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Directorate-General PRE authorisation/Research and Development Division
(human use)

Guidance document for clinical trials sponsors

Voluntary Joint pilot between FAMHP, the College, accredited Ethics Committees and sponsors for processing of applications for the authorisation of clinical trials and substantial modifications on medicinal products for human use in accordance with the spirit of the Regulation (EU) No 536/2014 and of the law on Clinical Trial Regulation (CTR).

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The Federal Agency for Medicines and Health Products (FAMHP) is the competent authority responsible for the quality, safety and efficacy of medicines and health products in clinical development and on the market.

Document Revision History

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08.05.2017, V2.0	• First page new specific email address for the pilot • § 8.1.2: annex II: zip file available with empty structure of pilot dossier • § 8: tables in annex II: some clarifications in the "references" column
06.10.2017, V3.0	• § 4.2.1: important points for the constitution of the CTR pilot dossier • § 4.2.4: clarification on evaluation of Inform Consent Forms by the EC • § 4.2.5 and § 5.5: clarification on approval • § 8: tables in annex II: some clarifications in the "references" column
15.05.2018, V4.0	• § 2.1: clarification of the scope • § 4.2.1: possibility of submission via CESP • § 4.2.2 and § 5.2: no fee for pilot CTA and substantial modifications (SMs). • § 4.2.3 and § 5.3: clarification on timelines • § 4.2.5 and § 5.5: clarification on conditional approval • § 5.4: clarification on SM assessment phase by the EC • § 7.1 and § 7.2: timelines ATMP dossiers • § 8 tables in annex II : some clarifications in the "references" column • § 9: annex III: guidance for CESP submission • § 10: annex IV: Important points for the submission of the dossier and Q&A
08.06.2018, V4.1	§ 8: annex II, table on initial dossier part II, point R: clarification GDPR
16.11.2018, V5.0	• § 4.1: information to be provided in the intention letter: official name of sites available on www.health.belgium.be and final list to be provided at the latest 15 days before submission • § 4.1: new version of the intention letter available on www.famhp.be • § 4.2.1: addition of sentence on the role of the site in de submission process • § 4.2.1: submission via CESP only since 01.10.2018 • § 4.2.1: OCR list of documents in the cover letter • § 4.2.3: clarification of timelines for phases I and mixed phases I/II • § 5.1: addition of site not possible before three months after the approval of the initial trial • § 7.1, § 7.2, § 7.3 and § 7.4: clarification on timelines for CTAs and SMs with ATMPs • § 8: annex II, table on content of part I: reference to annex IV for preparation of dossiers • § 10.1: two clarifications related to the protocol (synopsis separated and termination criteria should be included in the protocol) • § 10.1: protection of the data statement following GDPR • § 10.2. 2): substantial modifications: some folders may be left empty
25.02.2019, V6.0	• § 2.1 and 2.5: introduction of the VHP plus process in the BE CTR pilot • § 2.4: clarification on non-substantial modifications and reference to examples in the table in §10. Annex IV • § 4.1: all proposed national CTAs in principle accepted in the pilot from 1st March 2019. CTAs proposed for new VHP plus process still accepted on a case by case basis • § 4.2.1: list of submitted documents to be also submitted at the moment of the answers to the RFI if versions updated

	• Clarification on what is provided by the College to the local sites • § 4.2.4: clarification on ICF languages and translations • § 5.1: new evaluating EC if an added site is the site of the evaluating EC for the initial trial • Request for list of documents and versions that can be copied • § 5.4: clarification on ICF languages and translations • § 8.2.2: complete filenames not longer than one hundred characters (folder names included) • § 10.1: deletion of a link that is not related to the data protection statement • § 10.2: addition of question 8) table with examples of SMs and notifications and questions 9) related to GDPR implementation
22.07.2019, V7.0	• § 2.5: clarification on safety reporting • § 4.1: it is asked to the sponsor not to submit the letter of intent to the NCP before all sites have been selected • § 4.2.1: application form will be accepted without mentioning the EC's details • § 4.2.1: important reminders for the preparation of a complete and qualitative submission dossier • § 4.2.1: please use files and document's names as described in § 8.1.4 • § 4.2.1: importance of providing the updated list of documents and versions every time new versions are available • § 5.1: addition of the site of the evaluating EC announced a few days in advance if possible • § 5.1: please use files and document's names as described in § 8.2.2 • § 5.1: importance of providing the updated list of documents and versions every time new versions are available • § 8 table on content of part II: L.: publication of the new version of the ICF template for adults on http://www.ct-college.be M: clarifications on GCP statement (should not be older than three years) and new CV template available. R.: minimum requirement for data protection statement • § 8 table on content of the SM dossier: F. clarification on the mandatory submission of the initial Application form, updated or not • § 10.1: Important points: minimum requirement for the data protection statement, section R. of the part II of the dossier • § 10.2: Q&A: clarifications in questions 5) on safety, 8) on examples of SM and notifications
12.2019, V8.0	• § 4.1.: letter of intent no longer requested, except for VHP plus pilot dossiers • § 4.2.1: WORD document with list of submitted documents • § 4.2.1: name of the evaluating EC • § 4.2.1: protocol synopsis now requested in FR, NL & EN • § 4.2.5: timelines in case of conditional approval • § 4.2.5: clarification in case of refusal • § 5.1: WORD document with list of submitted documents • § 5.5: timelines in case of conditional approval • § 5.5: clarification in case of refusal • § 8: part II table in annex II: two new templates available in the zipped empty structure of the submission dossier: CV and DOI of investigator developed by the EU Commission • § 11: annex V: new annexed with proposed templates for the WORD document with list of submitted documents

Contents

1. Definitions, conventions and abbreviations

ATMP: Advanced Therapy Medicinal Product

Clinical Trial: clinical study as defined in article 2, §2, 2), of the Regulation (EU) No 536/2014

CESP: Common European Submission Portal – see procedure for submission via CESP in annex III of the present guidance

CTA: Clinical Trial Application

CTR: Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

College: an independent organ that coordinates the working of the Ethics Committees and is responsible for their quality assurance. It also acts as single point of contact between Ethics Committees and the FAMHP - http://www.ct-college.be

EC: the Ethics Committee as stated in article 2, §2, 11) of the Regulation (EU) No 536/2014

FAMHP: the federal agency for medicines and health products as defined in the law of 20 July 2006 related to the creation and functioning of the federal agency for medicines and health products

National contact point (NCP): the FAMHP is the national contact point as defined in article 83 of the CTR. This means that for the purpose of the present project, the FAMHP will be the single contact point for the sponsor (for Part I and Part II of the dossier), without prejudice of the organisation between the competent authority and the College at the time all functionalities of the portal will be available.
For practical reasons, CTRpilot@afmps-fagg.be will be the NCP for sponsors.

RMS: Reporting Member State as stated in article 5 of the CTR.

SM: Substantial Modification as stated in article 2, §2, 13) of the Regulation (EU) No 536/2014

VHP: Voluntary Harmonised Procedure

All periods mentioned in the present document are to be understood as **calendar days**.

The present guidance is a document that could be modified or completed as discussions are still ongoing at European and national level on the implementation of the CTR and discussions on the process are also still ongoing between the different instances responsible for the assessment of the CTA dossiers.

The excel file for the letter of intent of sponsors interested to participate to the CTR pilot is to be provided by email to the specific email address for the pilot: CTRpilot@afmps-fagg.be.

2. Scope and objectives of the pilot

2.1. Scope

Following current EU legislation (Directive 2001/20/EC) and the law of 7 May 2004 on experiments on the human person, the authorisation procedures at the FAMHP and the Ethics Committees are currently mostly independent from each other.

This will change when the CTR will apply as one "single decision" per member state will have to be provided to the EU portal. The assessment of the dossier will have to be performed independently and in parallel by the competent authority and by the Ethics Committee and will have to be consolidated as the single decision will have to be reached in a short timeline. Close collaboration between the (i) FAMHP and the College and (ii) between the College and the ECs will thus be crucial. Close collaboration between these stakeholders will be even more crucial when Belgium has the role of RMS in the EU clinical trials authorisation process.

Clinical trials that are eligible for the pilot are national submissions of all phases (including ATMP trials) **and trials submitted via the VHP plus procedure.**

The CTR pilot **VHP plus process** is applicable to Part I and Part II and involves a limited number of volunteer ethics committees. A VHP plus specific addendum of the present guidance is available on the FAMHP website.

2.2. Objectives

The purpose of the pilot is to (i) develop processes and procedures for the joint assessment of CTAs and for the compilation of the Assessment Report, (ii) to evaluate them and (iii) to proceed with the adjustments. This will be a learning by doing approach for all parties in the pilot. This is also an opportunity for the FAMHP, the College and the Ethics Committees to test the short timelines for phase I mono-national trials within the framework of the CTR.

Participating in the pilot gives sponsors the opportunity of adjusting and testing their own processes with regard to the timelines and procedures of the CTR.

2.3. Voluntary basis

Sponsors participate in the pilot on a voluntary basis (for initial CTAs).

2.4. Substantial modifications

Once the initial CTA has been approved in the CTR pilot procedure, substantial modifications related to these trials need to be submitted following the CTR pilot procedure as well.
In the spirit of the CTR and if possible, no substantial modification shall be submitted if the previous one has not been already approved or closed.

Non-substantial modifications should not be submitted, but should be kept by the sponsor and added to the documentation for the next substantial modification. If no new substantial modification is submitted before the end of the trial, remaining notifications may be added to the notification of the end of trial.

A table with examples of substantial modifications and of different categories of notifications has been added to the Q&A document in § 10, annex IV of the present document. This table can be updated with the next version of the guidance if new examples are available at that moment.

2.5. Out of scope

Trials with GMO products submitted following the deliberate release procedure are not accepted in the pilot.
Safety reporting will not be handled in the pilot. This means that the safety reporting documents (i.e. DSUR, SUSAR) must not be submitted to the NCP and that the current rules for submission to the FAMHP and to the EC issuing the single opinion have still to be followed.

This means that for DSUR & SUSAR the procedure as described in CT-3 detailed guidance and circular letters 586 and 593 available on the FAMHP website (reporting according to the directive) and following the law of 7 May 2004 has to be followed. For pilot dossiers the "EC issuing the single opinion" is to be understood as the independent evaluating EC. This means that in the CTR pilot project, the College does not inform local ECs or sites about safety reporting. Submission to additional partners (investigators or local ECs) remains the responsibility of the sponsor.

Exceptions regarding safety reporting
Urgent Safety Measures (USM, where an unexpected event is likely to seriously affect the benefit-risk balance) shall be notified to the NCP not later than seven days after implementation. USM are part of the

pilot project though, as the safety issues and measures taken have a direct impact on the way the clinical trial is managed and on the trial documents (e.g. protocol and/or ICF).

Protocol Deviations with a direct impact on the safety of the subject also have to be notified by the Sponsor to NCP.

The CT College will then forward the latter notifications to the evaluating EC for information. The CT College does not inform the local ECs (nor the sites) about USM and protocol deviations.

3. Legal basis

The new law of 7th May 2017 on CTR was published in the Belgisch Staatsblad/Moniteur Belge on the 22th of May 2017. This law contains article 58 which foresees that for the pilot, article 11 §1 to 3 and §7 of the law of 7th May 2004 related to the role of the EC is no longer valid. The other articles of the law of 7 May 2004 remain applicable, as are the authorisation of the CTA and substantial modifications.
Essentially, as expected the pilot follows the law of 7th May 2004, but it follows the spirit of CTR and the text of the new Belgian Law of 7 May 2017, with the selection of the EC by the College and the joint assessment (FAMHP and EC) with the use of the new European templates.
The publication of the new law on clinical trials allowed the start of the CTR pilot.
A set of Royal Decrees is also foreseen (e.g. operational RD of 9th October 2017 published on 10th November 2017).

The CTR pilot will also permit to test the joint assessment of phase I mono-national dossiers for which short deadlines are being kept in the text of the new law on CTR.
As one of the principles of the present project is a learning by doing approach, some flexibility will be accepted from all parties involved. The CTA dossiers and SM dossiers will not automatically be rejected if the sponsor cannot answer the questions within the CTR deadlines (12 days). This timeline, as foreseen in the CTR, should be respected as much as possible but exceeding it by maximum 20 % will in practice be accepted.
This pilot is limited in time. It will not continue once the CTR regulation.

