

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

Guidance for participating parties version 3.0, 06.10.2017

DISCLAIMER

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

The excel file for the letter of intent of sponsors interested to participate to the CTR pilot project is to be provided by E-mail to the [new specific E-mail address for the pilot](mailto:CTRpilot@afmps-fagg.be) : CTRpilot@afmps-fagg.be.

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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 the following mailbox: CTRpilot@afmps-fagg.be

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

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

VHP: Voluntary 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 College and (ii) between the 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 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 till further notice.

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 has been published in the Belgisch Staatsblad/Moniteur Belge on the 7th of May 2017. This law contains article 58 which foresees that for the pilot, Article 11 §§1 to 3 and §7 of the law of 7th May 2004 related to the role of the EC is not valid anymore. The other articles of the law of 7th May 2004 remain applicable, as is the authorisation of the CTA and substantial modifications. