

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

## Guidance document for clinical trials sponsors

**Voluntary Joint pilot project 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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## Document revision history

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19.12.2019, V8.0	<ul style="list-style-type: none"> <li>• § 4.1.: letter of intent no longer requested, except for VHP plus pilot project dossiers</li> <li>• § 4.2.1: WORD document with list of submitted documents</li> <li>• § 4.2.1: name of the evaluating EC</li> <li>• § 4.2.1: protocol synopsis now requested in FR, NL and EN</li> <li>• § 4.2.5: timelines in case of conditional approval</li> <li>• § 4.2.5: clarification in case of refusal</li> <li>• § 5.1: WORD document with list of submitted documents</li> <li>• § 5.5: timelines in case of conditional approval</li> <li>• § 5.5: clarification in case of refusal</li> <li>• § 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</li> <li>• § 11: annex V: new annex with proposed templates for the WORD document with list of submitted documents</li> </ul>
17.12.2020, V9.0	<ul style="list-style-type: none"> <li>• § 4.1.: pilot project number is provided in the COR e-mail which is sent after submission of each initial or SM dossier. If no COR e-mail yet received one week after submission via CESP, please contact the NCP</li> <li>• § 4.2.1.: points to pay a particular attention to when filing the dossier: written statement, zipped submission dossier, additional clarifications on GLP OECD declaration, DSMB charter if applicable, CV of the principal investigators, languages requested for protocol synopsis and patient documents (see also § 8. Part I and Part II content table)</li> <li>• § 4.2.1.: electronic signature is accepted</li> <li>• § 4.2.4.: clarification on the language(s) of the ICF in the submission dossier (see also § 8. Part I &amp; Part II content table).</li> <li>• § 4.2.5.: clarifications on process in case of re-submission</li> <li>• § 10.2: Q&amp;A: 8) new examples of notifications to be kept until the next SM</li> <li>• § 8.1.4.: files and document names: as pilot project number is unknown at the moment of submission of an initial dossier it can be replaced by pilot project XXX§ 8: Part II table in annex II: new template available: recruitment and ICF procedure template available in the zipped empty structure of the initial dossier on the FAMHP website</li> </ul>
08.02.2021, V9.1	<ul style="list-style-type: none"> <li>• General : harmonisation of the pilot number in denomination of files and documents for initials and SMs</li> <li>• § 3.: clarification on the end of the CTR pilot project</li> <li>• § 4.1.: new time slots system for submission of initial trials</li> <li>• § 4.2.1.: CV of the PI: most important trials experience <b>relevant for the submitted CTA</b> should be provided</li> </ul>

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|  | <ul style="list-style-type: none"><li>• § 10.2: Q&amp;A: 8) Clarification on change of coordinating investigator</li><li>• § 8: Part I &amp; Part II tables in annex II: request on RSI in cover letter</li></ul> |
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## 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>

**CV: Curriculum Vitae**

**DSUR: Development Safety Update Report**

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

**EU:** European Union

**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 Federal Agency for Medicines and Health Products

**GMO:** genetically modified organism

**NCP:** national contact point - 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 NCP will be the following email box: [CTRpilot@afmps-fagg.be](mailto: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

**SUSAR: Suspected Unexpected Serious Adverse Reaction**

**USM: Urgent Safety Measure**

**VHP:** voluntary harmonisation 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.

## 2. Scope and objectives of the pilot project

### 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 ECs 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 EC 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 the 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 project are national submissions of all phases (including ATMP trials) **and trials submitted via the VHP plus procedure.**

The CTR pilot project **VHP plus process** is applicable to Part I and Part II and involves a limited number of volunteer ECs. A [VHP plus specific addendum of the present guidance](#) is available on the FAMHP website.

### 2.2. Objectives

The purpose of the pilot project 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 project. This is also an opportunity for the FAMHP, the College and the ECs to test the short timelines for phase I mono-national trials within the framework of the CTR.

Participating in the pilot project 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 project on a voluntary basis (for initial CTAs).

### 2.4. Substantial modifications (SMs)

Once the initial CTA has been approved in the CTR pilot project procedure, SMs related to these trials need to be submitted following the CTR pilot project procedure as well.

In the spirit of the CTR and if possible, no SM shall be submitted if the previous one has not been already approved or closed.

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

A table with examples of SMs 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

**CTAs with genetically modified organisms (GMOs)** submitted following the deliberate release procedure are not accepted in the pilot project.

**Safety reporting** will not be handled in the pilot project. This means that the safety reporting documents (e.g. Development Safety Update Reports, Suspected Unexpected Serious Adverse Reactions) 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 DSURs and SUSARs 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 project 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** (USMs, 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. USMs 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 the 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 USMs and protocol deviations.

### 3. Legal basis

The new law of 7 May 2017 on CTR was published in the Belgisch Staatsblad/Moniteur Belge on 22 May 2017. This law contains article 58 which foresees that for the pilot project, article 11 §1 to 3 and §7 of the law of 7 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 CTAs and SMs. Essentially, as expected the pilot project follows the law of 7 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 project.

A set of royal decrees is also foreseen (e.g. operational royal decree of 9 October 2017 published on 10 November 2017).

The CTR pilot project 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 regulation 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 (twelve 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 project is limited in time. It will not continue once the CTR regulation will be implemented. However SMs for already approved CTR pilot initial dossiers before CTR implementation will still be accepted in the CTR pilot process until either the end of the trial or the switch of the trial from the Directive 2001/20/EC (law of 7 May 2004 in Belgium) to the CTR.

## 4. Procedure for sponsors – initial trials

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

From 15<sup>th</sup> February 2021 a Time Slots reservation system applies for submission of initial CTR pilot dossiers. Please see the Time Slots Info Session slides and Time Slots Q&A on the FAMHP website for details on the reservation system.

The Time Slots reservation system is not applicable for SMs, Covid-19 indication CTR pilot dossiers and CTR pilot VHP plus dossiers.

All dossiers must still be submitted via the CESP platform, as explained in §9. Annex III.

The CTR pilot project number will be provided by the NCP with the e-mail sent as confirmation of receipt of the dossier.

#### • Only for VHP plus dossiers

##### 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 NCP ([CTRpilot@fagg-afmps.be](mailto:CTRpilot@fagg-afmps.be)) with the following subject:

CTR pilot project – Letter of intent to participate in the CTR VHP plus pilot project procedure – CTA dossier 20XX-00XXXX-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 project VHP plus process, an acceptance e-mail containing a CTR pilot project 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:

PilotXXX\_VHP plus\_20XX-00XXXX-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 project dossier.**

- **Written statement** (statement of suitability of the site): please mention the name of the institution and not the name of the campus.
- In the zipped submission dossier 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.**
- **CV of each principal investigator:** diplomas have to be listed and the most important trials experience relevant for the submitted CTA should be documented. A template has been developed by the EU Commission and is available in the [zipped empty structure of the CTR pilot project dossier on the FAMHP website](#). Any other template (e.g. TransCelerate) can be accepted but should at least contain the same information.

- Applicants of CTR pilot project dossiers are kindly requested to provide a **WORD document** with the list of files with each submission (initial and SM). If additional files or newer versions are provided (via an answer to the validation questions, 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-00XXXX-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 English and at least in the official national language(s) of the region(s) where the trial is conducted (except in German) as according to the CTR and the Law of 7 May 2017 lay persons are part of the ethics committees. It has to be provided separated from the protocol.  
In general, for the content of the dossier, please consult Part I and Part II content tables in Annex II 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](#)). It should be clarified that the GLP studies were conducted in, or inspected by, a country that has implemented the OECD Mutual Acceptance of Data (MAD) system as recommended by the CTFG.
- **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. It can be provided next to the protocol, in folder "D. Protocol" of the submission dossier.
- **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](#), will not apply to a submission of a CTA dossier following the CTR pilot project process. The present guidance provides the details of the requirements for submission of the dossiers for the CTR pilot project 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 project. 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 as CESP has been selected as the unique way of submission to harmonise the way the different type of dossiers are submitted in the Research and Development Division (human use) of the FAMHP. A confirmation of receipt e-mail is sent for each submitted dossier. If not yet received one week after the submission via CESP, please contact the NCP.

The cover letter must be provided signed but electronic signature is accepted.

