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

Version 19, dated 24 November 2023 (all versions can be reviewed at the end of the document)

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In this document of instructions of the Spanish Agency of Medicines and Health Products (hereinafter AEMPS) for the Medicines and Medical Devices (hereinafter AEMPS) for the conduct of clinical trials in Spain provides, in a question and answer format, information on the practical information on the practical aspects involved in the application of the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 (hereinafter "Regulation") and Royal Decree 1090/2015, of 4 December 2015, which regulates clinical trials with medicinal products, the Ethics Committees for Research involving medicinal products (hereinafter "CEIm") and the Spanish Clinical Trials Register. The document is complementary to the "collaboration memo" between the AEMPS and the CEIm, which is also public. Issues requiring further clarification, or rectification in the light of experience, will be revised in subsequent versions of this document, which is intended to be dynamic and therefore easy to update.

Any questions or comments regarding the application of the Clinical Trial Regulation or this document should be emailed to aecaem@aemps.es quoting "Questions and Answers" as a reference in the subject line.

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 Trials Registry (REec) should be sent to reec_incidencias@aemps.es

Further information on clinical trials in the European Union and on the Clinical Trials Information System (CTIS) in Clinical Trials in the European Union - EMA (euclinicaltrials.eu). Incidents related to CTIS must be managed through the EMA Service Desk Log in - Service Desk (europa.eu).

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1. REGULATION OF CLINICAL TRIALS IN SPAIN

1.1 Entry into force and full application of Regulation No. 536/2014 on clinical trials of medicinal products for human use

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

For its part, the full application of the Clinical Trials Regulation (EU) No. 536/2014 (hereinafter, EC Regulation) in all countries of the EU and the European Economic Area (EEA) – Iceland, Liechtenstein and Norway – took place on 31 January 2022. It is therefore recommended to read the Documentation Set related to the aforementioned Regulation in volume 10 of Eudralex.

In applications sent through CTIS Portal, it is important to take into account the specific aspects of this document and in particular the following:

- For new test requests, a CEIm adhered to the new Collaboration Memorandum and work in CTIS must be chosen. Before submitting a request for clinical trial authorisation, the sponsor must contact the selected CEIm to confirm that it is available to be involved in the assessment of the application on the proposed dates, whether Spain is going to be proposed as RMS or not. You can consult the **Committees attached to the work in CTIS** here.

- CEIm must be selected in the electronic fee payment process (see section 2 of "Fees").

- It remains essential to give a clear name to the documents uploaded to CTIS, following the recommendations of Annex I of this Instructions Document.

You can find much more detailed information in the CTIS Guide for Sponsors published in the "Guides" section of the AEMPS website.

1.2 Submission of clinical trial applications

- From 31 January 2023 all initial clinical trial applications must be submitted in accordance with the EC Regulation and via the CTIS Portal.

- From 31 January 2022 until 30 November 2024, ongoing clinical trials, previously authorised, can either remain under the legislation they were authorised or can benefit from the provisions of the EC Regulation by submitting the transition request via CTIS. This means that sponsors of ongoing clinical trials can, at any time, avail themselves of these provisions via

CTIS. Sponsors should also bear in mind that this adaptation period can range from 60 to 106 days, so they should make the transition request in good time in case clarifications are needed.
This transition will be required and should be made within the next two years for clinical trials that will have an active site in the EU by 31 January 2025 (see section 11 of the Q&A document in Chapter V of Volume 10 of Eudralex).

All requests and communications following the authorisation of a clinical trial not uploaded to CTIS should continue to be made through the ECM Portal at the latest until the date on which the clinical trial is requested to be transitioned to the CTIS Portal.

- By 31 January 2025, all ongoing clinical trials will have to be transitioned to the EC Regulation and authorised in CTIS.

1.3 Transitional trials

The procedure for transitioning a clinical trial to the CTIS Portal is described in the **CTIS Guidance for Sponsors** published in the "Guidelines" section of the AEMPS website.

The documents to be submitted are indicated in questions 11.6 and 11.7 of the Q&A document in Chapter V of Volume 10 of Eudralex.

In the case of submission of substantial amendments of transitioned trials initially assessed by an CEIm that is not adhered to the Memo and the work in CTIS, it is the sponsor's responsibility to advise the non-adhering CEIm that a new assessing CEIm is selected for the substantial amendments of the trial after transition to the Regulation.

Initial applications for transitional clinical trials shall be exempt from the fee.

However, any subsequent substantial modification shall be subject to a fee.

1.4 What documents must be submitted to apply for authorisation of a clinical trial?

Applications and communications concerning a clinical trial made through the CTIS Portal should be in accordance with the **CTIS Guidance for Sponsors**, published in the "Guidelines" section of the AEMPS website.

The content of the initial application dossier is as set out in Annex I of the EC Regulation.

The available European templates can be found in Chapter I of Volume 10 of Eudralex and the national templates can be found in the Annexes to this instruction document in the "Guides" section of the AEMPS website.

1.5 When can a clinical trial start in Spain?

Clinical trials with medicinal products are subject to prior authorisation by the AEMPS, following a scientific and ethical assessment of Parts I and II.

In addition, in the case of a clinical trial with a medicinal product that includes a genetically modified organism, the sponsor must have the corresponding authorisation in accordance with Law 9/2003, of 25 April, which establishes the legal regime for the contained use, voluntary release and marketing of genetically modified organisms (see section 3.3).

In order to initiate a clinical trial at a participating site, the sponsor must have a favourable opinion from the CEIm, the authorisation resolution from the AEMPS, and a signed contract with the management of the site. In addition, the site must have been activated for the trial in the Spanish Clinical Trials Register (REec) (see section 11).

1.6 Should agreement of the management of the participating sites be submitted in order to obtain authorisation for the trial?

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 where the sponsor is an investigator belonging to the site and the signature of the contract is not required, the express agreement of the site management is required. However, this is a sponsor-only document.

The agreement of the site management also 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.

2.FEES

2.1 What is the fee for the assessment of a clinical trial?

Current fees for the AEMPS are specified in article 123 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 the following address.

During the online fee payment process, the assessing CEIm for the clinical trial should be selected (except in the case of substantial amendments affecting only the quality part) and pay special attention when entering the EU Number/EudraCT.

For payments made by bank transfer, it is essential to include the thirteen-digit model 317 number that has been previously completed in the concept of the transfer.