4. Procedure for sponsors – initial trials

4.1. What if a sponsor wants to participate in the CTR pilot?

Starting at publication of V8.0 of the present guidance document, if you want to participate in the CTR pilot, simply submit your complete dossier using the CESP platform, as explained in §9. Annex III. A CTR pilot number will be provided by the NCP in the validation e-mail.

Letter of intent for sponsors (only for VHP plus pilot dossiers)
The letter of intent available on the FAMHP website as the "form" should be submitted by email to the NCP (CTRpilot@fagg-afmps.be) with the following email title: CTR pilot – Letter of intent to participate in the CTR VHP plus pilot procedure – CTA dossier 20xx-xxxxxxx-xx (EudraCT number).

The following information should be provided in the intention letter:

- EUDRA-CT number of the clinical trial
- sponsor's trial code as stated when applying for the EUDRA-CT number
- title of the clinical trial
- planned submission date of the dossier
- name and site of the coordinating investigator of the clinical trial
- number and addresses of planned trial centres in Belgium as available at the moment of the submission of the letter of intent.

Please use the official name of the institution
The official name can be found on the Federal Public Service Health, Food Chain Safety and Environment's website.

If the dossier is accepted within the pilot VHP plus process, an acceptance email containing a CTR pilot number will be sent to the sponsor by the NCP.

After this, any communication between sponsor and NCP must at least contain the following title: CTR Pilot XXX VHP plus – CTA 20XX-XXXXXX-XX.

4.2. Practical procedure

4.2.1. Submission of the CTA

Sponsors are kindly requested to pay particular attention to the following when preparing the CTR pilot dossier

- Applicants of CTR pilot dossiers are kindly requested to provide a **WORD document** with the list of files with each submission (initial and SM). If during the evaluation additional files or newer versions are provided (via an answer to the RFI or response to conditions), please also provide an adapted list with a clear indication of which files have been updated. This list will be used by the EC to prepare their advice letter (**see recommended template of WORD document for initials and SMs in §11 annex V**).

  Additionally, we would like to encourage sponsors to mention the version number and/**or** the date (e.g. PilotXXX_20XX-XXXXXX-XX_Main ICF-Dutch_v2_20190823) in the **name of the files**.
  This would make it easier to compare the list with the files received and this would allow ECs to issue a complete approval letter at the end of the evaluation process.

- In order to guarantee the independence of the evaluating EC the applicant will not be informed of the name of the EC before the final conclusion of the dossier.
  As a consequence the application form will be accepted without mentioning the details of the EC and the name of the EC is no longer requested in the new proposed adult ICF template for patient interventional trials available on http://www.ct-college.be.

- The **protocol synopsis** is now requested in French, Dutch and English as according to the CTR and the Law of 7 May 2017 lay persons are part of the composition of the ethics committees. It has to be provided separated from the protocol.
  In general, for the content of the dossier, please consult tables in Annex II page 20 to 27 of the present guidance.

- **GLP CTFG guidance:** GLP statement has to be part of the IMPD (point 44 of annex I of the CTR and the Question and Answer document on Good Laboratory Practice).

- **RSI CTFG guidance:** the sponsor should fully comply with the Clinical Trial Facilitation Group (CTFG) Q&A during the IB updates following this publication.

- **Draft DSMB charter:** should be provided if a DSMB is part of the clinical trial.

- **Definition of the end of trial:** should be part of the protocol.

- **Helsinki declaration art.34 Post trial provisions**: "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial". If possible, this should be foreseen in the protocol.

- **The first act of recruitment** (e.g. advertising) should be specified in the protocol as according to the clinical regulation 536/2014 it defines the official start of the trial. As described in the Q&A document on CTR (Eudralex Volume 10, Q 10.1). For a phase I trial, the sponsor may justify to define the start of the trial differently than the first act of recruitment.

- Please pay attention to the quality of the translations of the ICF(s) in all the languages of the participants.

The Guidance for submission of clinical trial applications, substantial amendment notifications and end of trial declarations to the R&D division published on 13 November 2018, will not apply to a submission of a CTA dossier following the CTR pilot process. The present guidance provides the details of the requirements for submission of the dossiers for the CTR pilot procedure.
Please name files and documents as described in § 8.1.4.

The submission dossier (structure and contents) must comply with the requirements of annex I of the CTR. The regulation provides the option of separately submitting the documentations for part I and part II. However, it has been decided that the sponsor cannot use this option in the course of the pilot. Part I and part II packages have to be submitted together at the same moment to the NCP.

For the sake of swift processing of the dossier, the sponsor is asked to submit the CTA package by CESP[1] as CESP has been selected as the unique way of submission to harmonise the way the different type of dossiers are submitted in the R&D Division of the FAMHP.

The cover letter must be provided hand signed and scanned in the CESP submission.

All communications (additional information, responses to questions …) from the sponsor during the procedure are to be sent by CESP (if documents included) or by email to the NCP (CTRpilot@afmps-fagg.be).
No submission of the dossier to the local EC of the sites is necessary. However, the site can ask the sponsor the necessary information to be able to deliver the written statement of the suitability of the facilities.

The submission dossier and the approval letters from EC and FAMHP are sent to each concerned site. The modified documents following assessment and RFIs if applicable are not sent to the local sites by the College. It remains the responsibility of the sponsor to provide investigators with the necessary documents (e.g. updated protocol, ICF …).

4.2.2. Fee payment for an initial dossier

Currently no fee is due for the submission of a CTA initial dossier in the CTR pilot (not to the FAMHP or to the evaluating Ethics Committee).

4.2.3. Validation phase

The validation of the dossier (Part I & Part II) is performed by the NCP.
Timelines of the CTR apply to the validation phase, while once the T0 is given timelines of the law of 7 May 2004 (28 days or 15 days) apply to the start of the procedure. However as far as possible, timelines for validation will be kept short.

Short timelines (15 days) apply to all phase I trials, even multicentre trials as only one EC will be responsible for the evaluation of the dossier. In case the clinical trial is a mixed phase I/II trial, the 28-day timeline applies.

At the end of the validation phase which will last **a maximum** of 10 days (except for phase I mono-national trials for which the validation phase will last a maximum of 5 days), the sponsor will receive a validation notice (beginning of assessment) from the NCP. An operational calendar with a clear overview of the different timelines will be part of this notification to the sponsor.

If the validation shows deficiencies or shows relevant documentation is missing, leading to the CTA itself not being valid, the sponsor is granted a 10-day period to remedy the deficiencies. The corresponding response by the sponsor is to be sent to the national contact point via CESP.

The NCP evaluates supplemented documentation within five days after receiving comments or the amended application dossier. If the NCP comes to the conclusion that the documentation regarding part I and/or II is still not valid despite the supplement or if the sponsor neglects timely submission of the supplement, the FAMHP informs the sponsor that the CTA can no longer be processed within the pilot.

Upon successful validation, the national contact point sends the trial dossier to the College by means of an Eudralink.

It is to be noted that the EC will have access to the entire submission dossier part I with exception of the quality documentation.

[1] CESP: (Common European Submission Portal). See procedure for submission via CESP in annex III of the present guidance.

4.2.4. Assessment phase

After successful validation, the CTA is assessed by the FAMHP and the EC. The assessment regarding the aspects covered by part I of the CTA is performed in parallel by the FAMHP and the EC selected by the College. The aspects covered by part II are assessed by the EC.

During the assessment procedure of part I of the dossier, if the CTA dossier is not directly granted a positive assessment, the sponsor will receive a list of questions and/or requests for additional information (RFI) from the NCP.

Contents covered by part II of the CTA pursuant to the CTR are assessed in parallel by the EC. Questions and/or requests for additional information regarding these aspects are sent to the sponsor by the NCP at the same time with the list of questions related to Part I of the dossier.

Informed Consent Forms (ICFs) have to be provided in all languages of the participants but are reviewed by the EC in one language. If applicable, the modified ICF following comments from the EC is to be provided in this one language as part of the answers to the RFI. The correct translation into all other languages remains the responsibility of the sponsor and can be provided after approval of the CTA (added to a substantial modification: see question in the Q&A in annex IV).

Comments/remarks on the ICF could be provided by the EC into one of the language versions of the PDF document. In this case, the commented PDF will be added as an annex to the RFI letter and these comments/remarks have to be taken into account by the sponsor when providing the answers to the questions.

In the case of a RFI letter, the sponsor is called upon to remedy the deficiencies noted or to supply the requested information within twelve days at the most in order to comply with the deadlines specified in the CTR. As before, the answer here should also be as a single response sent via CESP to the NCP.
In case a question of the deficiency letter should be unclear it is recommended to contact the NCP by email.
As only one round of questions is foreseen in the CTR, it is recommended to formulate answers in a clear unambiguous way and check their completeness before sending them to the NCP.

4.2.5. Approval

After evaluation of the sponsor's response to questions related to part I and part II of the dossier by the FAMHP and the EC, the NCP compiles their final decisions on the basis of the assessment reports on part I and part II of the CTA. The final and unique conclusion is provided to the sponsor by the NCP.

If the CTA is "Authorised", the clinical trial can be started immediately.

If the CTA is "Authorised subject to conditions", the clinical trial can be started after the sponsor has fulfilled the conditions. The approval letter is sent at the time of the conditional approval. The sponsor is asked to answer the conditions within ten days. After reception of the answers to the conditions, the FAMHP and/or EC have five days to assess these answers. When all conditions are met, an email is sent by the NCP to the sponsor to indicate that "the conditions are met and the trial may start". No additional approval letter is sent.

If the CTA is "Refused", the clinical trial cannot be started.
In case of refusal, the CTA dossier can be re-submitted following the CTR pilot procedure.
In this case, the sponsor is asked:

- to adapt the dossier (to answer the objections given in the refusal letter);
- to add the refusal letter to the dossier;
- to add a description of the changes compared to the previous submission (preferably in track changes).

5. Procedure for sponsors - Substantial modifications

5.1. Submission of a substantial modification regarding a clinical trial approved in the CTR pilot

Substantial modifications (SMs) regarding clinical trials that were approved in the CTR pilot procedure will also need to be submitted following the CTR pilot procedure.
Please note that the addition of one or several new sites by the mean of a substantial modification is not possible before three months after the approval of the initial trial (law of 7 May 2004, art. 11 §14).

If one of the added sites is the site of the evaluating EC for the initial trial, a new evaluating EC will be selected by the College. In this particular case it is kindly asked to the sponsor to announce the foreseen submission of the substantial modification if possible a few days in advance to enable the College to already select a new evaluating EC.

Upon submission, the SM cover letter and any other communication should clearly state:
CTR Pilot XXX – CTA 20XX-XXXXXX-XX – SM n°XX
The submission dossier must comply with the requirements of annex II of the CTR.
Please use file and document names as described in § 8.2.2.

Applicants of substantial modifications are kindly requested to provide a **WORD document** with the list of files with each submission. If during the evaluation additional files or newer versions are provided (via an answer to the RFI or response to conditions), please provide an adapted list with a clear indication of which files have been updated. This list will be used by the EC to prepare their advice letter (**see recommended template of WORD document for SMs in §11 annex V**).

Additionally, we would like to encourage sponsors to mention the version number and/**or** the date (e.g. PilotXXX_20XX-XXXXXX-XX_Main ICF-Dutch_v2_20190823) in the **name of the files**.

This would make it easier to compare the list with the files received and this would allow ethics committees to issue a complete approval letter at the end of the evaluation process.

5.2. Payment of the fee for a substantial modification

No fee is currently due for the submission of a CTA substantial modification in the CTR pilot (not to the FAMHP or to the evaluating EC).

5.3. Validation phase

The validation of the substantial modification is performed by the NCP.
Timelines of the CTR apply to the validation phase, while timelines of the law of 7 May 2004 (28 days or 15 days) apply to the start of the procedure once the T0 is given. However as far as possible, timelines for validation will be kept short.

Short timelines (fifteen days) apply to all phase I trials, even multicentre trials as only one EC will be responsible for the evaluation of the dossier. In case the clinical trial is a mixed phase I/II trial, the 28-days timeline applies.

At the end of the validation phase which will last a maximum of 6 days (except for phase I mono-national trials for which the validation phase will last a maximum of 5 days), the sponsor will receive a notice of validation (beginning of assessment) from the NCP. An operational calendar with a clear overview of the different timelines will be part of this notification to the sponsor.

If the validation shows deficiencies or that relevant documentation is missing, leading to the SM itself not being valid, the sponsor is granted a ten-day period to remedy the deficiencies. The corresponding response by the sponsor is to be sent to the NCP via CESP.
The NCP evaluates the supplemented documentation within five days after receiving the comments or the updated SM dossier.

