

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

Research and Development Division (human use)

Tel.: 02 528 40 00

Fax: 02 528 40 01

e-mail: CTRpilot@fagg-afmps.be

Guidance for participating parties

Your letter from	Your reference	Our reference FAMHP/R&D	Annex	Date 25.02.2019
-------------------------	-----------------------	-----------------------------------	--------------	---------------------------

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 CTR.

Version 6.0

Dear Madam,

Dear Sir

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 Clinical Trial Regulation 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 E-mail to the specific E-mail address for the pilot: CTRpilot@afmps-fagg.be.

Document Revision History

Date of publication	Revision description
10.01.2017, V1.0	N/A
08.05.2017, V2.0	<p>First page new specific e-mail address for the pilot.</p> <p>§ 8.1.2.: annex II: zip file available with empty structure of pilot dossier.</p> <p>§ 8.: tables in annex II : some clarifications in the "references" column.</p>
06.10.2017, V3.0	<p>§ 4.2.1.: important points for the constitution of the CTR pilot dossier</p> <p>§ 4.2.4: clarification on evaluation of Inform Consent Forms by the EC.</p> <p>§ 4.2.5. and § 5.5.: clarification on approval.</p> <p>§ 8.: tables in annex II : some clarifications in the "references" column.</p>
15.05.2018, V4.0	<p>§ 2.1.: clarification of the scope</p> <p>§ 4.2.1.: possibility of submission via CESP.</p> <p>§ 4.2.2. and § 5.2.: no fee for pilot CTA & substantial modifications (SM).</p> <p>§ 4.2.3. and § 5.3.: clarification on timelines.</p> <p>§ 4.2.5. and § 5.5.: clarification on conditional approval.</p> <p>§ 5.4.: clarification on SM assessment phase by the EC.</p> <p>§ 7.1. and § 7.2.: timelines ATMP dossiers.</p> <p>§ 8. tables in annex II : some clarifications in the "references" column.</p> <p>§ 9.: annex III: guidance for CESP submission.</p> <p>§ 10.: annex IV: Important points for the submission of the dossier and Q&A</p>
08.06.2018, V4.1	<p>§ 8. : annex II, table on initial dossier Part II, point R: clarification GDPR.</p>
16.11.2018, V5.0	<p>§ 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.</p> <p>§ 4.1.: new version of the intention letter available on www.afmps-fagg.be.</p> <p>§ 4.2.1.: addition of sentence on the role of the site in de submission process</p> <p>§ 4.2.1.: submission via CESP only since 01/10/2018.</p> <p>§ 4.2.1.: OCR list of documents in the cover letter.</p> <p>§ 4.2.3.: clarification of timelines for phases I and mixed phases I/II</p> <p>§ 5.1.: addition of site not possible before 3 months after the approval of the initial trial.</p> <p>§ 7.1., § 7.2., § 7.3. and § 7.4.: clarification on timelines for CTAs/SMs with ATMP.</p> <p>§ 8.: annex II, table on content of part I: reference to annex IV for preparation of dossiers.</p> <p>§ 10.1.: two clarifications related to the protocol (synopsis separated & termination criteria should be included in the protocol).</p> <p>§ 10.1.: protection of the data statement following GDPR.</p> <p>§ 10.2. 2): Substantial modifications: some folders may be left empty.</p>

25.02.2019, V6.0	<p>§ 2.1. and 2.5.: introduction of the VHP plus process in the BE CTR pilot.</p> <p>§ 2.4.: clarification on non-substantial modifications and reference to examples in the table in §10. Annex IV.</p> <p>§ 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.</p> <p>§ 4.2.1.: list of submitted documents to be also submitted at the moment of the answers to the RFI if versions updated.</p> <p>Clarification on what is provided by the College to the local sites.</p> <p>§ 4.2.4.: clarification on ICF languages and translations.</p> <p>§ 5.1.: new evaluating EC if an added site is the site of the evaluating EC for the initial trial.</p> <p>Request for list of documents and versions that can be copied.</p> <p>§ 5.4.: clarification on ICF languages and translations.</p> <p>§ 8.2.2.: complete filenames not longer than 100 characters (folder names included).</p> <p>§ 10.1.: deletion of a link that is not related to the data protection statement.</p> <p>§ 10.2.: addition of question 8) table with examples of SMs and notifications & question 9) related to GDPR implementation.</p>
------------------	---