All communications (additional information, responses to questions ...) from the sponsor during the procedure are to be sent by CESP (if documents included) or by e-mail to the NCP ([CTRpilot@afmps-fagg.be](mailto: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. Payment of the fee for an initial dossier

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

#### 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 (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-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 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 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 project.

Upon successful validation, the NCP 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.

#### 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 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 RFI 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.

ICFs and other participants documents have to be provided at least in the official national language(s) of the region(s) where the trial is conducted 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 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 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 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.

In case of refusal, the CTA dossier can be re-submitted following the CTR pilot project 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).

The same pilot project number is kept in case of re-submission, with the addition of a letter A at the end, in analogy to the letter A at the end of the Eudra-CT number : PilotXXXXA\_20XX-00XXXX-XXA.

The same EC will be selected for the evaluation of the re-submission dossier and the evaluation of both the FAMHP assessors and the EC will focus on the answers to the remaining objections at the end of the first submission process.

## 5. Procedure for sponsors - SMs

### 5.1. Submission of a SM regarding a clinical trial approved in the CTR pilot project

SMs regarding clinical trials that were approved in the CTR pilot project procedure will also need to be submitted following the CTR pilot project procedure.

Please note that the addition of one or several new sites by the mean of a SM 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 SM 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:

#### **PilotXXX\_SMXXX\_20XX-00XXXX-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 SMs are kindly requested to provide a **WORD document** with the list of files with each submission. If additional files or newer versions are provided (via an answer to the validation questions, 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-00XXXX-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.

A confirmation of receipt e-mail is sent for each submitted dossier. If not yet received one week after the submission via CESP, please contact the NCP.

### 5.2. Payment of the fee for a SM

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

### 5.3. Validation phase

The validation of the SM 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 SM is related to an update of the ICF, that form has to be provided at least in the official national language(s) of the region(s) where the trial is conducted 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 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 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 SM can be implemented.

If the SM is "Authorised subject to conditions", the SM 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 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 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 SM cannot be implemented.

In case of refusal, the SM dossier can be re-submitted following the CTR pilot project procedure, with the next SM number.

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 project process to obtain a joint conclusion with recommendations and adaptations where required.



## 7. Annex I – Timetables for the CTR pilot project 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 + maximum 15 additional days if questions during validation + maximum 12 days if RFI during assessment → maximum 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: <ul style="list-style-type: none"> <li>- dossier complete → beginning of assessment</li> <li>- dossier still not complete after maximum 15 additional days (10 for the sponsor to answer the request for additional information + 5 for the NCP to verify if the dossier is complete after answer from the sponsor) → dossier refused</li> </ul>	T0 (+ maximum 10 + maximum 5 if validation questions)
Compiled assessment report for Part I and assessment for Part II available: <ul style="list-style-type: none"> <li>⇒ direct approval at T28 at the latest if no questions from FAMHP or EC</li> <li>⇒ list(s) of questions provided by the NCP to the sponsor</li> </ul>	T23
Response on questions by sponsor due by (maximum twelve 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 NCA 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 (+maximum 15 additional days if questions during validation) + maximum 12 days if RFI during assessment → maximum 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 maximum 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 (+ maximum 10 + maximum 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 (+maximum 12 days)
Review of the answers by the FAMHP and/or the EC and final coordinated decision sent by the NCA 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 SM (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 (+ maximum 10 + max. 5 days if questions during validation)+ maximum 12 additional days if RFI → maximum 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: <ul style="list-style-type: none"> <li>- dossier complete → beginning of assessment</li> <li>- dossier still not complete after maximum 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</li> </ul>	T0 (+ maximum 10 + maximum 5 if questions during validation)
Compiled assessment report for Part I and/or assessment for Part II available (depending from the scope of the SM):  ⇒ 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 NCA 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 SM 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 (+ maximum 10 + maximum 5 days if questions during validation) + maximum 12 additional days if RFI → maximum 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: <ul style="list-style-type: none"> <li>- dossier complete → beginning of assessment</li> <li>- dossier still not complete after maximum 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</li> </ul>	T0 (+ maximum 10 + maximum 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"> <li>⇒ direct approval at T15 at the latest if no questions from FAMHP or EC</li> <li>⇒ list(s) of questions provided by the NCP to the sponsor</li> </ul>	T10
Response on questions by sponsor due by (clock stop of maximum 12 days if list of questions)	T10 (+ maximum 12 days)
Review of the answers by FAMHP and/or EC and final coordinated decision sent by the NCA by	T15

