obtained from their legal representative. If the subject's condition so

permits, and in any event if the minor is aged twelve or more, he/she will also give his/her consent to participate in the study.

In the case of emergency situations, article 7 of Royal Decree 1090/2015 will apply.

Obtaining informed consent in studies already underway to continue the study

Consent must be obtained preferably in writing. However, taking into account the epidemiological situation of the pandemic, and to avoid the patient having to go to the sites to sign the consent, it is permissible to get the consent orally (for example, by telephone or video-call), documenting it in the patient's medical records and ratifying it later in writing by means of the patient's signature and that of the investigator.

The principal investigator or the person who has been designated by him/her must send the patient information sheet (PIS) to the patient by email or courier. The later ratification in writing by means of the patient's signature and that of the investigator can be carried out by mail, by audio-visual means or digital images. The patient can send the scanned, signed PIS by email, or can take a photo of the signed consent and send it to a telephone only accessible to the research team. This image file must be printed out and maintained in the investigator's file as proof of signature.

5. Monitoring visits

It is advisable for the sponsor to update the trial monitoring plans for the coming months for the duration of the pandemic, adapting the exceptional measures to the epidemiological situation. Priority will be given to centralised monitoring and remote monitoring of the participating sites that do not involve giving excessive work to site staff and postponing, as far as possible, the verification of source data until access to the medical records in person is possible. The sponsor will agree conditions for said monitoring with the participating sites and teams.

Remote verification of source data shall be considered for all ongoing clinical trials as long as it is carried out with all the safeguards and precautions shown in the directives of the UE[1] *and with the requirements established by the Spanish Data Protection Agency*[11]*, and therefore shall*

require the prior approval of each site with the approval of the data protection delegate of the same.

Previous approval will not be required for a substantial amendment by the CEIm nor the authorisation of the AEMPS. Neither will it be necessary to have the patient's express consent to carry out the verification of source data during remote monitoring, given that this activity is legally regulated as a necessary activity in the trial. For that reason, the informed consent given to participate in the trial implies that it is carried out in the terms established in the regulations which govern it, in that they establish that the monitor can access the necessary clinical information for the proper execution of the trial[12].

The changes adopted in the monitoring data plan together with the acceptance on the part of the principal investigator of the site where the remote monitoring with verification of source data will be carried out and the acceptance on the part of the data protection delegates of the sponsor and the research site will be adequately documented and will be kept in the clinical trial file. Also, they will be made available to the AEMPS if required.

The AEMPS is working on the necessary standards so that remote monitoring with data verification can be viable once the pandemic is overcome.

6. Transfer of patients from one site to another

If it were necessary to transfer a patient from one trial site to another trial site, this could be carried out as long as:

a) a transfer agreement between sites is signed

b) the new site has access to the case record form and the medical records of the patient (or, failing that, the original site sends them a copy of the same)

c) the original site sends a transfer report summarising the most relevant medical data of the patient with regard to the trial to facilitate their follow-up at the new site

d) the transfer of the patient is documented in the trial file of both sites. No prior acceptance of this change by the CEIm is required

The opening of a new trial site requires the prior approval of a substantial amendment by the CEIm and for clinical trials in COVID-19, depending on the urgency, submission of reduced documentation is being accepted. Said

approval will be notified later to the AEMPS as an extension of sites so that the new site can be published at REec [Spanish Clinical Studies Registry].

7. Notifications to the CEIm and the AEMPS

Any of the exceptional measures adopted due to these recommendations must be duly documented in the trial archive. However, their application does not require prior approval on a case-by-case basis as a substantial amendment by the AEMPS or CEIm and neither the individual notification of serious non-compliance they involve. Those changes carried out in the studies which do not affect the welfare and/or safety of the patients, or the quality of the data should not be processed as substantial amendments either.

As for urgent measures, the following shall not require individual notification within the period of 15 days:

– The dispatch of study drugs to the patient's home. This dispatch in all cases must be approved by the site's Pharmacy Department.

– The carrying out of tests in a local laboratory instead of at the expected site.

– The transfer of patients from one trial site to another trial site.

