MINISTERIO DE SANIDAD
agencia española de medicamentos y productos sanitarios

DEPARTMENT OF
MEDICINAL PRODUCTS
FOR HUMAN USE

Annex I

Trial documentation and identification of documents when loaded into the ECM Portal or CTIS Portal

Version 31st January 2022 (change of title)
Previous versions: 13th January 2016, 9th May 2016, 21st October 2016, 10th November 2016, 22nd February 2018, 10th December 2019.

The clinical trial documentation is differentiated into two parts, part I (documents to be submitted to the AEMPS and the CEIm and documents to be submitted only to the AEMPS) and part II (documents to be submitted only to the CEIm), which are listed in the following table.

The documents should be submitted with the name indicated in the following table in order to facilitate their validation and assessment. The name is descriptive of the content and includes the version date when this is pertinent. Submitting the documents without the indicated name shall be cause for rectification and/or refusal of the application with the consequent delay in the assessment.

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

1. Cover letter.

Name: automatically assigned by the ECM Portal

The relevant remarks that the sponsor wishes to highlight regarding the evaluation of the application should be indicated in the cover letter that is completed in the ECM Portal, within the free text box for including any information considered relevant.

In that space, it should be indicated:

- The date on which the application was submitted to the CEIm.
- If the sponsor considers that the trial is a low-intervention trial, suitable justification for this qualification should be provided, or a reference to the document where this is specified.
- A complete list of the auxiliary medicinal products (along with their regulatory status).
- If the application is addressed to the CEIm, it shall also indicate where the subject selection procedure is described as well as where management of the biological samples obtained in the trial is described (subject information sheet and/or specific section of the protocol).
- It shall include the sponsor's commitment that the data shall be collected and processed in accordance with current legislation on data protection.
- It shall identify where the reference safety information for the investigational medicinal products can be found.
- Any other information that the sponsor considers useful for assessment, such as the status of the trial worldwide.

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2. **Application form.**

   Name: automatically assigned by the ECM Portal

3. **Sponsor authorization of the applicant, if applicable.**

   Name: <<Authorise_applicant>>

4. **Protocol.**

   Name: <<Protocol_ yyyy_mm_dd>>

It is recommended that it has cross-references to the investigator's brochure instead of reproducing the information in the investigator's brochure. However, toxicity management guidance in the Investigator's Brochure should be placed in the protocol. It could be acceptable to include them in a specific dated annex.

5. **Protocol summary**

   Name: <<Protocol summary_ yyyy_mm_dd>>

6. **Investigator's brochure or summary of product characteristics of the investigational medicinal product.**

   Name: <<IB medicinalproductname_ yyyy_mm_dd >> or
   <<SPC_medicinalproductname_yyyy-mm-dd>>

7. **Summary of product characteristics or investigator's brochure of auxiliary medicinal products (noninvestigational medicinal products), if appropriate**

   Name: <<IB medicinalproductname_ yyyy_mm_dd >> or
   <<SPC_medicinalproductname_ yyyy_mm_dd >>

The summary of product characteristics must be submitted for auxiliary medicinal products not authorised in Spain. In exceptional cases when the auxiliary medicinal product is not authorised in the EU, a rationale for its use and an investigator's brochure must be submitted.

8. **Scientific advice and Paediatric Investigation Plan, if appropriate.**

   Names: <<ScientificAdvice_name of advisory entity>>
   <<Paediatric Investigation Plan>>

9. **Justification of low-intervention nature of the trial (if this is not included in cover letter)**

   Name: <<Reason_LICT>>

Part I documents to be submitted only to the AEMPS

1. **Authorisation by the sponsor of a prior clinical trial or by manufacturer of product in case of cross-reference to a PEI (qualification as product under clinical investigation).**

   Name: <<authorise_cross ref>>

2. **Documentation related to compliance with Good Manufacturing Practice of the investigational medicinal product, where applicable.**

   Name: Manufacturer: <<Manufacturer_name>>
   Importer: <<Importer_name>>
   Declaration of qualified person: <<QP_name>>

MINISTRY OF HEALTH
Spanish Agency for Medicinal Products and Medical Devices

3. Investigational medicinal product dossier quality part (IMPD Q), where applicable.

Name: <<IMPD_Q medicinal product name_ yyyy_mm_dd>>

The part with the quality data of the medicinal product shall be submitted separately.