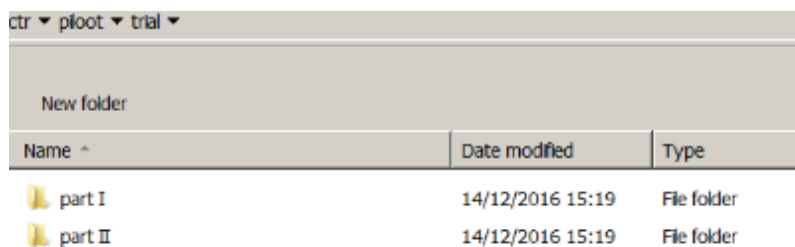
For an ATMP clinical trial, 30 days (as foreseen by the law of 7 May 2004) will be added to the 15 days legal delay. From these additional 30 days, 25 days will be added to the assessment period of 10 days and 5 days to the period foreseen for the assessment of the answers to the RFI.

## 8 Annex II – Dossier structure as per regulation 536

### 8.1 Initial application

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

#### 8.1.1 Initial application



The screenshot shows a file explorer window with the path 'ctr > pilot > trial'. Below the path, there is a 'New folder' button. A table lists the contents of the folder:

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](#) (recruitment and ICF procedure, written statement of the sites, Investigator's CV, DOI, ICF and WORD document with the list of submitted documents) 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 SM 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: PilotXXX (as the pilot project number is unknown at the moment of the submission) and EudraCT number first, followed by the file name in English (see list below).

Example

PilotXXX\_20XX-00XXXX-XX\_Name of file/document.pdf

**PilotXXX\_2010-090094-00\_Cover-Letter.pdf**

#### Special cases

1. To name scanned pages of documents with signatures (if applicable) we ask you to add "signature" in the name.  
Example: PilotXXX\_2010-090094-00\_Application\_Form\_Signature.pdf  
However as indicated in § 4.2.1.: electronic signatures are now accepted.
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 project dossier and Q&A)

File/Document	Name	Annex I Regulation No 536/2014	References
B. Cover letter	Cover Letter.pdf	B	<ul style="list-style-type: none"> <li>Pilot project number</li> <li>RSI : info on where it can be found in the dossier + if modified compared to last submitted version ( new SADR ?)</li> <li>WORD document with list of submitted documents (see <a href="#">zipped empty structure of the CTR pilot project dossier on the FAMHP website</a>)</li> </ul>
C. EU application form	Application form.pdf	C	EU application form (the current EU application form should be used during the pilot project as a new CTR application form is not yet available)
D. Protocol	Protocol.pdf	D 24	<ul style="list-style-type: none"> <li>See also ICH E6 GCP</li> <li>The protocol shall be accompanied by a synopsis of the protocol, provided as a separate document in EN and at least in the official national language(s) of the region(s) where the trial is conducted, except in German.</li> <li>The first act of recruitment (e.g. advertising) should be specified</li> <li>DSMB charter (if applicable)</li> </ul>
E. Investigator's brochure	Investigators_Brochure.pdf	E	See also ICH E6 GCP
F. Documentation relating to GMP for the IMP <ul style="list-style-type: none"> <li>Copy of the manufacturing authorisation</li> <li>Certification by the Qualified Person</li> </ul>	<ul style="list-style-type: none"> <li>Manufacturing-authorisation.pdf</li> <li>QP-Declaration.pdf</li> <li>...</li> </ul>	F	<ul style="list-style-type: none"> <li>GMP certificates not accepted, only GMP manufacturing authorisations</li> <li>EU template strongly recommended for QP declaration</li> </ul>
G. IMPD dossier	Impd.pdf	G	<ul style="list-style-type: none"> <li>See also Eudralex volume 10 chapter III for content and Common Technical Document (CTD) format</li> <li>GLP statement has to be part of the IMPD (see: point 44 of annex I of the CTR and <a href="http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/QAs_document_on_GLP_-_2017.pdf">http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/QAs_document_on_GLP_-_2017.pdf</a>)</li> </ul>
G. Simplified IMPD	Simplified-IMPD	G	See CTR (annex I points 50 to 53) to see cases when a simplified IMPD is accepted
G. SMPC	Smpc.pdf	G	If applicable
H. AMP 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 A template developed by the EU Commission is available in the <a href="#">zipped empty structure of the CTR pilot project dossier on the FAMHP website</a>
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	<ul style="list-style-type: none"> <li>• Use of the existing template is strongly recommended: see <a href="#">zipped empty structure of the CTR pilot project dossier on the FAMHP website</a></li> <li>• <b>A new version of the ICF template for interventional trials in adults and dated 28-06-2019 has been published on <a href="http://www.ct-college.be">http://www.ct-college.be</a></b></li> <li>• To be submitted at least in the official national language(s) of the region(s) where the trial is conducted</li> <li>• Sponsor is responsible for appropriate translations. The EC only reviews the ICFs in one language</li> </ul>
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 A template developed by the EU Commission is available in the <a href="#">zipped empty structure of the CTR pilot project dossier on the FAMHP website</a>
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	<ul style="list-style-type: none"> <li>• CV template developed by the EU Commission available: see <a href="#">zipped empty structure of the CTR pilot project dossier on the FAMHP website</a> 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</li> <li>• GCP training should be documented (in the CV or by a GCP certificate), mentioning the name of the certifying organisation <b>and should not be older than three years</b></li> <li>• Declaration of interest: template developed by the EU Commission available: see <a href="#">zipped empty structure of the CTR pilot project dossier on the FAMHP website</a></li> </ul>
N. Statement on the suitability of the sites	Suitability-statement-namesite.pdf	N	Most recent version of the written statement issued by the site. <b>Please mention the name of the institution and not the campus.</b> <ul style="list-style-type: none"> <li>• Template available in the structure zip file in on the FAMHP website</li> </ul>



