Voluntary Joint Pilot between FAMHP, the future 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 draft text of the law on CTR

Guidance for participating parties version 1.0, 10.1.2017

DISCLAIMER

The present guidance is a document that will evolve and 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 main purpose of this first published version of the guidance is to ask the sponsors to complete the letter of intent appended if they are interested in participation to the CTR pilot project in Belgium.

It is especially foreseen to provide a detailed description of the documents being part of the CTA submission package for the pilot and timetables for the different types of submitted dossiers.

Evolutions will be published on the FAMHP website as soon as available.

The excel file for the letter of intent of sponsors interested to participate to the CTR pilot project is to be provided by email to ct.rd@afmps.be prior to Tuesday 24th of January 2017.

Contents

1. Definitions, conventions and abbreviations

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

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.

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: 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 contacted through the following mailbox: ct.rd@fagg-afmps.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 Harmonisation Procedure

All periods that are being 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 come into force 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 future College and (ii) between the future College and the EC's 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.

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 future 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 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 and without additional costs. The fees of the law of 7th May 2004 remain.

The pilot project will be conducted with selected initial CTAs.

2.4. Substantial modifications

Substantial modifications related to trials approved in the CTR pilot procedure also have to be submitted following the CTR pilot project procedure.

2.5. Out of scope

Safety reporting will not be changed by the pilot. This means that the safety reporting documents must not be submitted to the national contact point 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, the position might be reviewed.

3. Legal basis

The new law on CTR will likely be published in the Belgisch Staatsblad/Moniteur Belge mid-March 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 draft text of the Belgian Law**, with the selection of the EC by the future College and the joint assessment (national contact point and EC) with the use of the new European templates.

A set of Royal Decree's is also planned (e.g. operational, and others).

Therefore, it is intended to start the CTR pilot project after publication of the new law on clinical trials.

The CTR pilot project will also permit to test the joint assessment of phases I mononational dossiers for which short deadlines are being kept in the draft text of the new law on CTR.

VHP dossiers for which Belgium is RMS could be part of the CTR pilot project. However as deadlines of the law of 7 May 2004 remain, a pre-submission of the dossier at European level as currently foreseen in the VHP process and a subsequent national submission will still be necessary. However, in the framework of the CTR pilot project, the CTA package would be submitted according to the Regulation 536/2014 and the assessment would be a joint assessment between the FAMHP and the Ethics committee. Both FAMHP and the EC would commit to approve the CTA dossier as soon as possible after a favourable decision at the end of the VHP process.

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. CTA's started prior to this date will continue.

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 appended letter of intent should be submitted by E-mail to the national contact point **prior to Tuesday 24th of January** 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
- name and site of the co-ordinating investigator of the clinical trial
- number and addresses of planned trial centres in Belgium if available at the moment of the submission of the letter of intent. Should be provided at the latest at the moment of the confirmation by the sponsor (see below).
- planned submission date for the dossier

The national contact point and the future College will decide on a case-by-case basis whether a CTA can be processed in the pilot project. The choice of the dossiers will be based on the type of dossier and on the proposed submission date in function of the capacities of the national contact point and the future College. The purpose would be to reach a good distribution of the assessment periods during the first semester of the CTR pilot project. As such, no single sponsor is automatically entitled to participate – the decision to include a study in the pilot project remains with the national contact point and the future College.

In case the dossier is accepted within the pilot an acceptation E-mail containing a CTR pilot project 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 project number : XXX – CTA 20XX-XXXXXX-XX**

Should it not be possible to process the CTA within the pilot project, the national contact point will inform the sponsor **at the latest** within **one week**. In this case the sponsor can submit the dossier in accordance to the current legislation. However, **the content of the dossier, as prepared according to the requirements of the CTR, will be accepted** even if the review process of the dossier will be performed in accordance with the Directive 2001/20/EC.

4.2. Practical procedure

4.2.1. Submission of the CTA

The national contact point (ct.rd@fagg-afmps.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 pilot CTR process, circular letter 575 will not be applicable. This present guidance provides the details of the requirements for submission of the dossiers for the pilot CTR 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 make use of this option in the course of the pilot project (first and second step). Part I and part II packages have to be submitted together at the same moment to the national contact point.

At the time of the submission the cover letter must point out that participation in the pilot project has been confirmed and must contain the pilot project number. The cover letter must be provided hand signed and scanned in the Eudralink submission.

For the sake of a quick treatment of the dossier it is asked to the sponsor to submit the CTA package by Eudralink. The expiry date of each Eudralink package in this pilot will be set to its maximum of 90 days.

In parallel, an E-mail is to be sent to the national contact point to announce the submission of the dossier.

All communications (additional information, responses to questions, …) from the sponsor during the procedure are to be sent by email and/or Eudralink to the national contact point.