5.4. Assessment phase

After successful validation, the SM is assessed by the FAMHP and in principle the EC that was responsible for the assessment of the initial dossier.

The assessment regarding the aspects covered by part I of the CTA is performed in parallel by the FAMHP and the EC with the exception of the modifications related to the quality part of the dossier which are only assessed by the FAMHP. The aspects covered by part II are assessed by the EC.

It is to be noted that the EC will have access to the submission dossier for a substantial modification on Part I (except quality documentation) even if "A.3 Notification for an opinion to the Ethics Committee" was not ticked in the EU application form. The EC will decide on case by case basis if an EC evaluation (and thus an EC approval) is needed.

During the assessment procedure of Part I of the dossier, if the SM dossier is not directly granted a positive assessment, the sponsor will receive a list of questions and/or requests for additional information from the NCP.

SM contents covered by the Part II of the CTA pursuant to the CTR are assessed in parallel by the EC. Questions and/or requests for additional information regarding these aspects are sent to the sponsor by the NCP at the same time with the list of questions related to part I of the SM dossier.

If the substantial modification is related to an update of the Inform Consent Form (ICF), the ICF has to be provided in all languages of the participants but is reviewed by the EC in one language. If applicable the modified ICF following comments from the EC is to be provided in this one language as part of the answers to the RFI. The correct translation into all other languages remains the responsibility of the sponsor and can be provided at the occasion of the next substantial modification (see question 8) in the Q&A in annex IV).

Comments/remarks on the ICF could be provided by the EC into one of the language versions of the PDF document. In this case, the commented PDF will be added as an annex to the RFI letter and these comments/remarks have to be taken into account by the sponsor when providing the answers to the questions.

In the case of a RFI letter, the sponsor is called upon to remedy the deficiencies noted or to supply the requested information within twelve days at the most in order to comply with the deadlines specified in the CTR. As before, the answer here should also be as a single response sent via CESP to the NCP.

In case a question of the deficiency letter should be unclear it is recommended to contact the NCP by email.

As only one round of questions is foreseen in the CTR, it is recommended to formulate answers in a clear unambiguous way and check their completeness before sending them to the NCP.

5.5. Approval

After evaluation of the sponsor's response to questions related to Part I and Part II of the SM dossier by the FAMHP and the EC, the NCP compiles their final decisions on the basis of the assessment report on part I and part II of the SM. The final and unique conclusion is provided to the sponsor by the NCP.

If the SM is "Authorised", the substantial modification can be implemented.

If the SM is "Authorised subject to conditions", the substantial modification can be implemented after fulfilment of the conditions by the sponsor. The approval letter is sent at the time of the conditional approval. The sponsor is asked to answer the conditions within 10 days. After reception of the answers to the conditions, the FAMHP and/or EC have five days to assess these answers. When all conditions are met an email is sent by the NCP to the sponsor to indicate that "the conditions are met and the SM can be implemented". No additional approval letter is sent.

If the SM is "Refused", the substantial modification cannot be implemented.
In case of refusal, the SM dossier can be re-submitted following the CTR pilot procedure.

In this case, the sponsor is asked:

- to adapt the dossier (to answer the objections given in the refusal letter);
- to add the refusal letter to the dossier;
- to add a description of the changes compared to the previous submission (preferably in track changes).

6. Survey

The NCP will organise a survey to the sponsors to collect comments, lessons learned, suggestions on the pilot process to obtain a joint conclusion with recommendations and adaptations where required.

7. Annex I – Timetables for the CTR pilot process

7.1. National initial dossier (other than phase I mono-national trial)

Maximum duration of the process: 28 days (timeline as foreseen in the law of 7 May 2004) + 10 days for validation + max. 15 additional days if questions during validation + max. 12 days if RFI during assessment => max. 65 days	
Step	DAY
Reception of the dossier via CESP and beginning of validation	Date submission= T0 - 10
Notification of the validation status to the sponsor: - Dossier complete → beginning of assessment - Dossier still not complete after max. 15 additional days (10 for the sponsor to answer the request for additional info + 5 for the NCP to verify if the dossier is complete after answer from the sponsor) → dossier refused	T0 (+ max. 10 + max. 5 if validation questions)
Compiled assessment report for Part I and assessment for part II available: ⇨ Direct approval at T28 at the latest if no questions from FAMHP or EC ⇨ List(s) of questions provided by the NCP to the sponsor	T23
Response on questions by sponsor due by (maximum 12 days clock stop if list of questions)	T23 (+ max. 12 days)
Review of the answers by the FAMHP and/or the EC and final coordinated decision sent by the national competent authority by	T28

For an ATMP clinical trial, 30 days (as foreseen by the law of 7 May 2004) will be added to the 28 days legal delay. From these additional 30 days, 25 days will be added to the assessment period of 23 days and 5 days to the period foreseen for the assessment of the answers to the RFI.

7.2. National initial phase I mono-national dossier

Maximum duration of the process: 15 days (timeline as foreseen in the law of 7 May 2004) + 5 days for validation (+ max. 15 additional days if questions during validation) + max. 12 days if RFI during assessment → max. 47 days	
Step	DAY
Reception of the dossier via CESP and beginning of validation	Date submission = T0 - 5
Notification of the validation status to the sponsor: - Dossier complete → beginning of assessment - Dossier still not complete after max. 15 additional days (10 for the sponsor to answer the request for additional info + 5 for the NCP to verify if the dossier is complete after answer from the sponsor) → dossier refused	T0 (+ max. 10 + max. 5 if validation questions)
Compiled assessment report for Part I and assessment for Part II available: ⇨ Direct approval at T15 at the latest if no questions from FAMHP or EC ⇨ List(s) of questions provided by the NCP to the sponsor	T10
Response on questions by sponsor due by (maximum 12 days clock stop if list of questions)	T10 (+ max. 12 days)
Review of the answers by the FAMHP and/or the EC and final coordinated decision sent by the national competent authority by	T15

For an ATMP clinical trial, 30 days (as foreseen by the law of 7 May 2004) will be added to the 15 days legal delay. From these additional 30 days, 25 days will be added to the assessment period of 10 days and 5 days to the period foreseen for the assessment of the answers to the RFI.

7.3. National Substantial Modification (other than phase I mono-national trial)

Maximum duration of the process: 28 days (timeline as foreseen in the law of 7 May 2004) + 6 days for validation (+ max. 10 + max. 5 days if questions during validation)+ max. 12 additional days if RFI → max. 61 days	
Step	DAY
Reception of the dossier via CESP and beginning of validation	Date submission = T0 - 6
Notification of the validation status to the sponsor: - Dossier complete → beginning of assessment - Dossier still not complete after max. 15 additional days (10 for the sponsor to answer the request for additional info + 5 for the NCP to verify if the dossier is complete after answer from the sponsor). → dossier refused	T0 (+ max. 10 + max. 5 if questions during validation)
Compiled assessment report for part I and/or assessment for part II available (depending from the scope of the substantial amendment): ⇨ Direct approval at T28 at the latest if no questions from FAMHP or EC ⇨ List(s) of questions provided by the NCP to the sponsor	T23
Response on questions by sponsor due by (Clock stop of maximum 12 days if list of questions)	T23 (+ max. 12 days
Review of the answers by the FAMHP and/or the EC and final coordinated decision sent by the national competent authority by	T28

For an ATMP clinical trial, 30 days (as foreseen by the law of 7 May 2004) will be added to the 28 days legal delay. From these additional 30 days, 25 days will be added to the assessment period of 23 days and 5 days to the period foreseen for the assessment of the answers to the RFI.

7.4. National substantial modification for a phase I mono-national trial

Maximum duration of process: 15 days (timeline as foreseen in the law of 7 May 2004) + 5 days for validation (+ max. 10 + max. 5 days if questions during validation) + max. 12 additional days if RFI → max. 47 days	
Step	DAY
Reception of the dossier via CESP and beginning of validation	Submission date = T0 - 5
Notification of the validation status to the sponsor: - Dossier complete → beginning of assessment - Dossier still not complete after max. 15 additional days (10 for the sponsor to answer the request for additional info + 5 for the NCP to verify if the dossier is complete after answer from the sponsor) → dossier refused	T0 (+ max. 10 + max. 5 if validation questions)
Compiled assessment report for Part I and/or assessment for Part II available (depending from the scope of the substantial amendment): ⇨ Direct approval at T15 at the latest if no questions from FAMHP or EC ⇨ List(s) of questions provided by the NCP to the sponsor	T10
Response on questions by sponsor due by (clock stop of maximum 12 days if list of questions)	T10 (+ max. 12 days
Review of the answers by FAMHP and/or EC and final coordinated decision sent by the national competent authority by	T15

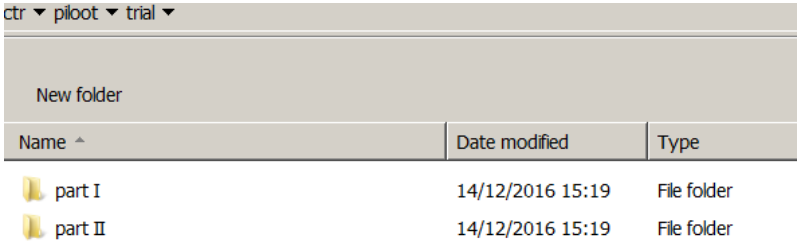
For an ATMP clinical trial, 30 days (as foreseen by the law of 7 May 2004) will be added to the 15 days legal delay. From these additional 30 days, 25 days will be added to the assessment period of 10 days and 5 days to the period foreseen for the assessment of the answers to the RFI.

8 Annex II – Dossier structure as per regulation 536

8.1 Initial application

During the course of the pilot, part I and part II packages have to be submitted together.

8.1.1 Initial application



A zip-file with the structured folders with the available templates (written statement of the sites and Investigator's CV) is available on our website next to the present guidance.

8.1.2 Consider to apply the following folder structure – an empty folder structure can be provided

APPLICATION DOSSIER FOR THE INITIAL APPLICATION

Part I

A. INTRODUCTION AND GENERAL PRINCIPLES
B. COVER LETTER
C. EU APPLICATION FORM
D. PROTOCOL
E. INVESTIGATOR'S BROCHURE
F. DOCUMENTATION GMP FOR THE IMP(s)
G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER
H. AUXILIARY MEDICINAL PRODUCT DOSSIER
I. SCIENTIFIC ADVICE AND PIP
J. LABELLING OF THE IMP

Part II (INFORMATION PER MEMBER STATE CONCERNED)

K. RECRUITMENT ARRANGEMENTS
L. SUBJECT INFORMATION, ICF AND IC PROCEDURE
M. SUITABILITY OF THE INVESTIGATOR
N. SUITABILITY OF THE FACILITIES
O. PROOF OF INSURANCE
P. FINANCIAL AND OTHER ARRANGEMENTS
R. STATEMENT DATA PROTECTION

8.1.3 Consider to apply the following folder structure – an empty folder structure can be provided

Please apply the PDF file format except for the EudraCT application form, which **in addition** to the PDF format, must be in XML format.
Some requirements for the preparation of these PDF files:

1. The files must allow "copy/paste" and other changes. If the source file is no longer available, the applicant can provide a scanned copy. However he must provide readable documents.
2. Certificates, licenses, authorisations and other documents with a signature must be scanned.
3. The layout should be as clear as possible. If possible a detailed table of contents must be included in order to find quickly specific sections of text.
4. Files should not be locked by a password.
5. Each part of the application dossier for clinical trial should be a separate file.
6. The names of these files must follow the syntax described below.
7. The PDF version of the European application form must be saved twice: a first part corresponding to the entire form and the second part with only the signed page that has been scanned. The same principle applies to the European substantial amendment notification form.

8.1.4 File and document names

Please consider to use **descriptive file and document names**. To name the different files/documents we ask you to respect a defined syntax: pilot number and EudraCT number first, followed by the file name in English (see list below).