			<ul style="list-style-type: none"> <li>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</li> </ul>
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	<ul style="list-style-type: none"> <li>Draft version of the contract with (draft) amounts is currently accepted</li> <li>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</li> </ul>
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 GDPR	Data-Protection-Statement.pdf	R	<p>A stand-alone document (statement) has to be provided</p> <p><b>This document should at least contain:</b></p> <p>"[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 (GDPR)"</p>

## 8.2 SMs

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

Please note that during the CTR pilot project, the submission of a SM should be made separately for trial(s) in the pilot project and trials approved within the current process. After implementation of the CTR, the same SM 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 SMs also need to be submitted to the NCP who will distribute them to the College and subsequently to the EC.

Non-SMs should not be submitted, but should be added to the documentation for the next SM.

[A zip file with the structured empty folders](#) is available on our website next to the present guidance.

### APPLICATION DOSSIER FOR SMs

- 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 SM 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 RSI: **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\_SMXXX\_20XX-00XXXX-XX\_Name of file. pdf

**Pilot999\_SM001\_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\_SM001\_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: Pilot999\_SM001\_2010-090094-00\_Manufacturing-Authorisation\_Name of the medicinal product.pdf

Document	Name	Annex II Regulation No 536/2014	References
B. Cover Letter	Cover-Letter.pdf	B	<ul style="list-style-type: none"> <li>• Pilot project number</li> <li>• RSI : where it can be found in the dossier + if modified compared to last version (new SADR ?)</li> <li>• WORD document with list of submitted documents</li> </ul>
C. Modification Application Form	Modification-Application-Form.pdf	C	Modification Application Form (the current SM Notification Form should be used during the pilot project 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	<ul style="list-style-type: none"> <li>• Protocol and IB: See ICH E6 GCP/EudraLex volume 10</li> <li>• <b>A new version of the ICF template for interventional trials in adults and dated 28-06-2019 has been published on <a href="http://www.ct-college.be">http://www.ct-college.be</a></b></li> <li>• ICF to be submitted at least in the official national language(s) of the region(s) where the trial is conducted</li> <li>• <b>For all updated documents a summary of changes and track changes version(s) must be provided</b></li> </ul>
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	<ul style="list-style-type: none"> <li>• The initial application form (updated or not) is also to be provided with each substantial modification</li> <li>• If the initial Application Form has been revised, changes must be clearly highlighted</li> </ul>