Contents

Document Revision History	2
1. Definitions, conventions and abbreviations	5
2. Scope and objectives of the pilot.....	6
2.1. Scope	6
2.2. Objectives	6
2.3. Voluntary basis	6
2.4. Substantial modifications	6
2.5. Out of scope.....	7
3. Legal basis	7
4. Procedure for sponsor – initial trials	8
4.1. What if a sponsor wants to propose a dossier for the CTR pilot ? Letter of intent for sponsors.	8
4.2. Practical procedure	9
4.2.1. Submission of the CTA	9
4.2.2. Payment of the fee for an initial dossier	9
4.2.3. Validation phase	10
4.2.4. Assessment phase	10
4.2.5. Approval	11
5. Procedure for sponsors - Substantial Modifications	12
5.1. Submission of a substantial modification regarding a clinical trial approved in the CTR pilot	12
5.2. Payment of the fee for a substantial modification.....	12
5.3. Validation phase	12
5.4. Assessment phase.....	13
5.5. Approval	14
6. Survey	14
7. Annex I – Timetables for the CTR pilot process	15
7.1. National initial dossier (other than phase I mono-national trial)	15
7.2. National initial phase I mono-national dossier	16
7.3. National Substantial Modification (other than phase I mono-national trial)	17
7.4. National substantial modification for a phase I mono-national trial.....	18
8. Annex II – Dossier structure as per regulation 536	19
8.1. Initial application.....	19
8.1.1. Initial application.....	19
8.1.2. Consider to apply the following folder structure – an empty folder structure can be provided..	19
8.1.3. Consider to apply the following folder structure – an empty folder structure can be provided..	20
8.1.4. Filenames.....	20
8.2. Substantial modifications	25



8.2.1	File format	25
8.2.2	Filenames.....	26
9.	Annex III - E-submission through the Common European Portal (CESP)	28
9.1	For which application CESP must be used ?	29
9.2.	How to submit an application through CESP?	30
9.2.1.	Account and connection	30
9.2.2.	E-submission	31
9.2.3.	Upload your files (i.e. the dossier) on CESP	36
9.3.	Training and support	38
10.	Annex IV: Important points for the preparation of the CTR pilot dossier and Q&A	39
10.1.	Important points for the preparation of the CTR pilot dossier	39
10.2.	Questions and answers	40

1. Definitions, conventions and abbreviations

ATMP: Advanced Therapy Medicinal Products

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. Website: <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.

From a practical point of view, for the sponsor the national contact point will be the following mailbox: CTRpilot@afmps-fagg.be

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**.

2. Scope and objectives of the pilot

2.1. Scope

Following the 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 consolidated as the single decision will have to be reached in a short timeline. Close collaboration between (i) FAMHP and the College and (ii) between the College and the ECs will thus become crucial. This 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 for Part I and Part II and involves a limited number of volunteer ethics committees. A VHP plus specific addendum of the present guidance is now 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.

The participation 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 also have to be submitted following the CTR pilot procedure.

In the spirit of the CTR and as far as 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 could 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 must not be submitted to the national contact point (NCP) and that the current rules for submission to the FAMHP, to especially the EC in charge of the evaluation and to the local Ethics Committee(s) have still to be followed. However, after evaluation and consensus, this position might be reviewed.