Example:
PilotXXX_xxxx-xxxxxx-xx_Name of file/document.pdf
Pilot 999_2010-090094-00_Cover-Letter.pdf

Special cases

1. To name scanned pages of documents with signatures we ask you to add "signature" in the name.
   Example: Pilot999_2010-090094-00_Application_Form_Signature.pdf
2. In case the document refers to a particular medicinal product (IMP or authorised medicinal product) we ask you to add the name of this medicinal product in the filename.
   Example: EudraCT Number-Manufacturing-Authorisation-Name of the medicinal product.pdf

PART I (see also **annex IV**: important points for the preparation of the CTR pilot dossier and Q&A)

File/Document	Name	Annex I Regulation No 536/2014	References
B. Cover Letter	Cover-Letter.pdf	B	• Pilot number • WORD document with list of submitted documents
C. EU application Form	Application-form.pdf	C	EU Application Form (the current EU Application Form should be used during the pilot as a new CTR Application Form is not yet available)
D. Protocol	Protocol.pdf	D 24	• See also ICH E6 GCP • The protocol shall be accompanied by a synopsis of the protocol, provided as a separate document in EN, FR and NL. • The first act of recruitment (e.g. advertising) should be specified
E. Investigator's brochure	Investigators_Brochure.pdf	E	See also ICH E6 GCP
F. Documentation relating to GMP for the IMP • Copy of the manufacturing authorisation • Certification by the Qualified Person • …	• Manufacturing-Authorisation.pdf • QP-Declaration.pdf • …	F	• GMP certificates not accepted, only GMP manufacturing authorisations • EU template strongly recommended for QP declaration
G. Investigational medicinal product dossier	Impd.pdf	G	• See also Eudralex volume 10 chapter III for content and Common Technical Document (CTD) format • GLP statement has to be part of the IMPD (see: point 44 of annex I of the CTR and http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/QAs_document_on_GLP_-_2017.pdf
G. Simplified investigational medicinal product dossier	Simplified-Impd	G	See CTR (annex I points 50 to 53) to see cases when a simplified IMPD is accepted
G. Summary of product characteristics	Smpc.pdf	G	If applicable
H. Auxiliary Medicinal product Dossier	Ampd.pdf	H	AMPD or SPC if applicable
I. Copy of the summary of scientific advice	Scientific-Advice.pdf	I 56	If applicable
I. Copy on the agreement on the PIP	PIP.pdf	I 57	If applicable
J. Content of the labelling	Labels.pdf	J	Example of the planned label in accordance with annex 13 of the GMP

Remark: Section A of part I "Fulfilment of Introduction and General Principles" may be left empty if no specific information as foreseen in annex I point A. of regulation 536/2014 is available.

PART II (no specific cover letter for part II)

File/Document	Name	Annex I Regulation No 536/2014	References
K. Recruitment arrangements, unless described in the protocol	Recruitment-arrangements.pdf	K 59	Stand-alone document or reference to the applicable section of the protocol has to be provided
K. Advertising material	Advertising-material-name.pdf	K 60	If applicable
L. Subject (and legally designated representative) information and informed consent ICF, questionnaires, participation card, diaries or other patient documents	ICF-language-target group.pdf	L 61&63	• Use of the existing template is strongly recommended • **A new version of the ICF template for interventional trials in adults and dated 28-06-2019 has been published on http://www.ct-college.be** • To be submitted in all languages that will be used in Belgium • Sponsor is responsible for appropriate translations. The EC only reviews the ICFs in one language
L. Informed consent Procedure	ICF-procedure.pdf	L 62	A stand-alone document or a reference to the applicable section of the protocol has to be provided
M. List of the planned sites, name and position of PI and planned number of subjects at the sites	Planning.pdf	M 64	Has to be provided
M. CV and declaration of interest of the principal investigator of each site	CV-name.pdf & DOI-name.pdf	M 65&66	• CV template developed by the EU Commission available: see zipped empty structure of the CTR pilot dossier on the FAMHP website Diplomas have to be listed and the most important trials experience should be documented (as in the Commission template). Any other template (e.g. TransCelerate) can be accepted but should at least contain the same information. • GCP training should be documented (in the CV or by a GCP certificate), mentioning the name of the certifying organisation **and should not be older than three years** • Declaration of interest: template developed by the EU Commission available: see zipped empty structure of the CTR pilot dossier on the FAMHP website
N. Statement on the suitability of the sites	Suitability-statement-namesite.pdf	N	Most recent version of the written statement issued by the site. • Template available in the structure zip file in on the FAMHP website • It is advised to contact the sites as soon as possible when

			identified in order to have the written statements ready at the time of submission
O. Proof of insurance cover or indemnification	Proof of Insurance Cover.pdf	O	Certificate with specification of the amount insured and reference to the Belgian law of 7 May 2004, art. 29 §1 (no fault insurance)
P. Brief description of the financing of the CT	Financing.pdf	P 69	If applicable
P. Information on financial transactions and compensation paid to subjects and investigator/site	Budget-namesite.pdf	P 70	• Draft version of the contract with (draft) amounts is currently accepted • It is advised to contact the CTCs of the concerned sites as soon as possible in order to gain time in the evaluation of the financial agreements
P. Description of any other agreement	Agreement-namesite.pdf	P 71	Clinical trial agreements and others related to the trial if applicable
R. Statement that data will be collected and processed in accordance with the General Data Protection Regulation (GDPR)	Data-Protection-Statement.pdf	R	A stand-alone document (statement) has to be provided. **This document should at least contain**: "[name of sponsor] confirms that collection and processing during clinical trials is done in full compliance with the European Regulation 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection regulation)".

8.2 Substantial modifications

The following folder structure should be applied and sections A to G should be provided upon submission of the substantial modification – an empty folder structure can be provided.

Please note that during the CTR pilot, the submission of a substantial modification should be made separately for trial(s) in the pilot and trials approved within the current process. After implementation of the CTR, the same substantial modification can be submitted again for all trials concerned.

Substantial modifications that are currently submitted for EC only, mainly correspond to part II of the dossier structure within CTR. These substantial modifications also need to be submitted to the NCP who will distribute them to the College and subsequently to the EC.

Non-substantial modifications should not be submitted, but should be added to the documentation for the next substantial modification.

A zip file with the structured empty folders is available on our website next to the present guidance.

APPLICATION DOSSIER FOR SUBSTANTIAL MODIFICATIONS
A. INTRODUCTION AND GENERAL PRINCIPLES
B. COVER LETTER
C. MODIFICATION APPLICATION FORM
D. DESCRIPTION OF THE MODIFICATION
E. SUPPORTING INFORMATION
F. UPDATE OF EU APPLICATION FORM

8.2.1 File format

Please apply the PDF file format except for the initial EudraCT application form, which should also be provided in XML format.

Some requirements for the preparation of these PDF files.

1. The files must allow "copy/paste" and other changes. If the source file is no longer available, the applicant can provide a scanned copy. However he must provide readable documents.
2. Certificates, licenses, authorisations and other documents with a signature must be scanned.
3. The layout should be as clear as possible. If possible a detailed table of contents must be included in order to quickly find specific sections of text.
4. Files should not be locked by a password.
5. Each part of the application dossier for the substantial modification should be a separate file.
6. The names of these files must follow the syntax described below.
7. The PDF version of the Modification Application Form must be saved twice: a first part corresponding to the entire form and the second part with only the signed page that has been scanned.
8. An extract from the amended documents or the amended document itself showing previous and new wording in track changes, as well as the extract/document only showing the new wording must be provided. A summary of changes must also be provided. If the summary of changes and the track changes version(s) of the updated documents are not present, this will be a validation question.
9. Regarding modifications to the Reference Safety Information: **in view of the update of the CTFG - Q&A document on RSI**, the sponsor should fully comply with the Q&A during the IB updates that follow this publication.

8.2.2 File and document names

Please consider using **descriptive file and document's names**. To name different files and documents we ask you to respect a defined syntax: EudraCT number first, followed by the file name in English (see list below).

Example
PilotXXX_SMX_xx-xxxxxx-xx__Name of file. pdf
Pilot999_SM1_2010-090094-00_Cover-Letter.pdf

Please assure that the complete filenames are not longer than hundred characters (folder names included)

Special cases:

1. To name the scanned pages of the documents with signatures we ask you to add "signature" in the name.
   Example: Pilot999_SM1_2010-090094-00_Application-Form-Signature.pdf

2. In case the document refers to a particular medicinal product (investigational medicinal product or authorised medicinal product) we ask you to add the name of this medicinal product in the filename. Example: Pilot999_SM1_xxxx-xxxxxx-xx__Manufacturing-Authorisation_Name of the medicinal product.pdf

Document	Name	Annex II Regulation No 536/2014	References
B. Cover Letter	Cover-Letter.pdf	B	• Pilot number • WORD document with list of submitted documents
C. Modification Application Form	Modification-Application-Form.pdf	C	Modification Application Form (the current Substantial Amendment Notification Form should be used during the pilot as a new CTR Modification Application Form is not yet available)
D. Description of the modification	e.g. Protocol-edition-date.pdf Protocol-edition-date-TC version.pdf Investigators-Brochure-edition-date.pdf Investigators-Brochure-edition-date-TC version.pdf Impd-edition-date.pdf Impd-edition-date-TC version.pdf Summary-of-changes.pdf ICF-language-target group-edition-date.pdf ICF-language-target group-edition-date-TC version.pdf…	D	• Protocol and IB: See ICH E6 GCP/EudraLex volume 10 • **A new version of the ICF template for interventional trials in adults and dated 28-06-2019 has been published on http://www.ct-college.be** • ICF to be submitted in all languages that will be used in Belgium • **For all updated documents a summary of changes and track changes version(s) must be provided**
E. Supporting information	e.g. Benefit-Risk.pdf, Justification-of changes.pdf…	E	Only if applicable, may be left empty
F. Update of the EU Application Form	Application-form.pdf	F	• The initial application form (updated or not) is also to be provided with each substantial modification • If the initial Application Form has been revised, changes must be clearly highlighted

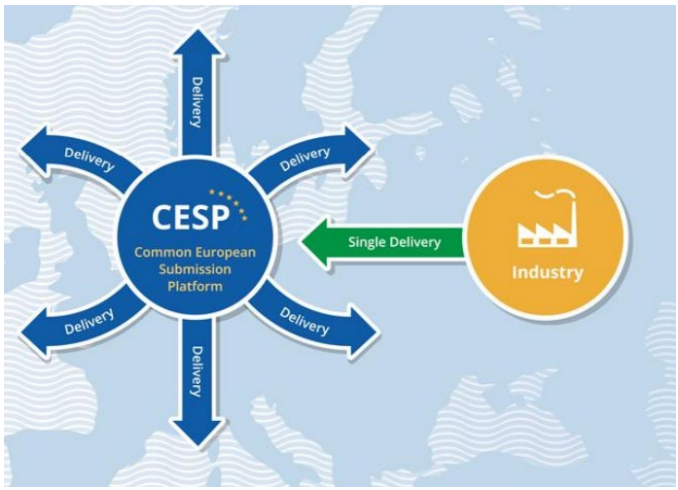
Remark: Section A. "Fulfilment of Introduction and General Principles" may be left empty if no specific information as foreseen in annex II point A of regulation 536/2014 is available

9. Annex III - E-submission through the Common European Portal (CESP)

The CESP is a simple and secure mechanism for the exchange of submission information between applicants and competent authorities in Europe. CESP is a secure web platform developed by HPRA (Ireland) under the supervision of the Heads of Medicines of agencies.

1. The main advantages of this portal include:

- a multipurpose delivery system, can be used for any type of digital information transfer,
- a tracking system,
- automatic notification by the application,
- a simple, fast, efficient delivery system for information,,
- easier, faster submission updates/responses to agency information requests
- a secure method of communicating with the regulatory authorities via one platform,
- reduced burden for both industry and regulators in submitting/handling applications on CD-ROM and DVD.