The sponsor must prepare, for each trial, a report about all the exceptional measures adopted, together with the risk assessment carried out and its justification which will be sent to the Agency and the CEIm in the four months following *21st June 2020,* the date in which it is considered that the state of alarm due to the health emergency caused by coronavirus COVID-19 crisis has ended in Spain[13], via the ECM Portal as E ii) Report on trial progress. The model indicated in annex XII of this document will be used. If it is necessary to take new exceptional measures, or there were updates on the exceptional measures taken after 21st June, these shall be notified to the AEMPS and CEIm in a complementary report on a four-month basis (i.e., reports covering 4-month periods, to be submitted within 30 days after the period covered by the report) using Annex XII and the same submission format. Section 5 of Annex XII shall indicate the sites where monitoring with remote verification of source data has been performed.

61. Application of the interruption of deadlines arising from the COVID-19 emergency for the authorisations of clinical trials

Created in v12

In accordance with that established in the third additional provision, section 1, of Royal Decree 463/2020, of 14 March, by which the state of alarm is declared for the management of the health crisis situation caused by COVID- 19, "Terms are suspended and deadlines are interrupted for the processing of the procedures of the entities of the public sector", from its entrance in validity, that is, **from 14 March 2020**.

Said suspension of deadlines was lifted effective **from 1 June 2020**, in accordance with that established in the sole repealing provision, section 2, of Royal Decree 537/2020, of 22 May, by which the state of alarm declared by Royal Decree 463/2020, of 14 March, is extended.

This section aims to clarify the doubts voiced with regard to the form in which the AEMPS is applying this suspension of administrative deadlines for the decision of authorisation applications for clinical trials and substantial amendments, in particular to calculate the date in which it would operate in tacit approval when applicable.

In the following assumptions, the date appearing in the calendar of the validation document which is sent to the applicant is considered the foreseen date of authorisation in case no information request has been sent and without taking into account the aforementioned deadline suspension. When the foreseen date of authorisation is 14 March or later, the new date of authorisation foreseen taking into account the period of deadline suspension mentioned above will be calculated as follows: first, the number of days from 14 March (inclusive) to the foreseen date of authorisation is calculated; then, the corrected foreseen date of authorisation is calculated by adding those days from 1 June.

Examples:

Foreseen date of authorisation in the Validation Calendar	*Days from 14 March*	*New foreseen date of authorisation with deadline suspension*
14-Mar-20	*0*	*1-Jun-20*
15-Mar-20	*1*	*2-Jun-20*
30-Mar-20	*16*	*17-Jun-20*
15-Apr-20	*31*	*2-Jul-20*

In case of doubt, you can consult with the Clinical Trials Unit aecaem@aemps.es

62. Clinical trials aimed at investigating new drugs against coronavirus

Created in v13

The situation produced by the COVID-19 crisis is evolving towards a new scenario in which the number of patients is decreasing day by day. However, cases have not disappeared, infected patients continue to evolve in the sites, and we must be prepared for possible changes in the epidemiological situation in the coming months.

In this context, it is important to join efforts around large clinical trials with statistical power to complete recruitment and obtain results that help in clinical decision making, as well as making the necessary decisions to be prepared for a potential increase in cases. Researchers should evaluate the interest of joining clinical trials that are already underway (see the Spanish Clinical Trials Registry (REec) https://reec.aemps.es/reec/publiclweb.html) before considering launching new trials.

The AEMPS, together with the CEIm, continues to prioritise the evaluation of clinical trials aimed at treating or preventing COVID-19, and these types of studies are evaluated as soon as possible, within a maximum period of fifteen days.

Sponsors or investigators with a clinical trial project of this type should send their application to both CEIm and the AEMPS through the ECM Portal (see Instructions for conducting clinical trials in Spain), alerting of the submission by sending a message to aecaem@aemps.es with the subject "URGENT COVID- 19" and identifying the trial with the EudraCT number. The title of the trial must include the word "COVID-19" and if it is a vaccine, also the word vaccine.

To consult only specific aspects of the trial design prior to formal application, it is necessary to indicate the specific questions by attaching a summary of the trial and the data justifying the biological plausibility of the effect sought in the conditions of use of the drug in the trial to aecaem@aemps.es, preferably adding the CEIm in the cc: field, indicating in the subject line: "URGENT new CT on COVID-19" and the name of the investigational drug. A reply will be given as soon as possible within a maximum of fifteen days.

Please note that for answers on more global aspects of drug development, the Nacional Scientific Advisors (ascina@aemps.es) or the Innovation Support Office (innov spain@aemps.es) shall be contacted.