When submitting the trial, both the form 317 and the bank proof of payment must be provided.

The information published on the Fees website should also be taken into account.

2.2 Exemptions

As from 28 June 2023, clinical trials with the following characteristics shall be exempted from fees:

1. The sponsor is a university, hospital, public scientific organisation, non-profit organisation, patient organisation or individual investigator.
2. The ownership of the research data belongs to the sponsor from the very beginning of the study.
3. There are no agreements between the sponsor and third parties that allow the use of the data for regulatory or proprietary uses.
4. The design, conduct, recruitment, data collection, and reporting of research results remain under the control of the sponsor.
5. By their nature, these studies cannot be part of a development programme for a marketing authorisation of a product.

A declaration signed by the Sponsor with these considerations must therefore be included and uploaded in the "Proof of payment" section of CTIS.

In addition, in these cases it will be essential to indicate the CEIm assessing the application in the cover letter.

In the case of substantial modifications of trials authorised under the Directive, this declaration must be attached together with the rest of the application documents in the ECM Portal.

Trials transitioned to the CTIS portal that were initially authorised under the Directive will also be exempted from payment.

However, any subsequent substantial modification will be subject to a fee.

2.3 Period of validity

As indicated in Article 125.2 of Legislative Royal Decree 1/2015, once the fee has been paid, the taxpayer must submit the application within a maximum period of **one month** from the date of payment.

3. AUTHORISATION PROCEDURE

3.1 What has changed with respect the authorization procedure of a clinical trial?

For applications submitted through the CTIS Portal, the deadlines and coordinated assessment process for Part I as set out in Regulation 536/2014 apply (more information in the CTIS Guide for Sponsors).

In case the application is not complete, generally only a single request for information will be feasible.

The sponsor is expected to submit updated versions of the relevant documents with the response. The request for information to the sponsor (RFI) will only include questions which, if not answered satisfactorily, will result in the rejection of the application or a condition in the authorisation.

It is considered of interest that Spain can be included in the initial application for authorisation of the clinical trial by receiving both Part I and Part II.

The trial authorisation will expire for MSCs in which no subjects have been included within 2 years.

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

The timeframe for the assessment of an application submitted via the CTIS Portal is as set out in Regulation 536/2014. Please refer to section 5 of the CTIS Guide for Sponsors for more information.

3.3 How should authorization be applied for, according to Law 9/2003[1] of April 25th , in the case of clinical trials with medicinal products containing a genetically modified organism?

Information can be found on the website of the Ministry for Ecological Transition Authorisation procedures for voluntary releases of GMOs.

[1] Law 9/2003 of 25 April 2003, on the legal regime for the contained use, voluntary release and placing on the market of genetically modified organisms.

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

Yes, in this case, the sponsor should maintain the same CEIm as in the previous application.

A resubmission implies that the application was withdrawn or refused in all MSCs involved in the trial, or that the application lapsed in all MSCs after authorisation.

If the application has been withdrawn or expired in one or more MSCs, but not in all MSCs, it is not possible to resubmit the application. MSCs that were withdrawn can be added through an additional MSC application, in accordance with Article 14 of the Regulation.

Where the previous application was not considered valid or where the withdrawal of the previous application took place during the validation phase, the sponsor may reuse the fee previously paid to the AEMPS, without having to pay it again and as long as it is within 30 days of payment.

The sponsor should indicate what has changed with respect to the previous application and should only attach the new versions of the documents that have changed. In this case, the document should summarise in one section what all the changes in the document are, or otherwise this summary of the changes will be provided in a separate document.

3.5 Particularities in time schedules during the Christmas period

Between 23 December and 7 January there shall be a clock stop in all applicable time frames, to both the AEMPS and CEIm as well as the sponsor during that period

3.6 Is the clinical investigational product (PEI) status designation maintained?

No, under the new Regulation the PEI concept disappears.

CTIS obtains the information of the products registered in the xEVMPD, which is the centralised dictionary of medicinal products managed by the EMA.

If the medicinal product is not included in this dictionary, the sponsor must proceed to include it. To do so, the sponsor must first be registered in EudraVigilance.

More information can be found on the EMA website.

4. LOW-INTERVENTION TRIALS

4.1 What is considered a low-intervention trial?

A low-intervention clinical trial is considered to be a clinical trial if all of the following conditions are met:

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

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

c) The additional diagnostic or monitoring procedures entail an additional risk or burden to the safety of the subjects that is minimal compared to routine clinical practice in any of the Member States concerned.

Annex I of the Q&A document (Chapter V of Volume 10 of Eudralex) includes a decision tree that can be used to determine whether a clinical trial is considered to be a low-intervention clinical trial, as defined in the EC Regulation.

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

The authorisation process for a low-intervention clinical trial is the same and takes place within the same time limits as any other trial. However, the trial documentation and insurance are simpler (see **Annex I**. Trial documentation and identification of documents when uploading to the ECM Portal or CTIS Portal).

In addition, monitoring, master file content and traceability of investigational medicinal products may be simplified and, depending on the trial characteristics, may be similar to those in routine clinical practice.

When the sponsor request for low-intervention designation, the sponsor shall indicate the request for qualification of the low-intervention clinical trial in the cover letter, and provide sutiable justification for this, indicating, where appropriate, the aditional trial procedures to those that would have been performed on participants in the context of routine clinical practice.

In cases where a clinical trial is claimed as a low-intervention clinical trial in which the medicinal products are used in accordance with the authorised SPC, this should be explicitly stated. Otherwise, a justification shall be provided which is based on published scientific evidence supporting the efficacy and safety of the investigational medicinal products used under the conditions of the trial. This

evidence may include data published in scientific journals, as well as relevant national, regional, or institutional treatment protocols or evaluation reports.

Likewise, when the diagnostic or follow-up procedures are in accordance with routine clinical practice, this must be explicitly stated, clarifying the context of routine clinical practice to which it refers (in Spain, or in another EU country, indicating which one), providing the corresponding evidence where appropriate. Otherwise, procedures that do not conform to rotuine clinical practice must be identified and justify that they entail only a minimal additional risk or burden to the safety of the subjects compared to routine clinical practice.

As stated in the Memorandum of Collaboration between the AEMPS and the CEIm, low-intervention trials will be assessed only by the CEIm.

5. CLINICAL TRIALS WITH MEDICAL DEVICES

5.1 Initial applications submitted under the Regulation (CTIS Portal)

See Annex I of the **CTIS Guidance for Sponsors** published on the AEMPS website in this section.