3. Legal basis

The new law of 7th May 2017 on CTR has been 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 not valid anymore. The other articles of the law of 7th May 2004 remain applicable, as is the authorisation of the CTA and substantial modifications. Essentially, the pilot follows as expected the law of 7th May 2004, but 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 Decree's 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 be automatically rejected if the sponsor cannot answer the questions within the CTR deadlines (12 days). As much as possible, this timeline, as foreseen in the CTR, should be respected but exceeding the time of maximum 20% will be accepted in practice.

This pilot is limited in time. It will not continue after the CTR regulation has come into place.

4. Procedure for sponsor – initial trials

4.1. What if a sponsor wants to propose a dossier for the CTR pilot ? Letter of intent for sponsors.

The letter of intent available on the FAMHP website as the “form” should be submitted by E-mail to the national contact point (CTRpilot@fagg-afmps.be) with the following E-mail title : CTR pilot – Letter of intent to participate to the CTR 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 for the dossier
- name and site of the co-ordinating 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.

The final list of sites should be provided as soon as possible and at the latest 2 weeks before submission of the dossier as the assigned evaluating EC must be independent from the sites.

Please use the official name of the institution:

The official name may be found by following this link:

<https://www.health.belgium.be/nl/gezondheid/organisatie-van-de-gezondheidszorg/delen-van-gezondheidsgegevens/gezondheidszorginstellingen>

or <https://www.health.belgium.be/fr/sante/organisation-des-soins-de-sante/partage-de-donnees-de-sante/institutions-de-soins>

A new version of the letter of intent (“form”) is available on the FAMHP website taking into account the latest clarifications and the introduction of the VHP plus option.

From 1st March 2019, all proposed national dossiers will in principle directly be accepted in the CTR pilot project. Yet it is still asked to the sponsors to send the letter of intent so that the evaluating EC can be selected timely by the College.

For candidate dossiers in the VHP plus process, the national contact point and the College will decide on a case by case basis whether a CTA can be processed in this new work process flow.

In case the dossier is accepted within the pilot an acceptance E-mail containing a CTR pilot number will be sent to the sponsor by the national contact point.

After this, any communication between sponsor and the national contact point must at least contain the following title: CTR Pilot XXX – CTA 20XX-XXXXXX-XX

4.2. Practical procedure

4.2.1. Submission of the CTA

The national contact point (CTRpilot@afmps-fagg.be) and the sponsor will stay in close contact in order to refine the submission date if necessary.

For a submission of a CTA dossier following the CTR pilot process, the “Guidance for submission of clinical trial applications, substantial amendment notifications and end of trial declarations to the R&D division”, also published on 15th May 2018, will not be applicable. The present guidance provides the details of the requirements for submission of the dossiers for the CTR pilot procedure.

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 national contact point.

For the sake of a swift processing of the dossier it is asked to the sponsor to submit the CTA package by CESP¹ as CESP has been selected as unique way of submission to harmonize the way the different type of dossiers are submitted in the R&D division of the FAMHP.

At the time of the submission the cover letter must point out that participation in the pilot has been confirmed and must contain the pilot number. The cover letter must be provided hand signed and scanned in the CESP submission. **Sponsors are kindly requested to provide a list of documents (supporting the submission), in a format (with optical character recognition, OCR) from which the content can be copied.** Sponsors are also kindly requested to provide an updated list of documents (and versions) with the answers to the Request For Information (RFI) in case some documents have been updated (e.g. protocol, ICF, ...).

All communications (additional information, responses to questions, ...) from the sponsor during the procedure are to be sent by E-mail and/or CESP to the national contact point (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 (see also section **Error! Reference source not found.**).

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. Payment of the fee for an initial dossier

No fee is currently due for the submission of a CTA initial dossier in the CTR pilot (nor to the FAMHP, nor to the evaluating Ethics Committee).

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

4.2.3. Validation phase

The validation of the dossier (Part I & Part II) is performed by the national contact point.

Timelines of the CTR apply for the validation phase, while timelines of the law of 7 May 2004 (28 days or 15 days) apply once the TO is given for the start of the procedure. However as far as possible, timelines for validation will be kept short.