9.1 For which application must CESP be used?

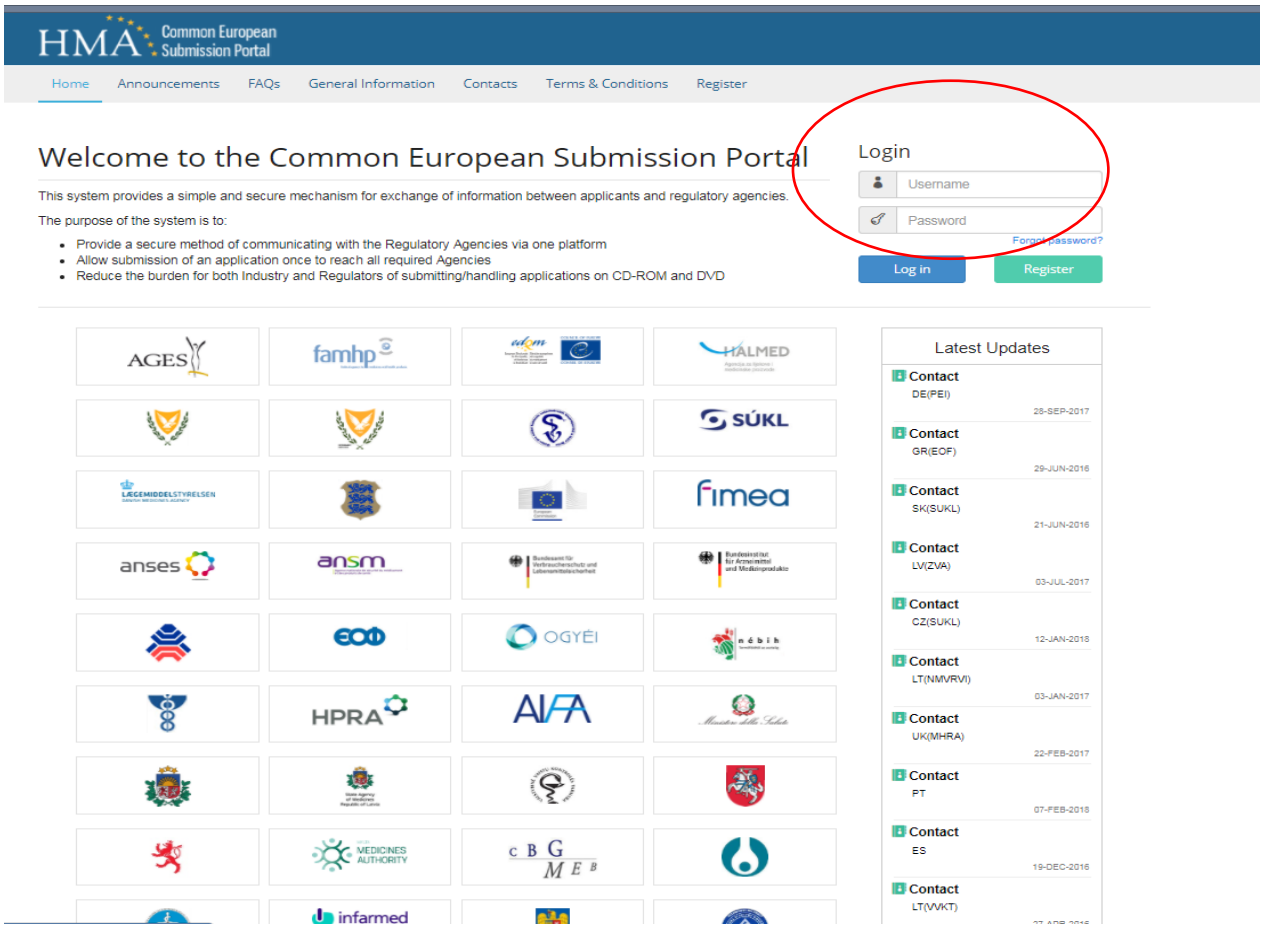
Clinical trials (medicines)	Initial application for a clinical trial
	Substantial amendment for a clinical trial
	ASR/DSUR submission
	Urgent safety measure
	Temporary halt notification
	End of trial declaration
	CTR Pilot – initial application for a clinical trial
	CTR Pilot – Substantial modification for a clinical trial
Clinical investigations (medical devices)	Initial application for a clinical investigation
	Serious Adverse Events Notification
	Notification of end of clinical investigation / performance study
Unmet Medical Needs	Initial application for a CUP/MNP
	Periodic Re-evaluation for a CUP/MNP
	Substantial Amendment for a CUP/MNP
Clinical investigations and Unmet Medical Needs	Approval of the EC

When using CESP, please do not send the same dossier via other ways to the FAMHP.

9.2. How to submit an application through CESP?

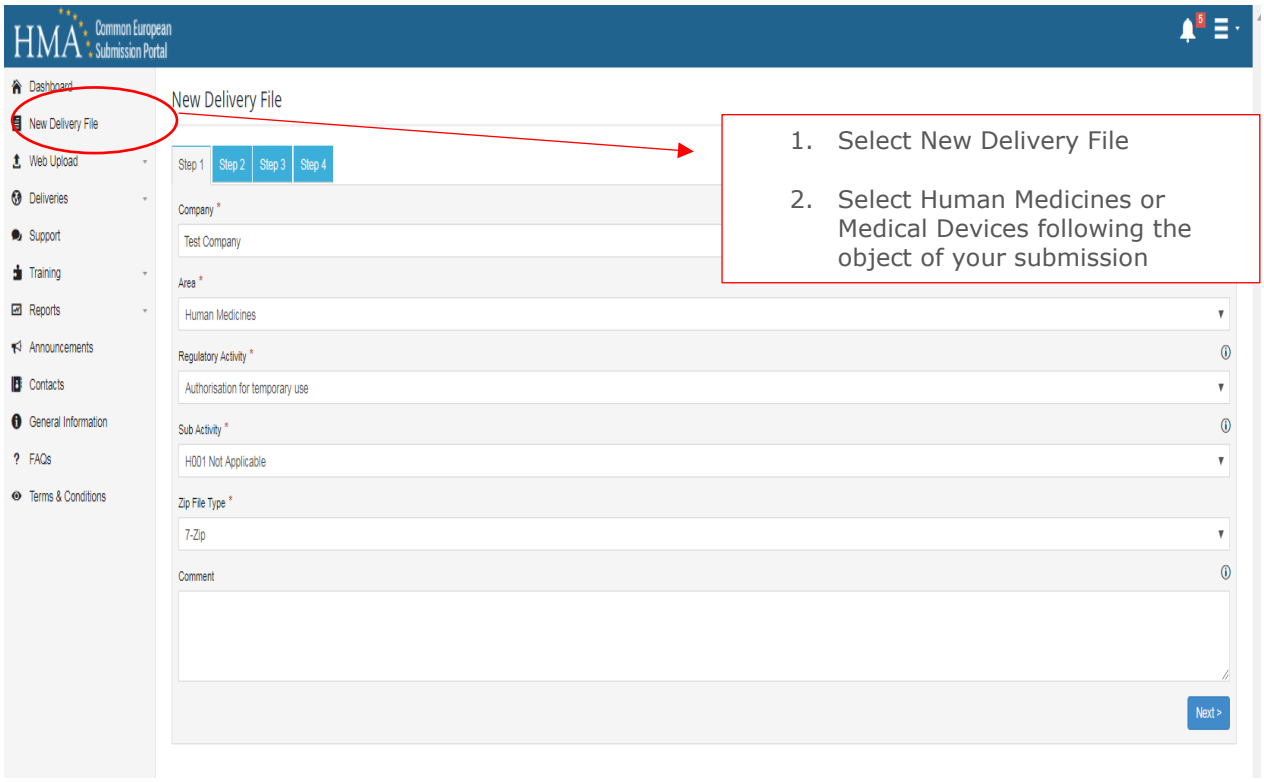
9.2.1. Account and connection

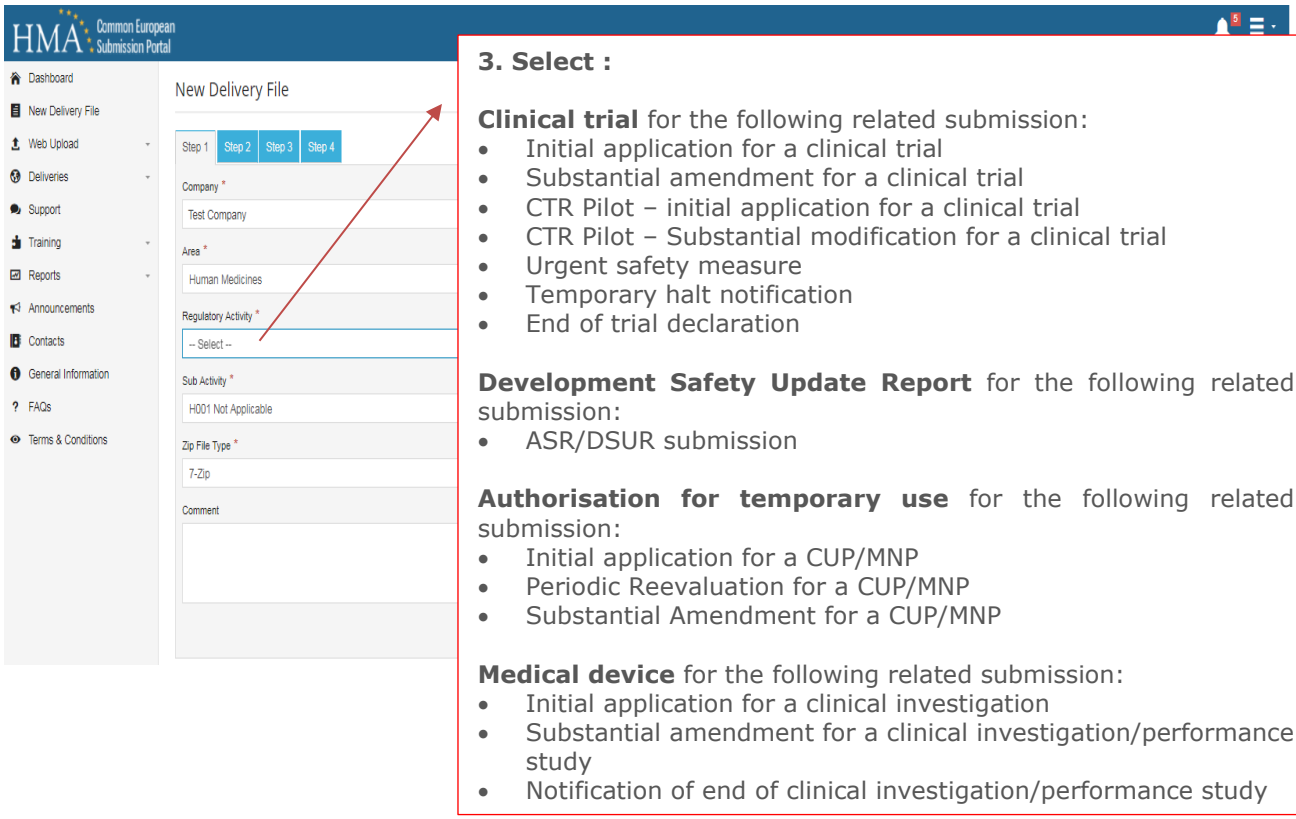
Link to the website: https://cespportal.hma.eu/Account/Login
If haven't got an account yet, select "register" or follow this link:
ehttps://cespportal.hma.eu/delivery/create



9.2.2. e-submission

First create a delivery file. A new delivery file has to be made for each submission.