The cover letter should indicate the use of the medical device in the clinical trial, whether it is a medical device without CE marking, a medical device with CE marking but not used in accordance with its intended purpose, or an integrated product in which the key action is that of the medicinal product.

5.2 Modifications of trials authorised under the Directive (ECM-portal) that have not yet been transitioned

A) Clinical trial with investigational medicinal products and medical devices without CE marking

In cases where a clinical trial intends to use a medical device without CE marking, or with CE marking but not used for its intended purpose, it would be a combined study in which there would be both a clinical trial with a medicinal product, a clinical investigation with a medical device, or a performance study with an *in vitro* diagnostic medical device, as appropriate, and it is necessary to apply to the AEMPS for the relevant authorisations.

- For clinical trials involving medicinal products, all clinical trial documentation should be submitted via the ECM Portal (in the case of trial amendments under directive).
- For clinical investigations with medical devices or performance studies with in vitro diagnostic medical devices covered by Article 58 of Regulation 2017/746, the required documentation, as well as the clinical trial protocol, must be submitted through the General Register of the AEMPS addressed to the Department of Medical Devices. This channel will be used until the European database Eudamed is operational. The same process applies to extensions to new centres.

In the case of modification of a trial under a directive in which a non-CE marked medical device was involved, even if the performance study or clinical investigation with the medical device was jointly authorised through the ECM portal, from now on, in addition to what is required for the modification of the clinical trial, the application for authorisation of the substantial modification of the performance study or clinical investigation must be sent separately to the Department of Medical Devices of the AEMPS.

Similarly, if a modification of a trial under directive processed and authorised by the ECM Portal consists of the inclusion of a new medical device without CE marking, in addition to what is required for the modification of the clinical trial, the application for authorisation of the performance study or clinical investigation must be made separately to the Medical Devices Department.

Both applications should be submitted simultaneously for evaluation, which should be carried out in parallel following the deadlines according to the legislation applicable to each of them. The evaluating CEIm must be the same for both the clinical trial with medicinal products and the clinical investigation with medical devices or the performance study of in vitro diagnostic medical devices.

In terms of fees, the fees for the assessment of clinical trial modifications as well as the application fee for the authorisation of clinical investigations of medical devices (or modifications, as appropriate) must be paid. For studies on the performance of in vitro diagnostic medical devices, the fees are the same as for clinical investigations of medical devices.

Two separate authorisations will be granted: one for the clinical investigation with medical devices or the performance study of *in vitro* diagnostic medical devices, and one for the conduct of the clinical trial with medicinal products.

In order to start the trial or implement the variation, it is essential that the sponsor has both authorisations.

B) Clinical trial with an integrated product

In clinical trials investigating an integrated product that has components which, when used separately, could be considered as a medical device or a medicinal product, the legislation applicable to it varies depending on whether the investigational product qualifies as a medicinal product or a medical device according to the mechanism of action through which it exerts its action. Two situations can be distinguished:

a) In the case where the **key action is the medicinal product**, the sponsor must submit the application for authorisation of the clinical trial modification through the ECM Portal and only the clinical trial fee is payable. In this case, no application needs to be submitted to the Medical Devices Department. The part of the product that could separately be considered as a medical device must comply with the safety and performance requirements set out in Annex I of the Medical Devices Regulation 2017/745.

b) In the case where the **main action is the medical device**, it would be consider a clinical investigation with medical devices, which must comply with the provisions of its legislation. The application must be sent through the General Register of the AEMPS addressed to the Department of Medical Devices and only the clinical investigation on medical devices fee must be paid.

Please contact aecaem@aemps.es for questions on clinical trials with medicinal products, and psinvclinic@aemps.es for questions on clinical investigations with medical devices.

6. AUXILIARY MEDICINAL PRODUCT

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

The term “auxiliary medicinal product” is equivalent to the term “non-investigational medicinal product”. Therefore, auxiliary medicinal products are described in Regulation 536/2014.

For more information, please refer to the Recommendations on auxiliary medicinal products in clinical trials in chapter III of Eudralex volume 10.

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

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.

7. CLINICAL RESEARCH WITH CELLS AND/OR TISSUES

7.1 Cells and/or tissues intended for the manufacture of advanced therapy investigational medicinal products

In the event that medicinal products are manufactured from cells and tissues of human origin, in accordance with Regulation 1394/2007 on advanced therapy medicinal products, the donation, procurement and testing of these tissues or cells shall be carried out in accordance with Directive 2004/23/EC, transposed by Royal Decree-Law 9/2014[2].

Therefore, Spanish centres in which human cells or tissues intended for the manufacture of advanced therapy medicinal products under investigation are to be obtained must be appropriately authorised for the donation of the specific cell type or tissue to be donated in accordance with the requirements established by Royal Decree-Law 9/2014[3].

For queries regarding the administrative procedure to be followed to obtain authorisation for donation, please contact ont@sanidad.gob.es.

7.2 Clinical research with cells and/or tissues that are not considered as medicinal products

The authorisation of clinical research studies with human cells and/or tissues that are not considered medicinal products, but are considered transplants, is governed by the provisions of article 29 of Royal Decree-Law 9/2014.

The principal investigator or, where appropriate, the sponsor, must submit the study for evaluation to a Research Ethics Committee (CEI), without also having to be accredited as an CEIm, and for authorisation to the competent authority of each Autonomous Community (usually the Autonomous Community Transplant Coordination). For authorisation, the report of the experts of the Transplant and Regenerative Medicine Commission of the Interterritorial Council of the National Health System is mandatory. This report will be requested by the Autonomous Community Transplant Coordination. If you have any doubts about the administrative procedure to be followed in these studies, you can send your queries to ont@sanidad.gob.es, indicating CLINICAL STUDY WITH CELLS and/or TISSUES.

[2] Royal Decree-Law 9/2014 of 4 July establishing the quality and safety standards for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells and approving the coordination and operational rules for their use in humans.
[3] Tissues and cells used as starting material in the manufacture of authorised advanced therapy medicinal products must meet the same requirement.

In case of doubts about whether human cells and/or tissues are considered advanced therapy medicinal product (in which the cells or tissues undergo substantial manipulation and/or are used for a function other than that for which they were originally intended), the principal investigator or, where appropriate, the sponsor of the study must submit the application for classification as an advanced therapy product to the AEMPS using the following form:

Application Form - AT Classification.