Short timelines (15 days) apply for all phase I trials, even if multicenter 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 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 notice of validation (beginning of assessment) from the national contact point. An operational calendar with a clear overview of the different timelines will be part of this notification to the sponsor.

If the validation shows that deficiencies are present or that 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 national contact point evaluates the supplemented documentation within 5 days after receipt of the comments or the amended application dossier. If the national contact point comes to the conclusion that the documentation regarding Part I and/or Part 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 the exception of the quality documentation.

4.2.4. Assessment phase

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

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 national contact point.

Contents covered by the Part II of the CTA pursuant to the CTR are assessed in parallel by the Ethics Committee. Questions and/or requests for additional information regarding these aspects are sent to the sponsor by the national contact point 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 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 12 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 national contact point.

In case a question of the deficiency letter should be unclear it is recommended to contact the national contact point by E-mail.

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 national contact point.

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 Ethics Committee, 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 "Authorized subject to conditions", the clinical trial can be started after fulfilment of the conditions by the sponsor. The approval letter is sent at the time of the conditional approval. When all conditions are met, an E-mail 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.

5. Procedure for sponsors - Substantial Modifications

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

Substantial modifications (SM) 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 3 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.

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.

Sponsors are kindly requested to provide a list of documents (supporting the submission), in a format (with optical character recognition, OCR) from which the content can be copied. Sponsors are also kindly requested to provide an updated list of documents (and versions) with the answers to the Request For Information (RFI) in case some documents have been updated (e.g. protocol, ICF, ...).

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 (nor to the FAMHP, nor to the evaluating Ethics Committee).

5.3. Validation phase

The validation of the substantial modification is performed by the national contact point.

Timelines of the CTR apply for the validation phase, while timelines of the law of 7 May 2004 (28 days or 15 days) apply once the TO is given for the start of the procedure. However as far as possible, timelines for validation will be kept short.

Short timelines (15 days) apply for all phase I trials, even if 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 national contact point. An operational calendar with a clear overview of the different timelines will be part of this notification to the sponsor.

If the validation shows that deficiencies are present or that relevant documentation is missing, leading to the SM 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 national contact point evaluates the supplemented documentation within 5 days after receipt of 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 Ethics Committee 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 national contact point.

SM contents covered by the Part II of the CTA pursuant to the CTR are assessed in parallel by the Ethics Committee. Questions and/or requests for additional information regarding these aspects are sent to the sponsor by the national contact point 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 12 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 national contact point.

In case a question of the deficiency letter should be unclear it is recommended to contact the national contact point by E-mail.

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 national contact point.

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 national contact point.

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

If the SM is "Authorized 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. When all conditions are met an E-mail 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.

6. Survey

The national contact point 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
Confirmation of receipt to Sponsor/beginning of validation	Date submission= T0 - 10
Notification of the validation status to the sponsor: <ul style="list-style-type: none"> - 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 national contact point 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 : <ul style="list-style-type: none"> ⇒ Direct approval at T28 at the latest if no questions from FAMHP or EC ⇒ List(s) of questions provided by the national contact point 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 FAMHP and/or Ethics Committee 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
Confirmation of receipt to Sponsor (dossier + payment)/beginning of validation	Date submission = T0 - 5
Notification of the validation status to the sponsor: <ul style="list-style-type: none"> - 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 national contact point 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 : <ul style="list-style-type: none"> ⇒ Direct approval at T15 at the latest if no questions from FAMHP or EC ⇒ List(s) of questions provided by the national contact point 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 FAMHP and/or Ethics Committee 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
Confirmation of receipt to Sponsor (dossier + payment)/beginning of validation	Date submission = T0 - 6
Notification of the validation status to the sponsor: <ul style="list-style-type: none"> - 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 national contact point 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) : <ul style="list-style-type: none"> ⇒ Direct approval at T28 at the latest if no questions from FAMHP or EC ⇒ List(s) of questions provided by the national contact point 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 FAMHP and/or Ethics Committee 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
Confirmation of receipt to Sponsor (dossier + payment)/beginning of validation	Submission date = T0 - 5
Notification of the validation status to the sponsor: <ul style="list-style-type: none"> - 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 national contact point 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) : <ul style="list-style-type: none"> ⇒ Direct approval at T15 at the latest if no questions from FAMHP or EC ⇒ List(s) of questions provided by the national contact point 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 Ethics Committee 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