The name of the documents that can be annexes of the IMPD, but which are submitted separately, shall be identified with the prefix IMPD Q, e.g. <<IMPD Q certif analysis>>, <<IMPD Q TSE certificate>>, etc.

A table of changes relative to the previous version of the IMPD available in the AEMPS should be submitted where applicable. This document shall be identified as:

Name: <<IMPD_changes medicinal product name_ yyyy_mm_dd>>

4. Investigational medicinal product dossier, where applicable

Name: <<IMPD_medicinal product name_ yyyy_mm_dd>>

It should contain the nonclinical and clinical data and the overall risk/benefit assessment of the IMP that are not included in the investigator's brochure and do not refer to the quality part.

5. Documentation related to compliance with Good Manufacturing Practice of the non investigational (auxiliary) medicinal product, where applicable.

Name:	Manufacturer:	<<Manufacturer_name>>
	Importer:	<<Importer_name>>
	Declaration of qualified person:	<<QP_name>>

6. Non investigational (auxiliary) medicinal product dossier quality part (NIMPD Q), where applicable.

Name: <<NIMPD Q medicinal product name_ yyyy_mm_dd>>

The indications given in point 3 for the IMPD Q shall also be taken into account.

7. Non investigational medicinal product dossier (NIMPD), where applicable.

Name: <<NIMPD_medicinal product name_ yyyy_mm_dd>>

It should only include the nonclinical and clinical data and the overall risk/benefit evaluation of the NIMP that are not contained in the investigator's brochure.

8. Medicinal product labelling

Name: <<Label_medicinal product name>>

9. Proof of payment of fee to the AEMPS

Name: <<Fee>>

MINISTRY OF HEALTH
Spanish Agency for Medicinal Products and Medical Devices

Part II documents to be submitted only to the CEIm

1. Documents related to the procedures and materials used for subject recruitment

The name of all the documents in this section shall be at the applicant's discretion but it is obligatory that all include some descriptive term of their content, for example:

Name: <<patient_leaflet Version1_yyyy_mm_dd>> or, for example,

<<web_text Version1_yyyy_mm_dd>>

A document should be included with the procedures for inclusion of subjects in the trial and providing a clear indication of what is the first act of recruitment. If this aspect is duly described in the protocol, it should be indicated in the cover letter of the application in order to justify the absence of this document.

Recruitment materials include letters, phone calls, advertising brochures, posters, advertisements and substitutes, regardless of the medium employed for their use (internet, radio, newspapers, TV, etc). It should be indicated how and where each one of the recruiting materials presented shall be used. Patient identification cards and medication use control cards shall not be considered recruitment materials, as well as summaries of additional visits to the PIS and other similar materials intended for the patient who is already participating in the study[1]. Therefore, in principle, these materials should not be included in the documentation to be submitted to the CEIm.

If the subject recruitment is done through advertising, copies of the advertising material, whether in print form, audio or video recordings or website material, shall be submitted. The proposed procedures for handling responses to advertisements, including copies of the communications used to invite subjects to participate in the clinical trial and foreseen arrangements for information or advice to the respondents found not to be suitable for inclusion in the clinical trial, shall be outlined.

The sponsor should take into account the European Commission guideline regarding the information that advertisements used in recruitment should contain[2].

2. Information sheet and informed consent documents

All information sheets and informed consent forms for participants should be submitted, both those referring to the study in general and to any sub-studies that may exist.

All these documents may be named at the applicant's discretion but it is obligatory that all include some descriptive term of their content, version and date. For example:

Name: <<PIS_general_code_version2_yyyy_mm_dd>>

or, for example,

<<HIP_FG_ code_version1_yyyy_mm_dd >>

The sponsor should take into account that in the CEIm opinion the documents shall be referenced as they are named here.