#### 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 CESP

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

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
	SM for a clinical trial
	ASR/DSUR submission
	Urgent safety measure
	Temporary halt notification
	End of trial declaration
	CTR pilot project- initial application for a clinical trial
Clinical investigations (medical devices)	CTR pilot project – Substantial modification for a clinical trial
	Initial application for a clinical investigation
	Serious Adverse Events Notification
Unmet Medical Needs	Notification of end of clinical investigation - performance study
	Initial application for a CUP/MNP
	Periodic Re-evaluation for a CUP/MNP
Clinical investigations and Unmet Medical Needs	Substantial Amendment for a CUP/MNP
	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://cesportal.hma.eu/Account/Login>

If haven't got an account yet, select "register" or follow this link:

<https://cesportal.hma.eu/delivery/create>

**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 your password?](#)

[Log in](#) [Register](#)

Latest Updates	
1 Contact (G/PE)	25-06-2017
2 Contact (RI/CP)	29-JUN-2018
3 Contact (S/UKPL)	21-JUN-2018
4 Contact (L/ZA)	03-JUL-2017
5 Contact (C/UKL)	13-JAN-2018
6 Contact (L/PA/PPV)	04-JAN-2017
7 Contact (U/BE-RA)	22-MAR-2017
8 Contact (PT)	07-MAR-2015
9 Contact (EE)	19-DEC-2018
10 Contact (L/PA/CE)	27-APR-2018

### 9.2.2. e-submission

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

1. Select New Delivery File

2. Select Human Medicines or Medical Devices following the object of your submission

3. Select

**Clinical trial** for the following related submission:

- Initial application for a clinical trial
- SM for a clinical trial
- CTR Pilot project – initial application for a clinical trial
- CTR Pilot project – 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
- SM for a CUP/MNP

**Medical device** for the following related submission:

- Initial application for a clinical investigation
- SM 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 \*  
HDM 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 \*  
HDM Not Applicable

Zip File Type \*  
7-Zip

Comment

Next >

Write any comments on the process here.  
e.g. for CTR pilot project, please put "CTR pilot project".

HMA Commission European Submission Portal

**New Delivery File**

Step 1 Step 2 Step 3 Step 4

Procedure Type \*  
National

Submission Type \*  
Other e-Submission Type

Technically Validated \*  
 Yes  
 No

< Previous Next >

Choose "National" as **Procedure type** and "Other e-Submission Type" as **Submission type** for all related processes.

Should always be "no" for all related

HMA Commission European Submission Portal

**New Delivery File**

Step 1 Step 2 Step 3 Step 4

National Agency (responsible for National Requirements) \*

AGES AT	<b>famhp</b> BE	HÄLMED HR	CY	SUKL CZ/SK
AGENCIJA ZA VEŠTAČENJE IZ OBLASTI ZDRAVSTVA DK	EE	fimea FI	ansm FR/NEU	European Agency for Medicines DE/BY/PL
AGENCIJA ZA VEŠTAČENJE IZ OBLASTI ZDRAVSTVA HU	GR	OGYE HU/OGYI	SI	HPRA IE
AIFA IT/AIFA	LV LV/PA	ITPAKT IT/PAKT	LI	Ministry of Health LT
e.B.G.M.E.P. LU	MD	PL PL/LEP	informed PT	RO/ANM RO/ANM
SUKL SK/SUKL	jazmp SK/JAZMP	m ES	SE	MHRA RO/ANM
CESP ES				

Choose Belgium – FAMHP to send in your submission



**HMA** Common European Submission Portal

Home | New Delivery File | Web Upload | Deliveries | Support | Training | Reports | Announcements | Contacts | General Information | FAQs | Terms & Conditions

### New Delivery File

Box 1 | Box 2 | Box 3 | Box 4

National Email Address

Email:

Agency

Agency	IPAS Number	Product Name
Select Agency	<input type="text"/>	<input type="text"/>

Product Details File Name:

You can enter the Name of the Product Details File, which is submitted instead of the product name.

**HMA** Common European Submission Portal

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### 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](mailto:cesp@hma.eu) are not blocked or sent to your junk mail.