Name ^	Date modified	Type
part I	14/12/2016 15:19	File folder
part II	14/12/2016 15:19	File folder

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, authorizations 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 Filenames

Please consider to use **descriptive filenames**. To name the different files 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.pdf

Pilot 999_2010-090094-00_Cover-Letter.pdf

Special cases:

1) To name the scanned pages of the 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 (investigational medicinal product or authorized 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 the **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 The cover letter preferably contains a list of submitted documents in a format with optical character recognition (OCR).
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 D 24.	See also ICH E6 GCP The protocol shall be accompanied by a synopsis of the protocol, provided as a separate document. 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 • ...	<ul style="list-style-type: none"> • 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 SmPC 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 the 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 strongly recommended. New version of the template ICF for interventional trials in adults foreseen Q4 2018. 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: diplomas have to be listed. GCP training should be documented (in the CV or by a GCP certificate) Proposed template (not mandatory): TransCelerate template (available in the structure zip file on the FAMHP website)

			<p>Declaration of interest: The FAMHP recommends to use the following FDA form: Please copy the following URL in your browser : https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048310.pdf</p> <p>An explanation is available on the e-CFR website (www.ecfr.fgov): Title 1 => Chapter 1 => Part 54 (financial disclosure by clinical investigators).</p>
N. Statement on the suitability of the sites	Suitability-statement-namesite.pdf	N	<p>Most recent version of the written statement issued by the site.</p> <p>Template available in the structure zip file in on the FAMHP website.</p> <p>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 .</p>
O. Proof of insurance cover or indemnification	Proof of Insurance Cover.pdf	O	<p>Certificate with specification of the amount insured and reference to the Belgian law of 7 May 2004, art. 29 §1 (No fault insurance).</p>
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	<p>Draft version of the contract with (draft) amounts is currently accepted.</p> <p>It is advised to contact as soon as possible the CTCs of the concerned sites in order to gain time in the evaluation of the financial agreements.</p>
P. Description of any other agreement	Agreement-namesite.pdf	P 71	Clinical trial agreements and others with relation 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.

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 the trial(s) in the pilot and the 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 national contact point 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 the 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, authorizations 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 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 , published on:

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf, the sponsor should fully comply with the Q&A during the IB updates that follow this publication.

8.2.2 Filenames

Please consider to use **descriptive filenames**. To name the different files 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 100 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 authorized 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 The cover letter preferably contains a list of submitted documents in a format with optical character recognition (OCR).
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	See ICH E6 GCP/EudraLex volume 10 Track changes version(s) must be provided! A summary of changes must be provided! Use of the existing template strongly recommended – possible update in 2017 To be submitted in all languages that will be used in Belgium.
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	Revised version of the EU Application Form (with changes 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 the Regulation 536/2014 is available

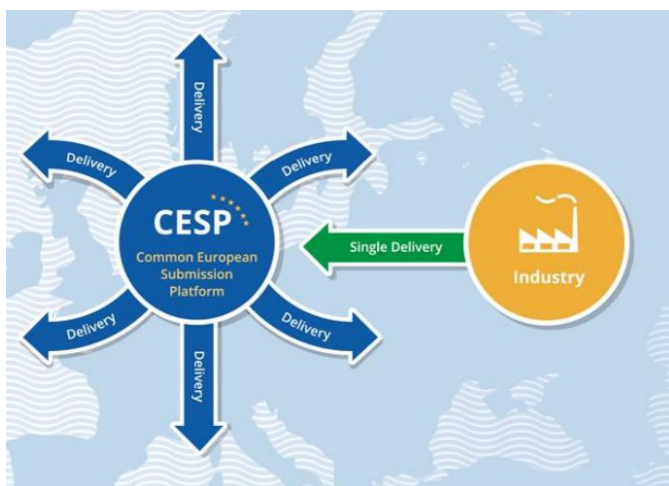
9. Annex III - E-submission through the Common European Portal (CESP)