To facilitate the implementation of these clinical trials, it is recommended that the contracts between the sponsor and the site be simplified. For non-commercial sponsor clinical trials, the contract may be replaced by a document of agreement from the site management.

It is essential to accelerate the analysis of the results of these trials as much as possible and to submit them to the AEMPS as soon as they become available.

63. In the field of data protection, should the monitor have a data processor contract with each site where he/she is involved because he/she has access to identifying data and medical records of the trial subjects?

Created in v14

No. The monitoring of the trial is a legally required activity and the monitor is the professional trained and chosen by the sponsor to ensure its obligation of direct monitoring of the conduct of the trial in accordance with the provisions of Article 40 of Royal Decree 1090/2015 of December 4, which regulates clinical trials with medicines, the Ethics Committees for Research with Medicines and the Spanish Registry of Clinical Studies. Given that the sponsor has already signed a contract with each participating site, this contract should be understood to cover all the activities involved in carrying out the trial.

The necessary separation of functions provided for in the legislation on clinical research, clearly distinguishing the research activities carried out at a given site by the trial investigators from those of trial monitoring, cannot be conditioned by instructions from that site to the monitor regarding trial monitoring. This is without prejudice to the precautions that each site may adopt in relation to the access and use of its facilities by third parties, including the authorization to access identification data and the clinical history of the trial subjects. In this regard, the site may request, if it deems it appropriate, the signature of a document by which the monitor undertakes to maintain confidentiality of the personal data to which he/she has access.

64. Full implementation of Regulation 536/2014 on clinical trials on medicinal products for human use

Created in v16

On 31st July 2021, the European Commission published, in the Official Journal of the European Union, Decision 2021/1240 of 13 July 2021, on the full functionality of the Clinical Trial Information System (CTIS) portal and the EU database for clinical trials.

Meanwhile, the full application of the Clinical Trials Regulation (EU) No 536/2014 (hereinafter CT Regulation) in all countries of the EU and the European Economic Area (EEA) – Iceland, Liechtenstein and Norway – will take place on 31 January 2022. It is therefore recommended to read the Set of Documents related to the aforementioned Regulation in EudraLex Volume 10.

In applications submitted via the CTIS Portal, it is important to consider the specific aspects of this document and in particular the following:

- **It is necessary to confirm in advance with the AEMPS and the evaluating CEIm chosen their availability to be a Reporting Member State (RMS) on the date that the application is expected to be submitted when intending to propose Spain as RMS.**
- **The evaluating CEIm should be indicated in the cover letter of the trial authorization application.**
- **It remains essential to clearly name any documents uploaded to CTIS, following the recommendations of Annex I of this Instruction Document.**

Much more detailed information can be found on the AEMPS website under this section.

The Annexes of this document are published separately and appear below:

Annex I. Trial documentation and identification of documents when loading these into the ECM Portal or CTIS Portal.

Annex II. Suppressed.

Annex III. Suitability of the investigator.

Annex IV. Suitability of the facilities.

Annex VA. Model of insurance certificate

Annex VB. Commitment to additional responsibility with regard to the coverage of the insurance of clinical trials.

Annex VI. Sponsor's model of commitment for clinical trials with no profit motive.

Annex VII. Model of certificate of the representative of the site or organisation for low-intervention clinical trials

Annex VIIIA. Guide to the correct preparation of a model of patient's information sheet and informed consent (PIS/IC).

Annex VIIIB. Paragraphs to include in the Informed Consent to obtain and use biological samples in clinical trials.

Annex IX. Minimum necessary documentation to apply for the management of the contract for the execution of clinical trials between the sponsor and the research sites.

Annex X. Contacts for the contract management with a research site.

Annex XI. Annual clinical trial monitoring report

Annex XII. Report on exceptional measures adopted to manage problems arising from the COVID-19 emergency

List of Versions of Instructions Document for the execution of clinical trials in Spain

Version 1: 13th January 2016

Version 2: 03rd February 2016

Version 3: 09th May 2016

Version 4: 10th November 2016

Version 5: 18th April 2017

Version 6: 08th May 2017

Version 7: 23rd June 2017

Version 8: 22nd February 2018

Version 9: 27th July 2018

Version 10: 17th December 2018 (correction of errors 11 January 2019)

Version 11: 10th December 2019

Version 12: 29th June 2020

Version 13: 30th November 2020

Version 14: 30th April 2021

Version 15: 16th September 2021

Version 16: 31st January 2022