In any case, the procurement of human cells and/or tissues in Spain for clinical research, **regardless of their final consideration as a medical device, transplant or starting material for obtaining a medicinal product, may only be carried out in centres duly authorised for the procurement of such cells and/or tissues** by the competent health authority and in accordance with the requirements established in Royal Decree-Law 9/2014.

8. CEIm AND PART II DOCUMENTATION

8.1 Which CEIm can perform assessment of a clinical trial?

The sponsor may choose the CEIm, in agreement with the CEIm, from among the Committees adhering to the new Memorandum of Collaboration and the work in CTIS. Before submitting a clinical trial authorisation application, the sponsor should contact the selected CEIm to confirm that it is available to be involved in the assessment of the application on the proposed dates, whether or not Spain is to be proposed as an RMS.

For contact details of the CEIm, please access the Directory of accredited CEIm in Spain.

To consult the Committees involved in CTIS work click here.

In all clinical trial authorisation applications submitted through the CTIS Portal, the sponsor is highly recommended to indicate in the cover letter the name of the CEIm that will assess the application.

8.2 What type of Ethics Committee can assess an observational study with medicinal products or a clinical study with medical devices?

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 accredited RECs in Spain, available at the URL Directory of accredited RECs in Spain - Spanish Agency for Medicines and Medical Devices.

When it is necessary to change the assessment committee of an observational study with medicinal products or a clinical study with medical devices, the new CEIm proposed by the sponsor must have previously agreed to assume the assessment of the study, for which the sponsor must have provided it with a complete version of the study documentation.

8.3 Which Part II documents must be submitted?

On page 18 of the CTIS Guide for Sponsors, the Spanish requirements for Part II documents submitted by CTIS, as well as the official templates and accepted languages, are described.

8.4 What information should be provided to the potential clinical trial participant before informed consent is obtained?

Annex VIIIA provides guidance on the proper preparation of a model clinical trial participant information sheet and on the informed consent document. **Annex VIIIB** lists the paragraphs to be included in the informed consent for the collection and use of biological samples in clinical trials.

8.5 What should the financial budget include?

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 case, 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 evaluation by the CEIm is considered necessary only of those modifications that imply changes in the compensation to participants and researchers presented in the initial financial budget.

8.6 Contract model and management

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

Annex IX includes the agreement reached on October 6th , 2016 between the AEMPS and the representatives of the Autonomous Communities involved in aspects of clinical trial management, regarding the minimum documentation necessary to request the management of the contract for carrying out of clinical trials between the Sponsor and the research centers, as well as to request the facility's suitability document.

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**.

9. MODIFICATIONS

9.1 What is considered a substantial amendment of the trial?

Examples of substantial modifications can be found in the Q&A document in volume 10 of EudraLex.

9.2 How should authorisation for a substantial amendment of a Clinical Trial be requested?

For those **Clinical Trials authorised under the Directive (ECM Portal)** and that have not yet been transitioned to CTIS, the procedure carried out until now will be followed:

The cover letter will indicate whether the modification refers only to part I, only part II or to both parts. In addition, it must be indicated if any information visible in REec changes with the attached updated form (for example, inclusion criteria) in order to keep the Registry updated.

Modifications that only affect part II must be sent only to the CEIm and those that affect the manufacture of medicines or compliance with correct manufacturing standards, only to the AEMPS.

Given that the same substantial modification can refer to many changes of different significance within the authorised clinical trial, the most important thing for its evaluation is that these changes are shown in a summarized and simple way 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 made of it, does not facilitate a quick evaluation 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 must be a summary of the changes introduced and their motivations in no more than 1,200 words that allow the assessor to access this information in a summarized way to be able to make decisions. Therefore, in it, the changes that are made must be adequately explained, without being a mere reference to the sections of the document that change, and must be accompanied by a clear justification of the reason for the same 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 its justification or with the table of changes.

When the information required in the “Summary and justification of changes” is included in another document, this will be stated in the cover letter.
It is common for the mere change made to be included as justification for a modification (for example, in the justification for a modification of a selection criterion, state "change in selection criteria"). This justification is not considered acceptable, and the reasons for making the modification must be briefly stated. In the case of an update of different points of the investigator's manual, reference should be made to the relevant information that is updated [for example, the results of 4 new clinical trials are added and the evaluation of all adverse events shows an increase (4% vs. 2%) in the number of cancers in the experimental group compared to placebo]. It is emphasized that this document should not be the “table of changes” in section F of the relevant amendment request form, or in a separate document, where an exhaustive listing of “previous text versus new text” is shown. in the different sections or documents in which each change indicated in the Summary of Changes is reflected, or the modified document with change control although it does not replace them.

Requests that do not include the "Summary and justification of changes" document that clearly explains the changes and the reasons for the modification and consequences thereof or lack modified documents with the trace of changes and justification thereof or, failing that, of a table of changes will not be accepted for processing as valid.

The authorisation and opinion of the CEIm regarding part II will refer only to the changes indicated in the table of changes and in the modified documents with control and justification of the changes that have been explained in the "Summary and justification of the changes" document. changes". The Sponsor is responsible for ensuring that all changes reflected in the summary and justification of changes correspond to the changes included in the change table and in the modified documents with a change control.

When a substantial modification is going to affect several clinical trials, it is important that it be requested simultaneously for all trials, identifying in the cover letter the clinical trials that it will affect. This is of special interest in modifications that refer to a change in the manufacturing or investigator's manual of the drug.

When a substantial modification refers to changes previously authorised for another clinical trial or to document changes already adopted as urgent safety measures previously communicated, this aspect must be indicated in the cover letter.

The documents that must be submitted with a substantial modification appear in **Annex I.**

In the case of a substantial amendment application involving Parts I and II, the sponsor should send the IRB/IEC opinion to the AEMPS as soon as it is available. Authorisation of the trial will always follow receipt of the IRB/IEC opinion.

To send the Part II opinion to the AEMPS, the sponsor may forward the CEIm's mail (sent via SIC-CEIC) to aecaem@aemps.es keeping the subject line of the mail or via the ECM portal.

For those **Clinical Trials authorised under Regulation 536/2014 (CTIS)** or that have already been transitioned, you can consult section 10 of the CTIS Guide for Sponsors and the CTR Questions&Answers document.