The Common European Submission Portal 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
- Tracking system
- Automatic notification by the application
- Simple, fast, efficient delivery system for information.
- Allows easier, faster submission updates / responses to agency information requests
- Provide a secure method of communicating with the Regulatory Agencies via one platform
- Reduce the burden for both Industry and Regulators of submitting/handling applications on CD-ROM and DVD



9.1 For which application CESP must 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 ethics committee

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

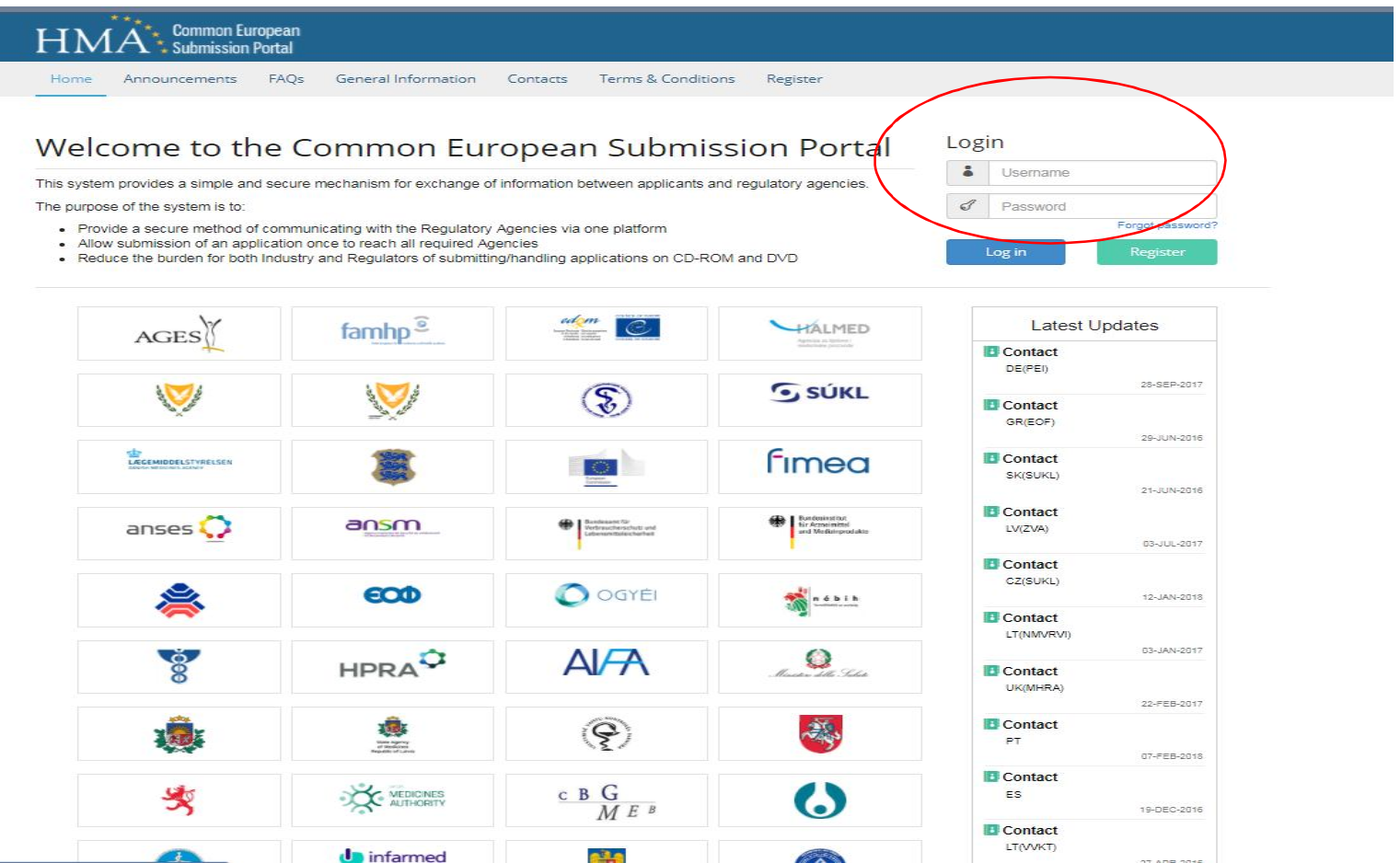


9.2. How to submit an application through CESP?

9.2.1. Account and connection

Link to the website : <https://cesportal.hma.eu/Account/Login>

If you don't already get an account, select "register" or follow this link <https://cesportal.hma.eu/delivery/create>



HMA Common European Submission Portal

Home Announcements FAQs General Information Contacts Terms & Conditions Register

Welcome to the Common European Submission Portal

This system provides a simple and secure mechanism for exchange of information between applicants and regulatory agencies.

The purpose of the system is to:

- Provide a secure method of communicating with the Regulatory Agencies via one platform
- Allow submission of an application once to reach all required Agencies
- Reduce the burden for both Industry and Regulators of submitting/handling applications on CD-ROM and DVD

Login

Username

Password [Forgot password?](#)

Log in Register

Latest Updates

Contact DE(FEI)	28-SEP-2017
Contact GR(Eof)	29-JUN-2016
Contact SK(SUKL)	21-JUN-2016
Contact LV(ZVA)	03-JUL-2017
Contact CZ(SUKL)	12-JAN-2018
Contact LT(NMVRVI)	03-JAN-2017
Contact UK(MHRA)	22-FEB-2017
Contact PT	07-FEB-2018
Contact ES	19-DEC-2016