Download the xml file and upload it with your files to submit the application (see next steps)

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

1. Select **Web upload**

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 remark

First upload your dossier – as a zip file. When the zip file is fully uploaded, upload your previously downloaded delivery file (e.g. 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 project dossier and Q&A

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

- In the zipped submission dossier 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 and Part II to avoid the presence of unnecessary levels in the dossier.**
- In the Part I and Part II content tables presented in Annex II 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 project.
- 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 and at least in the official national language(s) of the region(s) where the trial is conducted, except in German.
- 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.
  - CV 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.
  - Recruitment and ICF procedure template 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 project.
- 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 is foreseen for the trial (unless this will be part of the RFI).
- The statement related to the protection of the data (folder R in Part II of the dossier) must refer to the GDPR, e.g. 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 (GDPR)".

## 10.2. Questions and answers

### 1) What are the timelines?

Short timelines (annex I 7.2. and 7.4. 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 SMs, 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 project, 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. The evaluation has already been performed and the national approval issued by the evaluating independent EC => no new evaluation can be performed and/or approval can be issued at the local site. However each site can check if everything is OK and all information provided before the start of the trial on site".

### 5) What about safety reporting?

Safety reporting will not be handled in the pilot project. This means that the safety reporting documents (e.g. 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 DSURs and SUSARs 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 project 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:

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. A template developed by the EU Commission is available in the [zipped empty structure of the initial dossier available on the FAMHP website](#).

### 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 project:** the table below could be updated with new examples at the occasion of the next update of the present guidance.

<b>CTR pilot project: examples of SMs and of different categories of notifications</b>
<b>Examples of modifications that are considered SMs and have to be submitted following §5 of the present guidance</b>
<ul style="list-style-type: none"> <li>• New ICF version</li> <li>• New patient diary</li> <li>• Intervention of recruitment assistants (new recruitment procedure)</li> <li>• Addition of site(s) (not before three months after approval of the initial trial)</li> <li>• Update of the IB if substantial safety information is added/changed (included modification of the RSI)</li> </ul>
<b>Examples of notifications that are not SMs but have to be sent immediately to the NCP</b>
<ul style="list-style-type: none"> <li>• The updated site-specific annexes to the ICF containing the trial specific treatments, examinations, visits</li> <li>• Protocol deviations with a direct impact on the safety of the subject</li> <li>• Proof of insurance renewal, new insurance certificate</li> <li>• 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)</li> <li>• Yearly status of the study. This notification is normally done in January or at the birthday date of EC study approval</li> </ul>
<b>Examples of notifications that are not SMs and that should not be sent immediately to the NCP but added to the next SM</b>
<ul style="list-style-type: none"> <li>• Signed version of approved documents (e.g. protocol, finalised contracts)</li> <li>• Contract (under another template than the approved contract)</li> <li>• Site change in case of relocation</li> <li>• Translated version of approved documents (e.g. patient diary or ICF)</li> <li>• Evolution report at time of moving from one cohort to another cohort in the study</li> <li>• Protocol clarification letter related to non-substantial changes</li> <li>• Typo's</li> <li>• Removal of one or several sites</li> <li>• Update of the IB with no substantial changes (e.g. validity of IB is extended)</li> <li>• Change of coordinating Principal Investigator (PI) <b>if no new PI in the trial</b></li> </ul>
<b>Notification of USMs (where an unexpected event is likely to seriously affect the benefit-risk balance)</b>
<ul style="list-style-type: none"> <li>• Can be implemented without waiting for authorisation but shall be notified to the NCP not later than seven days from the implementation</li> </ul>
<b>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)</b>
<ul style="list-style-type: none"> <li>• 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 a SM</li> <li>• Declaration of the end of trial form</li> </ul>
<b>Notification of the summary of the results [Clinical Study Report (CSR) or synopsis of the CSR or Plain language summary]</b>
<ul style="list-style-type: none"> <li>• Should be submitted within one year from the end of a clinical trial in all MSs concerned</li> </ul>

**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 25<sup>th</sup> 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

In order to facilitate the delivering of the approval letter within the CTR pilot project, Applicants of CTR pilot project dossiers are kindly requested to provide a **WORD file with the list of documents**.