3. Select :

Clinical trial for the following related submission:

- Initial application for a clinical trial
- Substantial amendment for a clinical trial
- CTR Pilot – initial application for a clinical trial
- CTR Pilot – Substantial modification for a clinical trial
- Urgent safety measure
- Temporary halt notification
- End of trial declaration

Development Safety Update Report for the following related submission:

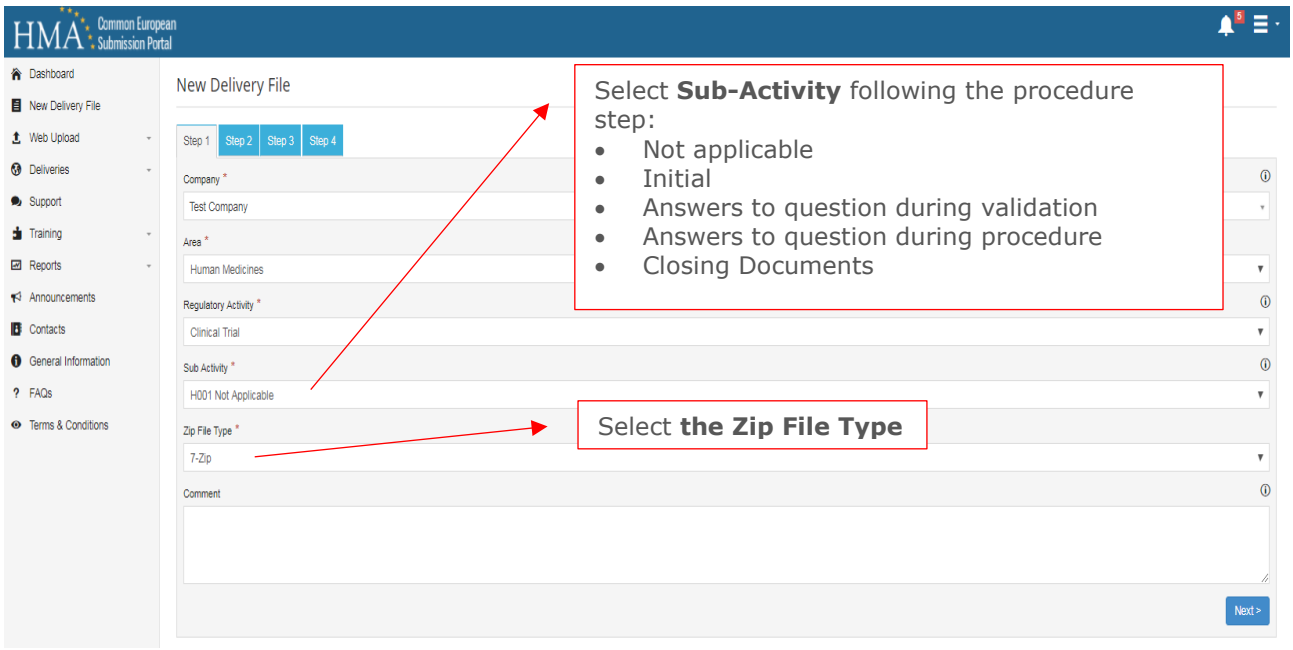
- ASR/DSUR submission

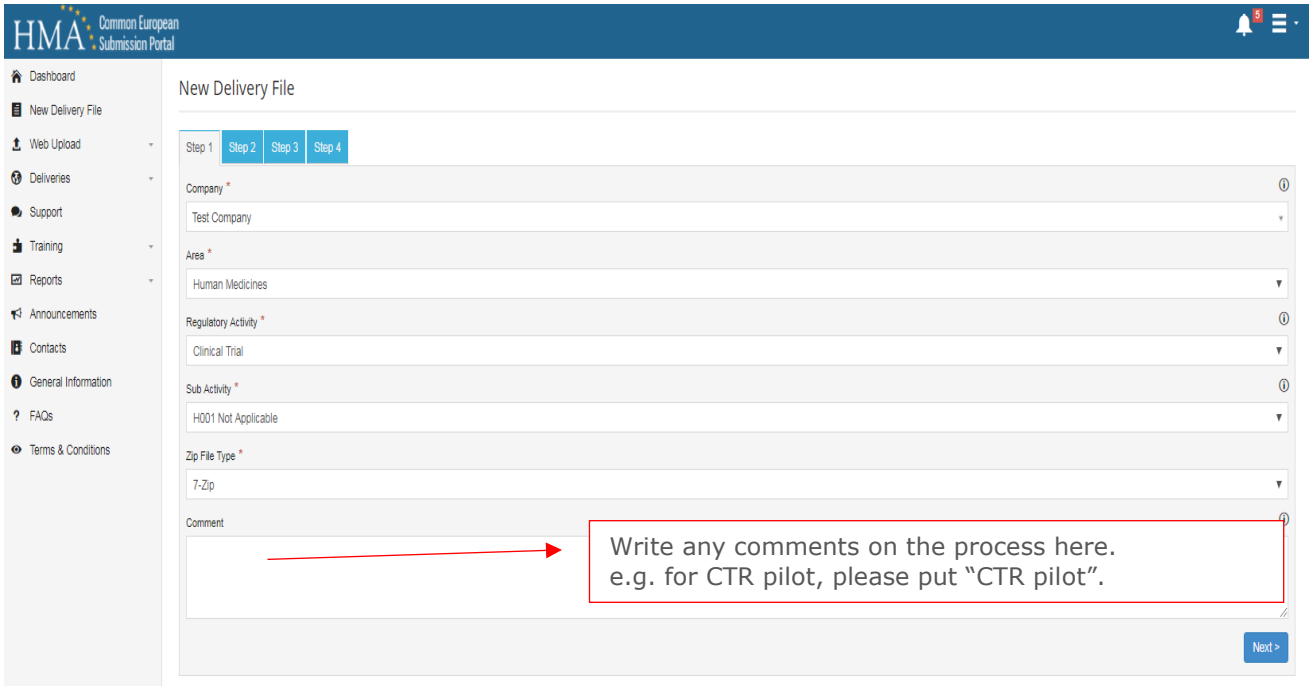
Authorisation for temporary use for the following related submission:

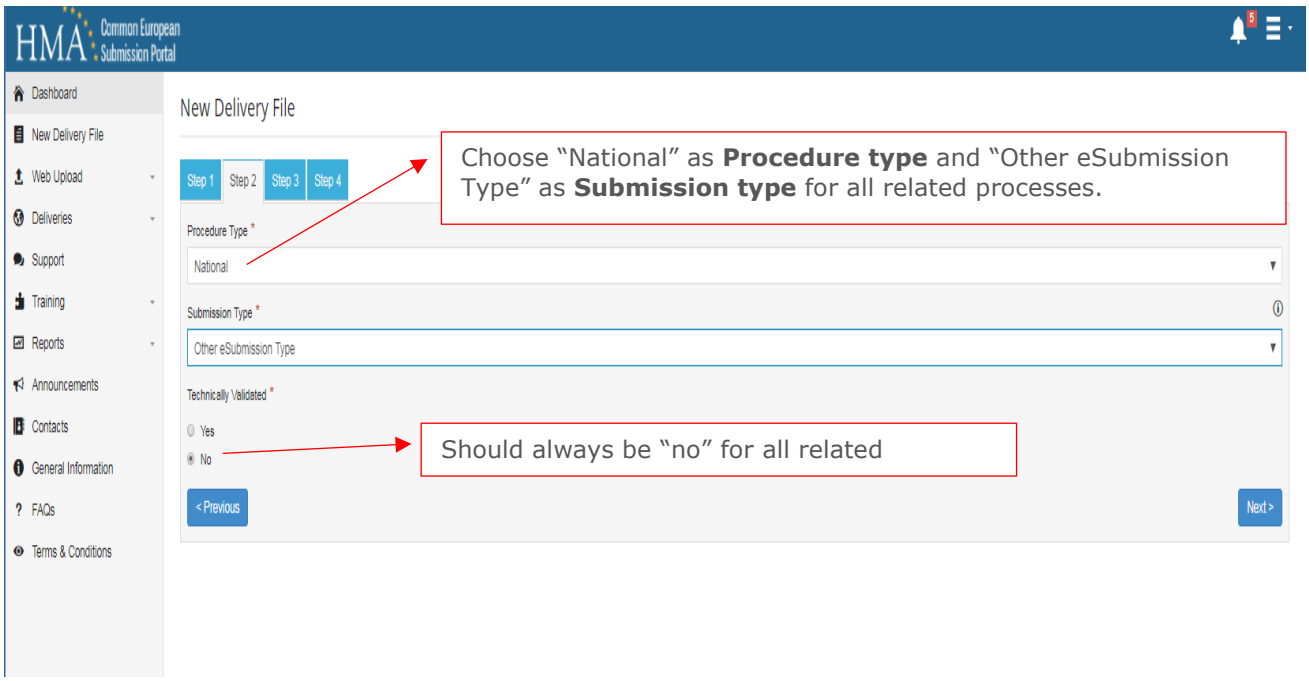
- Initial application for a CUP/MNP
- Periodic Reevaluation for a CUP/MNP
- Substantial Amendment for a CUP/MNP

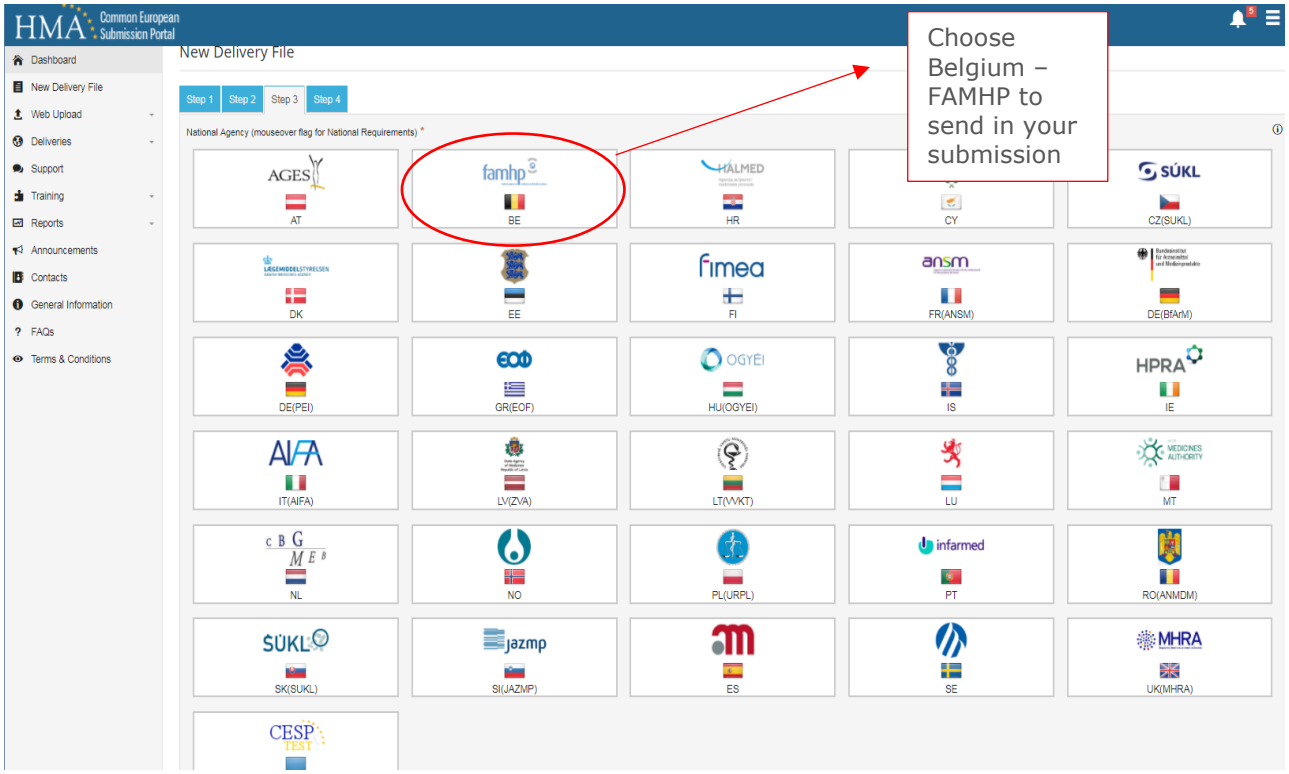
Medical device for the following related submission:

- Initial application for a clinical investigation
- Substantial amendment for a clinical investigation/performance study
- Notification of end of clinical investigation/performance study


HMA Common European Submission Portal
Dashboard
New Delivery File
Web Upload
Deliveries
Support
Training
Reports
Announcements
Contacts
General Information
FAQs
Terms & Conditions
New Delivery File
Step 1
Step 2
Step 3
Step 4
Company *
Test Company
Area *
Human Medicines
Regulatory Activity *
Clinical Trial
Sub Activity *
H001 Not Applicable
Zip File Type *
7-Zip
Comment
Next >
Select Sub-Activity following the procedure step:
Not applicable
Initial
Answers to question during validation
Answers to question during procedure
Closing Documents
Select the Zip File Type


HMA Common European Submission Portal
Dashboard
New Delivery File
Web Upload
Deliveries
Support
Training
Reports
Announcements
Contacts
General Information
FAQs
Terms & Conditions
New Delivery File
Step 1
Step 2
Step 3
Step 4
Company *
Test Company
Area *
Human Medicines
Regulatory Activity *
Clinical Trial
Sub Activity *
H001 Not Applicable
Zip File Type *
7-Zip
Comment
Next >
Write any comments on the process here.
e.g. for CTR pilot, please put "CTR pilot".