4.2.2. Payment of the fee for an initial dossier

The usual fee of 5669.55 EUR for phase I CTA dossiers and of 3780.46 EUR for other phases must be paid to the national contact point per dossier.

Payment must be made on the following account : 679-0001514-59

Contact details of the bank :

Poste financière
Chaussée d'Anvers 59
B-1100, Bruxelles (Belgium)

SWIFT code: PCHQBEBB
IBAN code: BE84 6790 0015 1459

For payments from abroad the transfer fees are paid by the payer.

The proof of payment of the fee must be added to the CTA package.

Please mention "Pilot XXX – CTA 20XX-XXXXXX-XX" on the bank statement.

For each file a separate payment should be made.

Once the EC responsible for the assessment of the dossier will be identified by the future College, a unique fee of 1280.23 EUR must be directly paid by the sponsor to this EC

The EC confirms reception of the fee to the future College – who confirms this to the national contact point with mentioning of the EudraCT number and the CTR pilot project number.

4.2.3. Validation phase

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

The validation phase may only begin if the CTA **and the corresponding fee** and the confirmation by the future College have been received by the national contact point.

At the end of the **validation phase** which will last a maximum of **ten days (except for phases I mononational trials for which the validation phase will last a maximum of five 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 remove the deficiencies. The corresponding response by the sponsor (E-mail) is to be sent to the national contact point.

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 project.

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

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 future College while 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 deficits from the national contact point.

Contents covered by the future 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.

In the case of deficiency letter(s), the sponsor is called upon to remedy the deficiencies noted or to supply the requested information within **12 days at the most (see table in annex I)** in order to comply with the deadlines specified in the CTR. As before, the answer here should also be as a single response sent by E-mail to the national contact point (ct.rd@fagg-afmps.be).

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

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 national contact point and the Ethics committee, the 2 instances compile their final decisions on the basis of the Assessment Reports on Part I and Part II of the CTA and the final notices are provided to the sponsor by the national contact point.

If the notices are positive, the clinical trial can be started.

5. Procedure for sponsors Substantial Modifications

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

Substantial modifications (SM) regarding clinical trials that were approved in the CTR pilot procedure will also need to be submitted following the CTR pilot project procedure.

Upon submission, the SM cover letter and any other communication should clearly state: **CTR pilot project number : XXX – CTA 20XX-XXXXXX-XX – Substantial modification**

The submission dossier must comply with the requirements of annex II of the CTR.

In parallel, an E-mail is to be sent to the national contact point (ct.rd@fagg-afmps.be) to announce the submission of the substantial modification.

5.2. Payment of the fee for a substantial modification

The usual fee of 622,45 EUR must be paid to the national contact point per substantial modification.

Payment must be made on the following account : 679-0001514-59

Contact details of the bank :

Poste financière
Chaussée d'Anvers 59
B-1100, Bruxelles (Belgium)

SWIFT code: PCHQBEBB
IBAN code: BE84 6790 0015 1459

For payments from abroad the transfer fees are paid by the payer.

The proof of payment of the fee must be added to the CTA package. Please mention "Pilot XXX – CTA 20XX-XXXXXX-XX – Substantial modification" on the bank statement.

For each file a separate payment should be made.

A unique fee of 320.05 EUR must be directly paid by the sponsor to the EC that was responsible for the assessment of the initial dossier.

The EC confirms reception of the fee to the future College – who confirms this to the national contact point with mentioning of the EudraCT number, the CTR pilot project number and references of the substantial modification.

5.3. Validation phase

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

The validation phase may only begin if the SM **and the corresponding fee** and the confirmation by the future College have been received by the national contact point.

At the end of the **validation phase** which will last a maximum of **six days (except for phases I mononational trials for which the validation phase will last a maximum of five 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 remove the deficiencies. The corresponding response by the sponsor is to be sent to the national contact point (ct.rd@fagg-afmps.be).

The national contact point evaluates the supplemented documentation **within 5 days** after receipt of the comments or the amended SM dossier.

5.4. Assessment phase

After successful validation, the SM is assessed by the FAMHP and 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 Ethics committee while the aspects covered by Part II are assessed by the Ethics committee.

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 deficits from the national contact point.

SM contents covered by the future 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.

In the case of deficiency letter(s), the sponsor is called upon to remedy the deficiencies noted or to supply the requested information within **12 days at the most (see table in annex I)** in order to comply with the deadlines specified in the CTR. As before, the answer here should also be as a single response sent by E-mail to the national contact point (ct.rd@fagg-afmps.be).

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

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 Ethics committee, the 2 instances compile their final decisions on the basis of the Assessment Reports on Part I and Part II of the SM and the final notices are provided to the sponsor by the national contact point.

If the notices are positive, the substantial modification can be implemented.

6. Survey

The national contact point will organise a survey to all the stakeholders (sponsor, future College and EC) to collect comments, lessons learnt, suggestions on the pilot process to obtain a joint conclusion with recommendations and adaptations where required.