Contact LT(VVKT)	07-SEP-2016

9.2.2. E-submission

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

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 *
Authorisation for temporary use

Sub Activity *
H001 Not Applicable

Zip File Type *
7-Zip

Comment

Next >

1. Select New Delivery File
2. Select Human Medicines or Medical Devices following the object of your submission

- 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 *

-- Select --

Sub Activity *

H001 Not Applicable

Zip File Type *

7-Zip

Comment

Next >

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 :

- ASR/DSUR submission

Authorization 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 >

Indicate here any comment on the process.
e.g. for CTR Pilot: please indicate 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

Procedure Type *

National

Submission Type *

Other eSubmission Type

Technically Validated *

Yes

No

< Previous

Next >

Choose 'National' as **Procedure type** and 'Other eSubmission Type' as **Submission type** for all related processes.

Should always be 'no' for all related processes.

HMA Common European Submission Portal




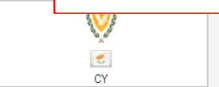



















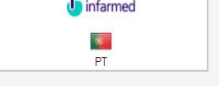







Dashboard

- 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) *

 AT	 BE	 HR	 CY	 CZ(SUKL)
 DK	 EE	 FI	 FR(ANSM)	 DE(BfArM)
 DE(PEI)	 GR(EOF)	 HU(OGYEI)	 IS	 IE
 IT(AIFA)	 LV(ZVA)	 LT(VKT)	 LU	 MT
 NL	 NO	 PL(URPL)	 PT	 RO(ANMOM)
 SK(SUKL)	 SI(JAZMP)	 ES	 SE	 UK(MHRA)
 CEP				

Choose Belgium – famhp to send your submission



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 your submission zip file to the remote server, ensuring that it is 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

You must download the xml file and upload this with your files to submit the application (see next steps).