HMA Common European Submission Portal
Dashboard
New Delivery File
Web Upload
Deliveries
Support
Training
Reports
Announcements
Contacts
General Information
FAQs
Terms & Conditions
New Delivery File
Step 1
Step 2
Step 3
Step 4
Choose "National" as **Procedure type** and "Other eSubmission Type" as **Submission type** for all related processes.
Procedure Type *
National
Submission Type *
Other eSubmission Type
Technically Validated *
Yes
No
Should always be "no" for all related
< Previous
Next >


HMA Common European Submission Portal
Dashboard
New Delivery File
Web Upload
Deliveries
Support
Training
Reports
Announcements
Contacts
General Information
FAQs
Terms & Conditions
New Delivery File
Step 1
Step 2
Step 3
Step 4
National Agency (mouseover flag for National Requirements) *
Choose Belgium – FAMHP to send in your submission
AGES AT
famhp BE
HALMED HR
CY
SÚKL CZ(SUKL)
DK
EE
fimea FI
ansm FR(ANSM)
DE(BfArM)
DE(PEI)
EOF GR(EOF)
OGYÉI HU(OGYEI)
IS
HPRA IE
AIFA IT(AIFA)
LV(ZVA)
LT(VVKT)
LU
MT
CBG MEB NL
NO
PL(URPL)
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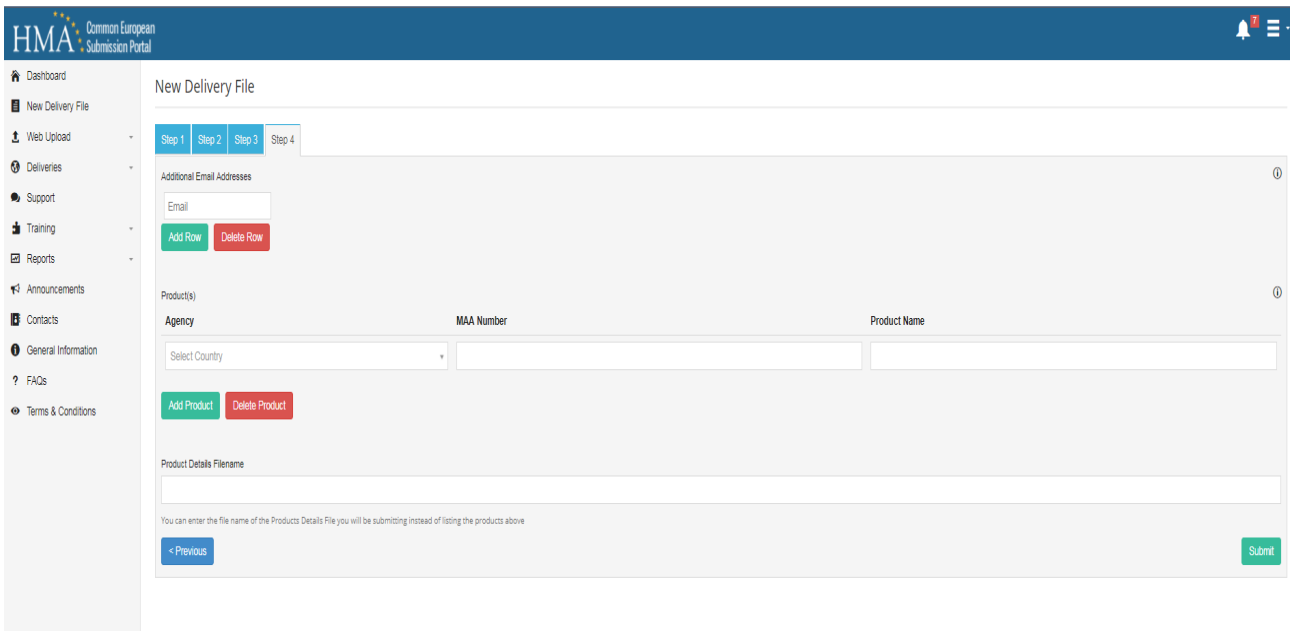
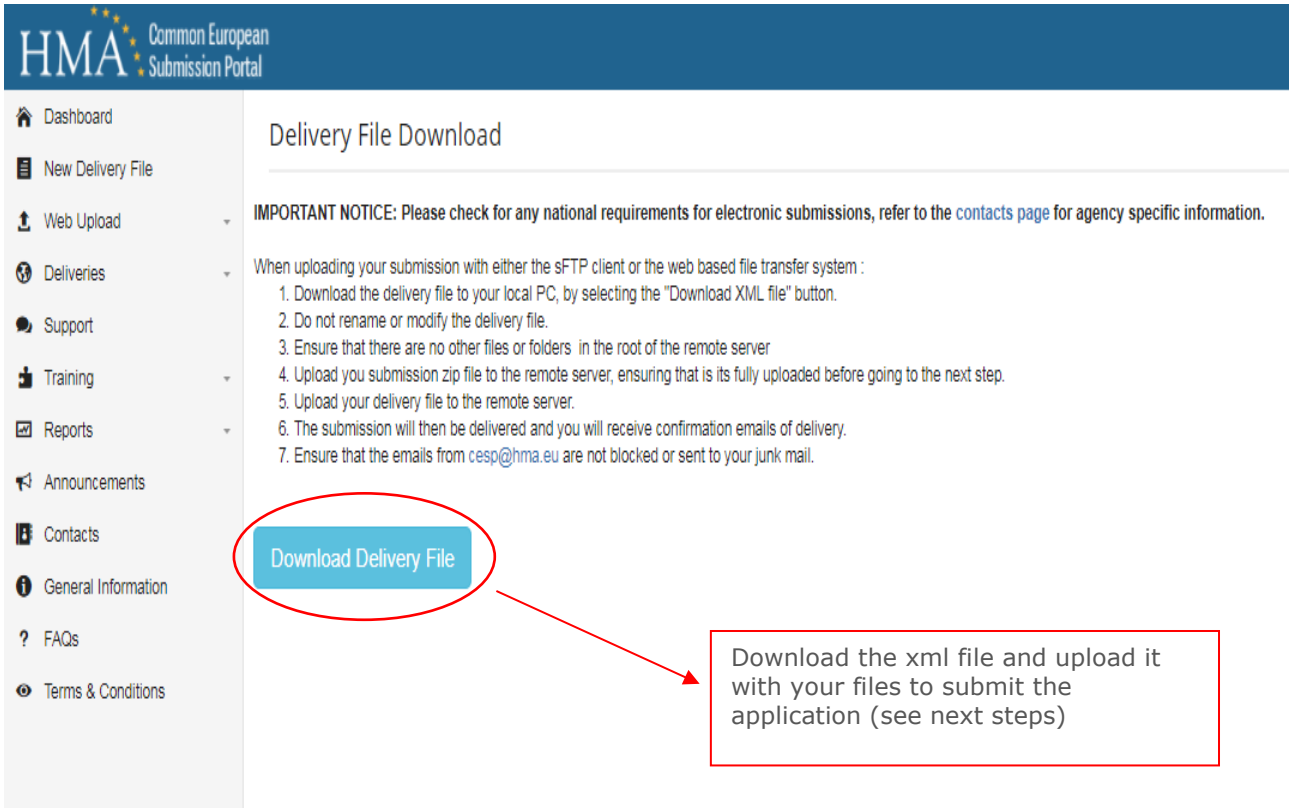
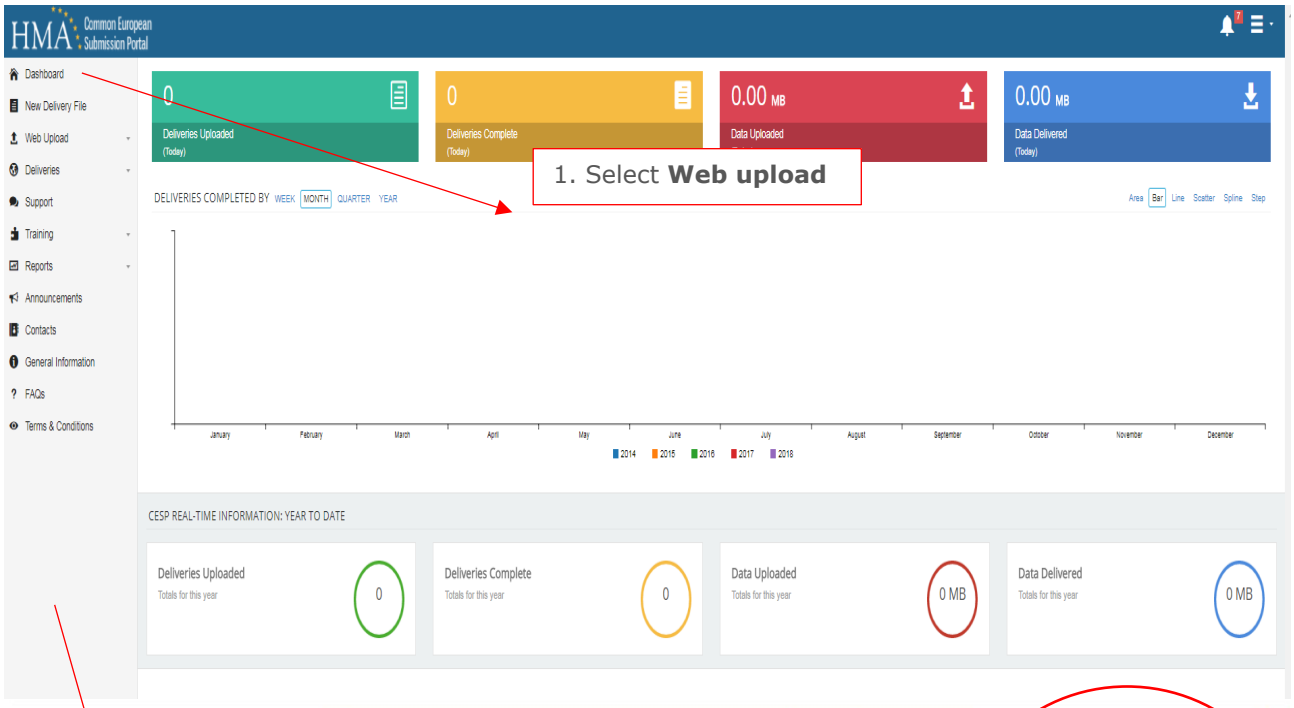
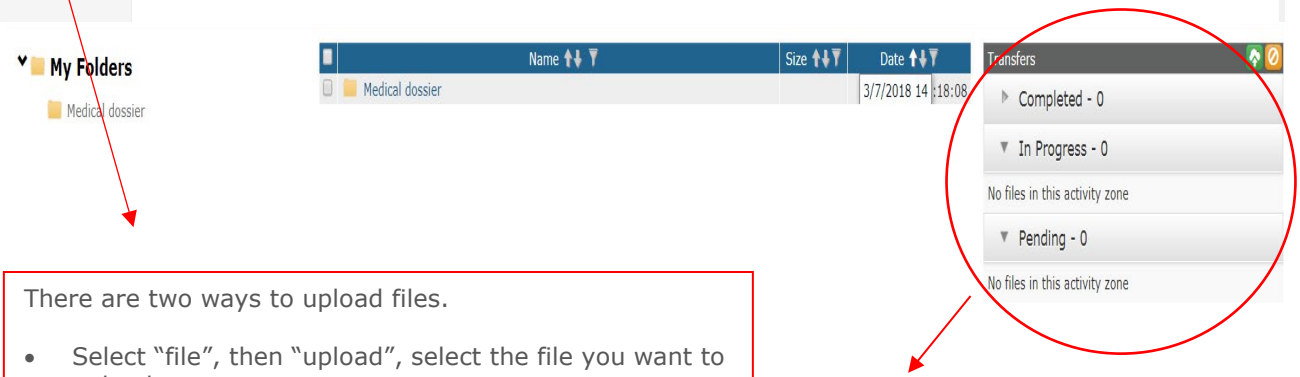
jazmp SI(JAZMP)
ES
SE
MHRA UK(MHRA)
CESP TEST


HMA Common European Submission Portal
Dashboard
New Delivery File
Web Upload
Deliveries
Support
Training
Reports
Announcements
Contacts
General Information
FAQs
Terms & Conditions
New Delivery File
Step 1
Step 2
Step 3
Step 4
Additional Email Addresses
Email
Add Row
Delete Row
Product(s)
Agency
MAA Number
Product Name
Select Country
Add Product
Delete Product
Product Details Filename
You can enter the file name of the Products Details File you will be submitting instead of listing the products above
< Previous
Submit


HMA Common European Submission Portal
Dashboard
New Delivery File
Web Upload
Deliveries
Support
Training
Reports
Announcements
Contacts
General Information
FAQs
Terms & Conditions
Delivery File Download
IMPORTANT NOTICE: Please check for any national requirements for electronic submissions, refer to the contacts page for agency specific information.
When uploading your submission with either the sFTP client or the web based file transfer system :
1. Download the delivery file to your local PC, by selecting the "Download XML file" button.
2. Do not rename or modify the delivery file.
3. Ensure that there are no other files or folders in the root of the remote server
4. Upload you submission zip file to the remote server, ensuring that is its fully uploaded before going to the next step.
5. Upload your delivery file to the remote server.
6. The submission will then be delivered and you will receive confirmation emails of delivery.
7. Ensure that the emails from cesp@hma.eu are not blocked or sent to your junk mail.
Download Delivery File
Download the xml file and upload it with your files to submit the application (see next steps)

9.2.3. Upload your files (i.e. the dossier) on CESP





There are two ways to upload files.