We strongly recommend applicants to **keep the list of documents provided at the initial submission and to submit it at each change (validation question, response to RFI, etc.) with a clear indication of which documents have been updated/added.**

We recommend the sponsor to use the following table template

Documents	Version and/or date	Assessed (completed by ECs)	Approved (completed by ECs)
<b>PART I</b>			
<b>A. INTRODUCTION</b>			
...			
<b>B. COVER LETTER</b>			
Example: Pilot222_2019-111111-22_Cover-Letter_20190910.pdf	10/09/2019		
...			
<b>C. EU APPLICATION FORM</b>			
Example: Pilot222_2019-111111-22_Application-Form_20190910.pdf	10/09/2019		
...			
<b>D. PROTOCOL</b>			
Example: Pilot222_2019-111111-22_Protocol_v1.1.pdf	V1.1		
Example: Pilot222_2019-111111-22_Protocol_v1.2.pdf	V1.2		
...			
<b>E. INVESTIGATOR'S BROCHURE</b>			
Example: Pilot222_2019-111111-22_IB_v1.2_20190901.pdf	V1.2 / 01/09/2019		
Example: Pilot222_2019-111111-22_IB_v1.3_20190930.pdf	V1.3. /30/09/2019		
...			
<b>F. DOCUMENTATION RELATING TO COMPLIANCE WITH GOOD MANUFACTURING PRACTICE (GMP) FOR THE INVESTIGATIONAL MEDICINAL PRODUCT</b>			
...		NA	NA
<b>G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)</b>			
...		NA	NA
<b>H. AUXILIARY MEDICINAL PRODUCT DOSSIER</b>			
...		NA	NA
<b>I. SCIENTIFIC ADVICE AND PIP</b>			
...			
<b>J. LABELLING OF THE IMP</b>			
...			

Documents	Version and/or date	Assessed (completed by ECs)	Approved (completed by ECs)
<b>PART II</b>			
<b>K. RECRUITMENT ARRANGEMENTS</b>			
...			
<b>L. SUBJECT INFO, ICF AND ICF PROCEDURE</b>			
Example: Pilot222_2019-111111-22_Patient Card-NL.pdf	V1.0		
...			

<b>M. SUITABILITY OF THE INVESTIGATOR</b>			
Example: Pilot222_2019-111111-22_Application-Form_20190910.pdf	10/09/2019		
...			
<b>N. SUITABILITY OF THE FACILITIES</b>			
Example: Pilot222_2019-111111-22_CV-Janssens_20160223.pdf	23/02/2016		
...			
<b>O. PROOF OF INSURANCE</b>			
Example: Pilot222_2019-111111-22_IB_v1.2_20190901.pdf	V1.2 / 01/09/2019		
Example: Pilot222_2019-111111-22_IB_v1.3_20190930.pdf	V1.3 /30/09/2019		
...			
<b>P. FINANCIAL AND OTHER ARRANGEMENTS</b>			
...			
<b>R. STATEMENT DATA PROTECTION</b>			
...			

### 11.2 SMs

In order to facilitate the delivering of the approval letter within the CTR pilot project, Applicants of CTR pilot project dossiers are kindly requested to provide a **WORD file with the list of documents**.

We strongly recommend applicants to **keep the list of documents provided at the initial submission and to submit it at each change (validation question, response to RFI, etc.) with a clear indication of which documents have been updated/added.**

We recommend the sponsor to use the following table template:

Documents	Version and/or date	Assessed (completed by ECs)	Approved (completed by ECs)
<b>A. INTRODUCTION AND GENERAL PRINCIPLES</b>			
...			
<b>B. COVER LETTER</b>			
Example: Pilot222_2019-111111-22_SM002_Cover-Letter_20190910.pdf	10/09/2019		
...			
<b>C. MODIFICATION APPLICATION FORM</b>			
Example: Pilot222_2019-111111-22_SM002_Modification_Application-Form_20190910.pdf	10/09/2019		
...			
<b>D. DESCRIPTION OF THE MODIFICATION</b>			
Example: Pilot222_2019-111111-22_SM002_ICF_French_v1.2.pdf	V1.2		
Example: Pilot222_2019-111111-22_SM002_Protocol_v1.2.pdf	V1.2		
...			
<b>E. SUPPORTING INFORMATION</b>			
Example: Pilot222_2019-111111-22_IB_v1.2_20190901.pdf	V1.2 / 01/09/2019		
...			
<b>F. UPDATE OF EU APPLICATION FORM</b>			
Example: Pilot222_2019-111111-22_Application-Form_20190910.pdf			