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[1] EU CT Regulation: "All information that has been provided to the subjects shall be submitted BEFORE they decided to participate…"

[2] Attachment 5: Advertising for trial subjects document. Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use. EudraLex vol 10. Feb 2006. Available at: http://ec.europa.eu/health/files/eudralex/vol-10/12_ec_guideline_20060216_en.pdf

3. Investigator suitability document.

A single document shall be submitted for each clinical trial, specifying the list of participating sites and the name and position of the principal investigators, as well as the planned number of trial subjects in each site (see model for investigator suitability document in Annex III).

Name: <<Investigators_versionX_yyyy_mm_dd>>

4. Documents to be provided for each site

A folder with the documents specified in a) and b) should be submitted for each site.

(a) Abbreviated curriculum vitae (CV) of the principal investigator in each site

In the CV (approximately 2 pages), accreditation should be provided for the principal investigator's training in good clinical practice, professional experience in clinical trials and patient care. In the CV of each principal investigator is where "***any circumstance that could influence the impartiality of the investigators***", if there is any, should be indicated. The sponsor is responsible for informing the investigator of those circumstances that should be declared (see next paragraph), which appear as free text in a section of the CV if there are any, *or in a specific appendix to the CV with the conflict of interest statement.* The absence of any reference in the CV shall be understood as the absence of any of these circumstances.

The judgment of a professional concerning his/her primary interest (e.g., the health of the patients or the integrity of an investigation) may be unduly influenced by a secondary interest of any nature, not only economic/financial interests with the sponsor, but also personal or professional prestige and promotion. This may be summarized as:

a.1. Personal interests:

- fees or personal benefits in kind (economic/financial interests)
- personal or professional promotion

a.2. Institutional interests:

- funding which benefits the department or unit under the direct responsibility of the investigator, without it being received personally by him/her.
- financial aids to create a unit or department
- financial support for hiring of staff in these units or funding of research in the unit.

a.3. Temporal coincidence and competition of studies with the same selection criteria:

- Acceptance to participate in more than one clinical trial in the same disease and with the same population (similar selection criteria) may create a conflict as to which of the coexisting studies the patient is to be invited to participate in.

(b) Suitability of facilities.

A written statement from the director or designee of the healthcare centre or institution where the clinical trial site is located shall be submitted, justifying the suitability of the clinical trial site, taking into account the nature and use of the investigational medicinal product, the suitability of the facilities, equipment, human resources and a description of specialized knowledge. The full name of the signatory and position held should be clearly indicated in the signature footer (see model suitability of facilities document in Annex III).

The type of document and name of the site shall be indicated for each site. For example,

Name: <<Facilities_PuertadeHierro>>

<<CV PI_PuertadeHierro>>

<<Facilities_ ValleHebron>>

<<CV PI_ValleHebron>>

5. Proof of insurance cover or financial guarantee

The documents referring to insurance shall be submitted with the word 'insurance', taking into account the considerations stated below:

Name: <<Insurance>>

The sponsor should submit a certificate from the insurance company (see model insurance certificate in Annex V), where it is stated that it is compliant with current legislation. When a change of insurance company or a modification for site extension occurs, a new certificate should be submitted from the insurance company including all the participating sites. In cases where the certificate from the insurance company raises doubts, the CEIm may request the complete policy. For cases of policies that contain exclusion clauses of doubtful acceptance regarding the insurance coverage legally required in Spain, given the possible difficulty of modifying these clauses and as an exceptional solution to this situation, the CEIm may assess the acceptance of an additional commitment of the sponsor's responsibility by which the sponsor undertakes to indemnify the damages and losses suffered as a result of the trial that may not be covered by said policies following the template of Annex VB.

In clinical trials with medicinal products falling within the definition of "non-commercial clinical research", the sponsor may submit a commitment to contract insurance (see model sponsor commitment in Annex VI). The CEIm shall issue a favourable opinion subject to submission by the sponsor of a certificate from the insurance company (see model insurance certificate in Annex V) within 30 calendar days. The study may not be started until the CEIm issues the favourable opinion because it considers that the required insurance cover or financial guarantee is available.