- Select "file", then "upload", select the file you want to upload.
- You can also select a file in windows explorer and then drag and drop it onto the webpage.

You can create several folders for each application.

Transfer details:

- Completed upload
- Upload in progress
- Pending upload

Very Important: First upload your dossier – as a zip file. When the zip file is fully uploaded, upload your previously downloaded delivery file (i.e. the xml file). Also important – do not include a zip file inside the zip file as CESP does not allow this.

You will find the uploaded files in your folder:

- **CESP_Submission_xxxxxx.xml”**: the delivery information, downloaded previously from CESP. It is different for each application. It should thus be systematically done for each application (whatsoever).
- **“name of your file.zip”**: the content of your application in zip format.

Note

- Reminder: first upload your dossier to the website in ZIP format. When it is uploaded, add the XML file.
- No further action is requested, the portal will send your dossier to the selected agency and send you an email regarding the notification. You can check it in the “deliveries” section on CESP.

9.3. Training and support

- An on demand training module is available to all CESP users. This module contains the latest video guides and training documentation.
- Support: the CESP group will provide support in respect of the portal to authorised users during normal working hours on Monday to Friday (not on public holidays). Contact details for accessing CESP Group support are available on the portal.
- A FAQ is available for your common questions regarding the system.

10. Annex IV: Important points for the preparation of the CTR pilot dossier and Q&A

10.1. Important points for the preparation of the CTR pilot dossier

- In the tables presented from page 20 to page 27 of the present document, the column "References" gives some guidance on the way to complete each file of the provided empty structure of the pilot submission dossier. This column "References" has been updated based on the most frequent questions received from the sponsors who already participated to the pilot.

- Protocol
  - Following Helsinki declaration art.34 Post trial provisions, "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial". This should be foreseen in the protocol as far in advance as possible.
  - The first act of recruitment (e.g. advertising) should be specified in the protocol as according to the clinical regulation 536/2014 it defines the official start of the trial.
  - Clinical trial termination criteria should be included in the protocol.
  - The protocol synopsis should be submitted as a separate document, in EN, NL and FR.

- Written statements from the sites on their suitability (section N. of part II, see template in the annexed empty file) are crucial documents for the completeness of the submission dossier as only 1 EC (independent of the participating sites) will evaluate the application dossier. It is thus important to contact the sites as soon as possible in order to obtain these documents in due time for the submission.

- The following templates are available in the annexed empty structure for submission.

  - Curriculum Vitae of the principal investigator (section M. of part II). It is not mandatory to use the template developed by the European Commission. Any CV containing the same information would be accepted.
  - DOI of the principal investigator developed by the European Commission.
  - Written statement of the site (section N. of part II). It is not obligatory to use the template provided as a written statement. However, this is strongly recommended as it has been discussed and agreed on among ECs who are volunteers to participate to the CTR pilot.
  - In the zipped empty structure the names of the folders have been shortened so that final folder names are not too long. Issues can be encountered at the extraction of a zip file when the full path length is too long. When sending the submission dossier via CESP, please make sure the files are comprised at the level of the folders part I & part II to avoid the presence of unnecessary levels in the dossier.
- Insurance: it is important to refer to art.29 §1 of the law of 7 May 2004 (related to the no fault insurance) in the proof of insurance document.

- The DSMB charter must be part of the submission dossier if a DSMB (Data Safety Monitoring Board) is foreseen for the trial (unless this will be part of the RFI – Request For Information).

- The statement related to the protection of the data (Folder R in part II of the dossier) must refer to the General Data Protection Regulation (GDPR), i.e. it should at least contain the wordings: "[name of sponsor] confirms that collection and processing during clinical trials is done in full compliance with the European Regulation 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection regulation)".

10.2. Questions and answers

1) What are the timelines?
Short timelines (annex I page 16 of the present guidance) will apply for all phase I trials even if multicentre in Belgium as only one independent EC will assess the dossier.
For mixed phase I/II trials the normal timeline (28 days) will apply.
For ATMP trials an additional period of 30 days will be added to the normal timeline (28 + 30 for phase II, III or IV ATMP trials and 15 + 30 for phase I ATMP trial).

2) Which folders of the zipped empty structure can be left empty?
Folders A, H and I of Part I are only to be completed if applicable. All folders of part II have to be completed, either with documentation or a statement or a reference to the protocol (e.g. a reference to the protocol can be accepted in folder K and L but a statement from the sponsor has to be provided in folder R.)

For substantial modifications, folders A & E may be left empty if not applicable.

3) Do I need to pay a fee?
No fee has to be paid for the submission of a CTA initial dossier or a SM in the CTR pilot, not to the FAMHP and not to the EC. Folder Q. has been deleted from part II in the zipped empty structure.

4) What is the role of the local ECs?
The submission dossier will be provided for information to the local ECs by the College. The sponsor only provides the submission dossier to the NCP. The College will also communicate the final decision to the local ECs for information.

5) What about safety reporting?
Safety reporting will not be handled in the pilot. This means that the safety reporting documents (i.e. DSUR, SUSAR) must not be submitted to the NCP and that the current rules for submission to the FAMHP and to the EC issuing the single opinion have still to be followed.

This means that for DSUR & SUSAR the procedure as described in CT-3 detailed guidance and circular letters 586 and 593 available on the FAMHP website (reporting according to the Directive) and following the law of 7 May 2004 has to be followed. For pilot dossiers the "EC issuing the single opinion" is to be understood as the independent evaluating EC. This means that in the CTR pilot project, the College does not inform the local ECs or the sites about safety reporting. The submission to additional partners (investigators or local ECs) remains the responsibility of the sponsor.

Exceptions regarding safety reporting:
Urgent Safety Measures (USMs, where an unexpected event is likely to seriously affect the benefit-risk balance) shall be notified to the NCP no later than seven days after implementation. USM are part of the pilot project as these safety issues and taken measures have a direct impact on the way the clinical trial is managed and on the trial documents (e.g. protocol and/or ICF).
Protocol Deviations with a direct impact on the safety of the subject also have to be notified by the Sponsor to NCP.

The CT College will then forward the latter notifications to the evaluating EC for information. The CT College does not inform the local ECs (nor the sites) about USM and protocol deviations.

6) What is awaited as recruitment procedure (section K)?
Reference is made to regulation 536/2014: page 62. K 59. Unless described in the protocol, a separate document shall describe in detail the procedures for inclusion of subjects and shall provide a clear indication of what the first act of recruitment is.

7) Who needs to provide the CV and DOI in the clinical team?
The CV and DOI are only to be provided for the principal investigator of each site.

8) Examples of substantial modifications and different categories of notifications in the context of the CTR pilot: the table below could be updated with new examples at the occasion of the next update of the present guidance.

CTR pilot: examples of SMs and of different categories of notifications
Examples of modifications that are considered SMs and have to be submitted following §5 of the present guidance
• New ICF version • New patient diary • Intervention of recruitment assistants (new recruitment procedure) • Addition of site(s) (not before three months after approval of the initial trial) • Update of the IB if substantial safety information is added/changed (included modification of the RSI)
Examples of notifications that are not SMs but have to be sent immediately to the NCP
• The updated site-specific annexes to the ICF containing the trial specific treatments, examinations, visits • Protocol deviations with a direct impact on the safety of the subject • Proof of insurance renewal, new insurance certificate • Notification of a general precaution further to the release of drug safety communication if not an USM or temporary halt (e.g. Dear Investigator Letter) • Yearly status of the study. This notification is normally done in January or at the birthday date of EC study approval
Examples of notifications that are not SMs and that should not be sent immediately to the NCP but added to the next SM
• Signed version of approved documents (e.g. protocol, finalised contracts) • Translated version of approved documents (e.g. patient diary or ICF) • Evolution report at time of moving from one cohort to another cohort in the study • Protocol clarification letter related to non-substantial changes • Typo's • Removal of one or several sites • Update of the IB with no substantial changes (e.g. validity of IB is extended)
Notification of Urgent Safety Measures (USMs - where an unexpected event is likely to seriously affect the benefit-risk balance)
• Can be implemented without waiting for authorisation but shall be notified to the NCP not later than seven days from the implementation
Notifications of end, temporary halt and early termination of a CT: to be sent directly to the NCP (start of the trial, start and end of recruitment are not required for pilot dossiers as the portal is not yet available)
• Notification of temporary halt of the trial or of recruitment only (can be the result of an USM) in the EU application form for SM, completed with date of halt of the CT and reason why/restart only after submission of an SM • Declaration of the end of trial form
Notification of the summary of the results [Clinical Study Report (CSR) or synopsis of the CSR or Plain language summary]
• Should be submitted within one year from the end of a clinical trial in all member states concerned

9) **Regarding the implementation of the GDPR, which supplementary information needs to be provided to participants?**
More information on the informed consent procedure in trials ongoing at or completed before the 25th May 2018 can be found in the publication on the website of the CT-College.

11. Annex V: Proposed template for the Word document to be annexed to the cover letter

11.1 Initial trials

Document	Version and/or Date
PART I	
A. INTRODUCTION **…** **…**	
B. COVER LETTER Example: Pilot222_2019-111111-22_Cover-Letter_20190910.pdf Example: Pilot222_2019-111111-22_Table-of-Content_20190925.docx	 10.09.2019 25/09/2019
C. EU APPLICATION FORM Example: Pilot222_2019-111111-22_Application-Form_20190910.pdf	 10.09.2019
D. PROTOCOL Example: Pilot222_2019-111111-22_Protocol_v1.1.pdf Example: Pilot222_2019-111111-22_Protocol_v1.2.pdf **…**	 v1.1 v1.2.
E. INVESTIGATOR'S BROCHURE Example: Pilot222_2019-111111-22_IB_v1.2_20190901.pdf Example: Pilot222_2019-111111-22_IB_v1.3_20190930.pdf **…**	 V1.2/01.09.2019 V1.3./30.09.2019
I. SCIENTIFIC ADVICE AND PIP **…** **…**	
J. LABELLING OF THE IMP **…** **…**	
PART II	
K. RECRUITMENT ARRANGEMENTS **…** **…**	
L. SUBJECT INFO, ICF AND ICF PROCEDURE Example: Pilot222_2019-111111-22_Patient Card-NL.pdf **…**	 V1.0
M. SUITABILITY OF THE INVESTIGATOR Example: Pilot222_2019-111111-22_CV-Janssens_20160223.pdf Example: Pilot222_2019-111111-22_CV-Janssens_20190920.pdf	 23.02.2016 20.09.2019
N. SUITABILITY OF THE FACILITIES **…** **…**	
O. PROOF OF INSURANCE **…** **…**	
P. FINANCIAL AND OTHER ARRANGEMENTS **…** **…**	
R. STATEMENT DATA PROTECTION **…** **…**	

11.2 Substantial modifications

Document	Version and/or Date
A. INTRODUCTION **…** **…**	
B. COVER LETTER Example: Pilot222_2019-111111-22_SM1_Cover-Letter_20190910.pdf Example: Pilot222_2019-111111-22_SM1_Table-of-Content_20190925.docx	 10.09.2019 25.09.2019
C. MODIFICATION APPLICATION FORM Example: Pilot222_2019-111111-22_SM1_Modification_Application-Form_20190910.pdf	 10.09.2019
D. DESCRIPTION OF THE MODIFICATION **…**	
E. SUPPORTING INFORMATION Example: Pilot222_2019-111111-22_Protocol_v2.1.pdf Example: Pilot222_2019-111111-22_Protocol_v2.2.pdf Example: Pilot222_2019-111111-22_IB_v2.2_20190901.pdf Ex:Pilot222_2019-111111-22_IB_v2.3_20190930.pdf **…**	 V2.1 V2.2. V2.2/01.09.2019 V2.3./30.09.2019
F. UPDATE OF EU APPLICATION FORM **…** **…**	