9.3 What is the schedule for a substantial amendment authorisation request?

In the memoranda published in the "Guides" section of the AEMPS website, you can consult the authorisation and evaluation schedule of a Substantial Modification, both those presented through the ECM Portal and those carried out through CTIS.

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

As a general rule, it is not acceptable. The presentation of several simultaneous applications would be admissible when one of them affects changes only in part I and the other only changes in part II, not related to the change in part I and when the modification refers to the adoption of an urgent measure for security reasons.

In the case of applications sent through the CTIS Portal, consult the CTR Questions&Answers document.

9.5 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?

No, it is not possible.

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

In order to simplify the evaluation, it is recommended to the sponsor that the substantial modifications that refer to a change of the principal investigator or an

addition of centers, be presented in substantial modifications that only refer to part II and therefore directed only to the CEIm.

When the modification refers to an expansion of centers, the sponsor must send a notification of expansion of centers to the AEMPS so that the new centers can be seen in the REec. In said notification, you will send the CEIm's favorable opinion for the modification and the XML of the substantial modification form with the centers included in the opinion. Section 11.6 indicates the necessary steps so that the trial can be started in a center, keeping the trial information updated in the REec.

In the case of applications sent through the CTIS Portal, consult the CTR Questions&Answers document.

10. NOTIFICATIONS

10.1 Submission of applications and communications of a clinical trial.

All applications and communications subsequent to the authorisation of a **clinical trial not uploaded to CTIS** must continue to be made through the ECM Portal at the latest until 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 done in the next three years for clinical trials that will have an active center in the EU as of January 31, 2025.

- The response to a condition in the authorisation of a clinical trial or a substantial modification must be submitted to the AEMPS through the ECM Portal using «C.- Response to a condition in the authorisation (of an initial application or an MS) or response to a data request (e.g. Security)".

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

- The annual safety report (DSUR) will be communicated to the AEMPS through the ECM Portal using «E. iv) Informe anual de seguridad (DSUR)» as follows:

  - When a DSUR refers to a medicinal product classified as an investigational product (PEI)[4], a single and simultaneous application may be sent for all trials related to said PEI. To do this, the XML of the initial application form of all the clinical trials referred to by the DSUR must be uploaded, clicking the "Add Trial" button and answering in all cases the question "3. Does the application refer to a medicine classified as a product in the clinical investigation phase (PEI)? » with a "YES" and indicating the corresponding PEI number, which must be in the "yy-nnnn" format.

  - When a clinical trial is linked to more than one PEI, the DSUR corresponding to each PEI must be sent in a separate request, as indicated in the previous paragraph.

  - When a DSUR refers to several clinical trials refers to medicines without PEI qualification, an application must be sent for each trial.

[4] Medicines not authorised in any country of the European Economic Area that contain an active ingredient or a combination of active ingredients not authorised in Spain require PEI qualification.

- The DSUR will be sent to the CEIm through the ECM Portal using the sending option «E ii) Informe sobre la marcha del ensayo».

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

- Changes in the sponsor, applicant or legal representative contact informartion, and applicant changes must be communicated using H.- Change in contact details. In this case, the XML and PDF formats of the updated application form must be sent as attached documents. If at the time of making this submission, there is a Substantial Modification (SM) under evaluation for the same essay, it is advisable that it be indicated in the accompanying letter, to facilitate sending the resolution of that MS to the new contact address. that is being communicated. The way in which the test dates must be communicated is indicated in section 11.5.

- The summary of results must be sent to the AEMPS and the CEIm and also uploaded to EudraCT within one year from the date of overall completion of the trial.

  The submission must be made through the ECM Portal, selecting “Ensayo clínico autorizado” and the “E.- Informe sobre el ensayo iii) Informe final de resultados” functionality.

  The summary of results must preferably follow the European format required for EudraCT and must present at least the Spanish version, and it is also advisable to present a version in English; However, for essays authorised before 2013, translation into Spanish is not necessary. You can consult a multimedia tutorial on how to provide results in EudraCT at https://eudract.ema.europa.eu/whatsnew.html (it is recommended to read the “overview” on that page before downloading and viewing those tutorials).

- Lay summary: In addition, for trials authorised under the Regulation, a lay summary of results must be submitted, which can be understood by lay persons.

  For trials authorised under the Directive, this lay summary is recommended but not mandatory.

Applications and communications regarding a clinical trial made through the CTIS Portal must comply with what is indicated in the Q&A document in chapter V of volume 10 of Eudralex EudraLex - Volume 10 (europa.eu) and the CTIS Guidance.
CTIS notification is unique for both the AEMPS and the CEIm.

10.2 How should early termination of a clinical trial be reported when follow-up of subjects after the termination date is anticipated?

In cases where a sponsor decides to end a clinical trial early, in the notification of end of the trial, it will indicate that it is an early termination and fill in the corresponding sections.

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 in the REec.

The cover letter (section 2 Comments to be taken into account with the application) will indicate the action plan and whether or not additional monitoring of the subjects in the trial and its characteristics are planned.

In cases where monitoring is considered necessary, the trial completion date will continue to be considered the initial date on which the sponsor communicated the early termination of the trial. It is not necessary to communicate the end date of the monitoring period.

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

Notifications of early termination of **clinical trials that appear in CTIS** will be notified in the CTIS Portal. You can consult section 9 of the CTIS Guide for Sponsors.

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

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

The narrative of the cases may be done in English or Spanish, in this case preferably accompanied by a summary in English.
It is not necessary to submit semi-annual reports regarding serious and unexpected adverse reactions.

10.4 Should suspected unexpected serious adverse reactions and other necessary communications related to the trial be reported to the Autonomous Communities?

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

10.5 Steps to be followed when a change is necessary in the assessor CEIm of an authorised clinical trial

A. Trials authorised under the Directive (ECM Portal)

When it is necessary to change the CEIm evaluator of a clinical trial:

1. The new CEIm proposed by the Sponsor must have previously agreed to undertake the evaluation of the Trial.

2. Before making an application or communication to the new CEIm, it is necessary to change the CEIm in the AEMPS computer system and in SIC-CEIC. To do this, the following must be done:

a) Request a change of CEIm from the AEMPS through the ECM Portal using the option "E i) Informes Ad Hoc o notificación inicial de medidas urgentes de seguridad ya adoptadas", indicating in the free text box of the cover letter that A change of CEIm and the justification for this is requested, providing as attached documents the XML and PDF of the updated application form in which the new CEIm appears. A separate application must be submitted for each trial.

b) Request the change of CEIm by sending an email in which you attach the acknowledgment of receipt of having sent the Ad hoc report to incidensayos@aemps.es so that the change can occur in the SIC-CEIC computer system.