In clinical trials with medicinal products classified as "low-intervention clinical trials", it is not required to contract a specific insurance if any damage to the study subject that could result from the clinical trial is covered by the insurance of individual or collective professional civil liability insurance of the healthcare site or organisation where the clinical trial is conducted, for which the sponsor must submit a certificate from the representative of the site or organization where it is indicated that the insurance policy of the site or organisation covers this type of clinical trials (see model site/organisation representative certificate in Annex VII). Nevertheless, if the sponsor decides to contract a specific insurance for the study, it is not necessary to submit the certificate from the representative of the site/organisation, but the certificate of the insurance company should be submitted (see Annex V).

6. Financial budget

The financial budget should have the structure indicated in section 15 of the instructions document.

Name: <<Financial Budget>>

7. Proof of payment of fee to the CEIm, if applicable

Name: <<Fee>>

Documents for a substantial modification

Both the AEMPS and the CEIm shall only receive modifications on the documents that they are responsible for assessing.

1. Cover letter

Name: automatically assigned by the ECM Portal

The relevant remarks that the sponsor wishes to highlight regarding the assessment of the application should be indicated in the free text space “2. Comentarios a tener en cuenta con la solicitud” of the cover letter that is completed in the Portal ECM.

In this space, it should be indicated:

- Identification of the substantial modification by a date and a number or code.
- If the substantial modification only affects part I, part I and II, or part II, and which of the trial documents are changed.
- Specification of the parts affected by the modification (Quality (IMPD or GMP), non-clinical or clinical), indicating where appropriate that the modification affects reference safety information or if the modification refers to a previously reported urgent safety measure.

2. Application form for substantial modification

Name: automatically assigned by the ECM Portal

In order to prevent errors, the substantial modification should be identified with a date and a number or code in section E.1 of the substantial modification form, which should identify globally all changes in the modification.

This date and number is not the identification of the new version of the protocol or of other documents that are changed. The modification should have the same identification for the AEMPS and the CEIm and in all countries in the case of an international modification.

In section F of the application form shall be included the table of changes with a list of the previous text and the new text detailing the changes indicated in the “Summary and justification of changes” and making reference in each case to the document and section of the document that are changed. When the length of this section is insufficient, reference shall be made to a separate document.

3. Summary and justification of changes

Name: <<Summary_Changes_ yyyy_mm_dd_number or code of SM>>

The “Summary and justification of changes” document should have a maximum length of 1,200 words and contain a summary of the changes introduced and reasons for the changes.

4. Comparative table of previous text and new text

The previous text, new text and justification for the change shall be indicated for each change, identifying the document and section of the document that is changed. This table shall be submitted when the information does not fit in section F of the substantial modification form.

Name: <<Table_Changes_ yyyy_mm_dd_number or code of SM>>

5. **New version of documents that are changed**, including the revised initial application form when appropriate, identified with a new date

A copy of the modified documents shall be submitted with the updated date and in which the changes are visible (change tracking). When appropriate, the updated initial application form shall also be submitted.

Name: Each document shall be named as indicated in the documents of part I and part II.

6. **New documents** (e.g., when new sites are added, only those corresponding to the new sites shall be submitted to the CEIm), when appropriate.

Name: Each document shall be named as indicated in the documents of part I and part II.

7. **Documents supporting the changes (e.g. a publication), when appropriate**

Name: <<Supporting_info>>

8. **The consequences of the modification:**

Name: <<Consequences_SM>>

It shall include (a) an updated overall assessment of the risk-benefit ratio, (b) possible consequences for the subjects included in the trial, and (c) possible repercussions on assessment of the results.

9. **Proof of payment of fee to the CEIm, if applicable**

Name: <<Fee>>

All part I documents may be submitted in English. However:

- The application form should contain the information provided in the free text fields in Spanish and English as it supplies the data for the Spanish clinical studies registry (REec).
- The protocol summary must be submitted in Spanish.
- As a rule, the labelling must be in Spanish, though multilingual labellings are acceptable. The availability of labelling in another language may be assessed, provided the sponsor justifies the difficulty of having the labelling in Spanish and the labelling in another language shall not cause confusion in the distribution and administration of the medicinal product.
- The part II documents addressed to the trial subjects and assessed by CEIm must be written only in Spanish. However, if requested, the sponsor shall be responsible for providing an accurate translation of this information into other languages. These translations do not need to be submitted to the CEIm.