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

1. Select **Web upload**

Common European Submission Portal

Dashboard

New Delivery File

Web Upload

Deliveries

Support

Training

Reports

Announcements

Contacts

General Information

FAQs

Terms & Conditions

0 Deliveries Uploaded (Today)

0 Deliveries Complete (Today)

0.00 MB Data Uploaded (Today)

0.00 MB Data Delivered (Today)

DELIVERIES COMPLETED BY WEEK MONTH QUARTER YEAR

Area Bar Line Scatter Spline Step

January February March April May June July August September October November December

2014 2015 2016 2017 2018

CESP REAL-TIME INFORMATION: YEAR TO DATE

Deliveries Uploaded
Totals for this year
0

Deliveries Complete
Totals for this year
0

Data Uploaded
Totals for this year
0 MB

Data Delivered
Totals for this year
0 MB



Two ways to upload files :

- Select "file" and "upload", select your file that you want to upload.
- You can also directly select your file from your windows explorer, and slip it up to the webpage.

You can create several folders for each application

The details over the transfers :

- Completed upload
- Upload in progress
- Pending upload

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

File View Account

My Folders / TEST2

Name	Size	Date	Transfers
My Folders			
TEST2			
CESP_Submission_664289.xml	1.75 KB	3/8/2018 10:47:19	Completed - 2
CESP.zip	2.65 MB	3/8/2018 10:47:20	In Progress - 0
			No files in this activity zone
			Pending - 0
			No files in this activity zone

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 applications. It has thus to be systematically done for each application (whatever it is).
- **“name of your file.zip”** : the content of your application in zip format.

NB :

- Reminder: first upload your dossier in ZIP format on the website. When fully uploaded, then add the XML file.
- No further action is requested, the portal will send it to the selected agency and send you an e-mail 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 contains the Latest Video Guides and Training documentation.
- Support : the CESP Group shall provide support in respect of the Portal to authorised users during normal working hours on Monday to Friday (other than public holidays). Contact details for accessing CESP Group support are available on the Portal.
- FAQ is available for your common questions regarding the system : <https://cespportal.hma.eu/Public/FAQs>



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 in the present version of the guidance for sponsors, 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”. As far as 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.
 - ⇒ Clinical trial termination criteria should be included in the protocol.
 - ⇒ The protocol synopsis should be submitted as a separate document.
- 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 TransCelerate CV template. Any CV containing the same information would be accepted.
 - => Written statement of the site (section N. of Part II). It is not obligatory to use the template provided as written statement. However, this is strongly recommended as it has been discussed and agreed among ECs that 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).

10.2. Questions and answers

1) Timelines ?

Short timelines (annex I page 16 of the present guidance) will apply for all phase I trials even if multicentric 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) Fee ?

No fee has to be paid for the submission of a CTA initial dossier or a substantial modification in the CTR pilot, neither to the FAMHP nor to the EC. Folder Q. has been deleted from Part II in the zipped empty structure.

4) 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 national contact point. The College will also communicate the final decision to the local ECs for information.

5) Safety reporting?

It is not performed via the national contact point but directly to each concerned as usual and following the rules of the CT3 (Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use) and circular letters 586 and 593 available on the FAMHP website.

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) From whom is the CV and DOI to be provided 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 below table could be updated with new examples at the occasion of the next update of the present guidance.

CTR pilot : examples of substantial modifications and of different categories of notifications
Examples of modifications that are considered substantial modifications 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 3 months after approval of the initial trial)
Examples of notifications that are not substantial modifications but have to be sent immediately to the NCP
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 substantial modifications and that should not be sent immediately to the NCP but added to the next substantial modification
Signed version of approved documents (e.g. protocol, finalised contracts) Translated version of approved documents (e.g. patient diary, 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
Notification of Urgent Safety Measures (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 7 days from the implementation
Chapt. 6 of CTR: notifications of start, end, temporary halt and early termination of a CT: to be sent directly to the NCP
Declaration of the start of a trial
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]
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 (www.ct-college.be).