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

B. Applications submitted under the Regulation (CTIS Portal)

The acceptance by the new CEIm of the evaluation must be included in the Cover letter.

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

No, it´s not necessary.

10.7 How to present urgent safety measures including temporary halts of a clinical trial?

If circumstances arise that could endanger the safety of the subjects, the sponsor and the researcher will adopt the appropriate urgent measures to protect the subjects from any immediate risk. The sponsor will inform both the AEMPS and the CEIm of these circumstances and the measures adopted to minimize risks and inconveniences for participants as soon as possible.

In said communication, it is necessary to indicate the date on which the interruption took place (in the event that it involves a partial or total interruption of the trial), the justification for adopting said measure, its effect (countries or centers affected when they are not all, interruption of recruitment, interruption of treatment, complete interruption of the trial, number of patients affected, etc.) and a report on the current situation of the trial, at least in Spain.

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

- « Informes Ad Hoc o notificación inicial de medidas urgentes de seguridad ya adoptadas »

- «Modificación sustancial»

The notification will be used as "Ad hoc report or initial notification of urgent safety measures already adopted" when these measures do not imply a substantial change that affects any of the trial documents (for example, protocol, investigator manual, etc.). and when the measures adopted imply substantial changes but at the time of making the communication, the necessary documents to request the substantial modification are not yet available.

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

When requesting authorisation of a “Substantial Modification” on the relevant modification form, the box “E.2.5 This modification refers to urgent security measures already adopted” must be marked affirmatively. When the urgent safety measure also implies a temporary stoppage of the trial, the box “E.2.6 This modification is to notify an urgent stoppage of the EC” will also be marked affirmatively in the modification form and section E.4 will be filled out. Furthermore, as in the rest of the substantial modifications, the "Summary and justification of the

changes" document and the table of changes will be provided or, failing that, the modified documents with corresponding change control.

It is recommended to indicate in the free text box of the cover letter whether the urgent security measure was notified as an ad hoc report prior to the modification.

If the end of trial as a result of the reason that led to a temporary stoppage, the corresponding notification of the end of a clinical trial must be made.

In the case of **applications sent through the CTIS Portal**, consult the CTR Questions&Answers document and Guide for sponsors.

10.8 Communication of serious breaches

For those trials authorised under the Directive, the Sponsor of a clinical trial must comply with article 29 of RD 1090/2015 and must notify the AEMPS and the CEIm of serious non-compliance that has occurred in Spain, without delay and within the maximum period. of seven calendar days from the date on which he became aware of the breach.

For these purposes, serious non-compliance will be understood as one that may significantly compromise the safety and/or rights of the test subjects or the reliability and solidity of the data obtained in the clinical trial.

Serious non-compliance must be reported to the AEMPS at the Department of Inspection and Control of Medicines at the email address breachesgraves@aemps.es.

Communication will be made using the form and as indicated in the section "Publication of dates and summary of the final results report in the Reec" at http://www.aemps.gob.es/industria/inspeccionBPC/home.htm.

Communication of serious breaches to the CEIm will be done by email.

From the publication of these instructions, only deviations that are considered a serious non-compliance should be reported to the AEMPS and the CEIm. Deviations that are not considered serious non-compliance do not need to be notified to either the AEMPS or CEIm; However, it is important to note that a deviation that is repeated several times could be considered a serious non-compliance.
In the case of **applications sent through the CTIS Portal**, article 52 of Regulation 536/2014 must be followed. For more information you can consult the CTR Questions&Answers document and the CTIS Guide for Sponsors.

Questions about this topic should be directed to area_bpc_bpfv@aemps.es.

11.REEC

11.1 What information is published in the REec?

A. Applications submitted under the Directive (ECM Portal)

The data published in the REec comes from the application form, dates and results of the trial provided by the Sponsor through the ECM Portal. The only information that must be included directly in REec is that related to the management of the centers' states.

From 2023 January 31st, it is no longer necessary to include the justification of the trial.

Management of the status of the sites.

It is done with a click directly on the center in the study detail and the value it has at that moment is modified, being able to go from “not started” to “active” when the trial begins in said center or to “closed” when it has finished.

Publication of Phase I studies pediatric population.

Publication in the REec is automatic for all authorised clinical trials. However, when they are phase I and do not include a pediatric population, only reduced information about the trial is published (EudraCT number, Sponsor, phase, type of study population and number of subjects, scope of the study, participating centers, dates of the trial). The REec Manager can extend the publication to standard information for all trials.

Publication of trial dates and reasons for early termination

See section 11.5.

Publication of clinical trial summary of results

The summary of the results report sent to the AEMPS will be automatically published in the REec, as soon as it is received, and the veracity of the data provided is the sole responsibility of the sponsor.

B. Applications submitted under the Regulations (CTIS Portal)

In the case of trials authorised based on the Regulation, the data that is automatically published in REec from the CTIS platform are: trial title, disease

investigated, objectives, variables, selection criteria and the trial dates reported by CTIS.
The only information that must be included directly in REec, through the person responsible for the study, is that related to the management of the centers' states.

11.2 Person or entity designated by the Sponsor as responsible for the study at REec

The person responsible for the trial in REec designated by the sponsor is responsible for updating the trial information at REec.

To link a REec user to a trial submitted by the CTIS Portal, once authorised it is necessary to send an email to reec_incidencias@aemps.es with the following information:

- EU Number.
- Complete name.
- CIF/NIF/NIE.
- Email.

Once assigned, you will receive an email with the access codes, which you can modify.

The responsible for the trial at Reec may create new users (without limit) and assign them to their clinical trials or delete them and must manage the activation or closure of the centers.

In case of difficulty, please indicate what the problem is by sending an email to reec_incidencias@aemps.es

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

By entering the REec page with your username and password, the person responsible for the clinical trial will be able to:

- Change the states of the trial centers (not started, active, and closed).

- Assign or delete users to your studio. These users can be created by the person responsible for the REec.

- In a phase I clinical trial that does not include a pediatric population, reduced information about the trial will be published in the REec. The person responsible for the study will be able to have all the data of his trial published by pressing the green button F1 “publish phase I data”, thus leaving the same information as the rest of the trials published in REec.

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

The person responsible for the test in REec can create a new responsible user and cease to be responsible. To do this, you must enter the registry with your access codes, access the study and press the blue “reassignment of studies” button.

11.5 Publication of dates and final summary of results report at REec

A. Applications submitted under the Directive (ECM Portal)

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

1. *Trial start date in Spain.*

In general, it is the first act of selecting possible subjects for a clinical trial. It could be understood as such, the start date of the first center, that is, the date on which it is considered that everything in the first center is ready to begin recruiting.

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

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

3. *Recruitment end date in Spain*.

The date on which the selection of subjects in Spain is completed is considered.

4. *End of trail date in Spain and globally.*

In general, the end of trial date will be considered as the date of the last visit of the last patient. In cases where the end of trial without having recruited patients, the termination of the trial will be considered an early termination.

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

The maximum communication period in all cases will be 15 calendar days from when said circumstance occurred, indicating the reasons in the case of early termination (see also section 10.2).

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 in the REec.

All trial dates will be communicated through the ECM Portal using the applications for an authorised clinical trial:

- The start date of the trial will be indicated in section “A.- Notificación de fechas de inicio del ensayo”.

- The date of the first visit of the first patient, the end date of recruitment in Spain and the global end date will be indicated in the cover letter in section «E) i) Informes Ad Hoc o notificación inicial de medidas urgentes de seguridad ya adoptadas».

- The end date of the trial in Spain will be notified using «F. Notificación de fin de ensayo. In the event that the end date in Spain and the global end date coincide or have a difference of less than 15 days, a single notification may be made using «F. Notificación de fin de ensayo", indicating this situation in the accompanying letter and specifying the global end date when it differs from the end date for Spain.

In addition, the sponsor will send to the AEMPS and the CEIm a copy of the summary of the results that is published in EudraCT no later than one year after the date of completion of the trial. The only case in which sending results will not be applicable will be when the trial has been carried out only in Spain and has ended early without having recruited patients.

The test results must be sent through the ECM Portal using section «E.- Informe sobre el ensayo iii) Informe final de resultados».

When the analysis of the results of a sub-study of a clinical trial is completed at a later date than the rest of the trial, the summary of the trial results should be submitted to the AEMPS and the CEIm within one year after the end of the trial, without any delay in the submission of the results of the rest of the trial.

All the above-mentioned information will be published without delay in the REec.
It is important that the sponsor communicate to the AEMPS all the dates and information that must be published in the REec, even in the event that there is some delay with respect to the deadlines established for said communication.

B. Applications submitted under the Regulations (CTIS Portal)

For trials authorised based on the Regulation, consult sections 9 (notifications) and 12 (summary of results) of the CTIS Guide for Sponsors.

11.6 Update of participating sites in a clinical trial at REec

When the AEMPS authorizes a clinical trial or processes a notification of expansion of sites, the sites accepted by the CEIm in the opinion of part II will be visible in the REec, appearing as a non-initiated status.

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

- **Not started**: the trial is authorised and the center has a favorable opinion from the CEIm to participate in the trial, but the trial has not started at the center (red color). If the center finally decides not to participate in the clinical trial, it must be left in the status "Not Started" and not "Closed", since it could generate confusion as it appears to have been open at some point.

- **Active:** from when the center begins to admit new subjects to participate in the trial until the last visit of the last treated subject takes place and the center closes (green).

- **Closed:** The trial has ended at that center (white).

11.7 Sponsor contact at Reec

A. Applications submitted under the Directive (ECM Portal)

The contact 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" of the initial application form.

B. Applications submitted under the Regulations (CTIS Portal)

In the case of tests authorised based on the Regulation, the contact that will appear by default in REec will be the one indicated in the "Public contact point" section of CTIS.

To modify it you must send an email to reec_incidencias@aemps.es.

Given that this is a contact of interest to researchers and potential participants in the trial, it is necessary for the Sponsor to select an institutional mailbox, where possible, where it would be advisable to be able to respond in Spanish to queries made in that language. It is also of great interest and highly recommended that the contact telephone number be Spanish.

11.8 What about the trials transitioned to the CTIS Portal?

At the moment, trials authorised under the Directive that have been transitioned to CTIS continue to appear in REec associated with the initial Eudra CT, and not with the EU Number.

The AEMPS is working on the computer system that links both applications.

11.9 When should observational studies be uploaded at REec?

You can find information in Instrucciones-GESTO-REEC.pdf (aemps.gob.es).

12. MANUFACTURE/IMPORT AUTHORISATION

12.1 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?

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.

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.

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

Magistral formulas and officinal preparations are medicinal products for human use that are defined in Article 8, paragraph 1b and 1c 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 .

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.

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

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

These documents shall be attached in the CTIS section: "Part I - Product- Test - GMP Compliance."

The accompanying letter should indicate the involvement of the Pharmacy Department in the manufacture.

12.4 Import/Export of investigational medicinal products

12.4.1. Import

The request for authorisation of investigational medicinal products shall be submitted by a importer lab duly authorised to conduct importation activities of investigational medicinal products and in accordance with the provisions of Royal Decree 824/2010, of June 25th, regulating pharmaceutical laboratories, manufacturers of active ingredients for pharmaceutical use and foreign trade in medicines and medicines under investigation.

The import authorisation for investigational medicinal products for human use for clinical trials authorised in Spain, as well as their intermediates and bulk products, may also be requested by the sponsor, as soon as provisions of point 1.2.4 of Circular 1/2015 on foreign trade in medicinal products are met.

These import requests shall be submitted through ECM Portal, accessible through the AEMPS website, attaching the completed **Annex III** of Circular 1/2015, until the electronic pathway that contemplates the complete procedure is available.
For investigational medicinal products for **clinical trials authorised under Regulation 536/2014**, submitted via the CTIS Portal, import authorisation requests will be sent to the Clinical Trials Divison via email at aecaem@aemps.es , attaching **Annex III**, until the electronic pathway that contemplates the complete procedure is available.
It is possible to request the import authorisation together with the trial authorisation application, but it will be conditioned to the prior authorisation of the trial.
All of the above is also applicable to investigational medicinal products without marketing authorization for clinical trials not authorised in Spain, when they have been previously used in a clinical trial authorised in Spain.

12.4.2. Export

Export authorisation request for investigational medicinal products for human use intended for centers in other countries participating in a clinical trial authorised in Spain, as well as their intermediate or bulk products, must be accompanied by the trial approval documentation or the import authorisation of the destination country. Requests can be submitted by either the manufacturing pharmaceutical laboratories or the sponsor.

All applications will be sent to the Clinical Trials Divison via email at aecaem@aemps.es, attaching **Annex X**, until the electronic pathway that contemplates the complete procedure is available.
All of the above is also applicable to investigational medicinal products without marketing authorization for clinical trials not authorised in Spain, when they have been previously used in a clinical trial authorised in Spain.
More information about import/export at Circular 1/2015 on foreign trade in medicinal products.

13. DECENTRALISED ELEMENTS IN CLINICAL TRIALS

Clinical trials on Investigational Medicinal Products are increasingly using procedures conducted outside the traditional 'clinical trial site', a concept usually referred to as **decentralisation**. In addition, there is increasing use of digital tools within clinical trials. The COVID-19 pandemic highlighted the importance and usefulness of digital tools and decentralised procedures in a healthcare setting and in clinical trials

Exceptional measures applicable during the COVID-19 emergency will continue to be generally accepted. However, it won't be necessary to submit the report on exceptional measures to either to CEIm or AEMPS.

In December 2022, the European Commission (EC), the Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) released a Recommendation paper on decentralised elements in clinical trials that aim to facilitate the conduct of decentralised clinical trials (DCTs) while safeguarding the rights and well-being of participants as well as the robustness and reliability of the data collected.

The aim of DCTs is to make it easier for patients to participate in clinical trials by reducing the need to travel to central trial sites. This approach has the potential to make clinical trials available to a wider demographic of participants and reduce drop-out rates.

This paper address general principles in the conduct of clinical trials with decentralised elements, including the roles and responsibilities of the sponsor and investigator, remote informed consent process and electronic signature, delivery of IMP to the trial participant, procedures at home, data management, and trial monitoring. In addition, an overview of the current national provisions per EU member state is outlined in an appendix to the paper.

A summary of the decentralised elements planned in the clinical trial should be provided in the **cover letter** of the clinical trial application.

If it is determined that decentralised elements are likely to have a significant impact on scientific validity, data integrity, benefit-risk ratio or impact on the protection of trial participants' rights, these should be considered in a specific and documented risk benefit assessment.

13.1 Decentralised Elements in Spain

In addition to the general recommendations, specific aspects of Spanish regulation should be addressed, which mainly affect the following points:

13.1.1 Informed consent

As part of the process of obtaining informed consent, it is considered essential that face-to-face communication takes place between the potential trial participant and the investigator, or a qualified person designated by the investigator. If this discussion is done in a digital/virtual meeting, it is recommended that this takes place in real time where the parties can both see and communicate with each other via audio and video.

Consent must be obtained preferably in writing. However, in exceptional and justified circumstances 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.

Electronic informed consent is possible as long as it is obtained with a **high security level signature**, in accordance with eIDAS Regulation nº 910/2014 [5], and confidentiality and security of personal data, as well as secure access, is guaranteed. Only this type of signature meet the specifications, procedures or controls to avoid the misuse or alteration of the identity.

Guideline on computerised systems and electronic data in clinical trials and chapter 3 of Recommendation paper on decentralised elements in clinical trials should be taken into consideration too.

The entire procedure for obtaining informed consent should be described step-by-step in the clinical trial application, part II, to ensure appropriate CEIm ethical review.

[5] REGULATION (EU) No 910/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 23 July 2014 on electronic identification and trust services for electronic transactions in the internal market and repealing Directive 1999/93/EC

13.1.2 Delivery of IMPs directly to trial participants

Direct shipment to patient's home is not possible without the involvement of a Hospital Pharmacy Service.
In case of trial sites do not have pharmacy services, it will be possible for the sponsor to send the investigational drugs to the research center, with the investigator's assumption of the responsibilities with regards to handling and shipping of IMP, in accordance with the study protocol specifications. [6]
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.

Direct shipment to patient's home by the Pharmacy Service shall be stated in the authorised clinical trial protocol and must be adequately documented during the trial course.

13.1.3 Trial monitoring

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 and with the requirements established by the Spanish Data Protection Agency[7], 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.

[6] 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
[7] https://www.aepd.es/es/documento/monitorizacion-remota-verificacion-datos-fuente.pdf

14. TRANSPARENCY AND DATA PROTECTION

14.1 Where can I find more information on the publication of commercially confidential information and personal data? [8]

Please consult the Guidance document on how to approach the protection of personal data and commercially confidential information while using the Clinical Trials Information System (CTIS) version 1.1 together with its annexes.

The guidance aims to assist sponsors and authorities in fulfilling the **transparency obligations** set out in the Clinical Trials Regulation. Annex I provides an overview of the expected personal data contained in referenced documents/fields and Annex II is a template for Good Clinical Practice (GCP) inspections carried out in category 1 trials where the publication of clinical trial information is delayed by a deferral.
Please also refer to the associated ACT EU_Q&A on the protection of Commercially Confidential Information and Personal Data while using CTIS which included recommendations from the member states and product owners on frequently asked questions.
More information on the protection of publication of commercially confidential information and personal data is provided in the Appendix on Disclosure Rules, to the "Functional specifications for the EU portal and EU database to be audited – EMA/42176/2014".

14.2 Where can I find more information on the joint responsibilities for data protection?[8]

Please consult the Joint Controllership Arrangement with regards to CTIS and the related Q&A document for more information.

14.3 Where can I find an overview of the information and documents uploaded into CTIS that are subject to publication?[8]

Please consult the section Additional reference materials for CTIS users on the Clinical Trials Information System: training and support | European Medicines Agency (europa.eu), where structured data forms are published for applications, modifications, notifications, requests for information and annual safety reports. These lists provide a complete overview of data fields and documents per topic and indicate whether these are subject to publication and if publication is deferable.

[8] https://euclinicaltrials.eu/guidance-and-q-as/#qas-transparency

14.4 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?

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 authorisation 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.

15. Annexes

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. Suppressed.

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. Suppressed.

Annex XII. Suppressed.

Anexo XIII- Cumplimiento Normativa para la Gestión de Muestras Biológicas.

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

Version 17: 18th November 2022

Version 18: 26th June 2023

Version 19: 24 November 2023

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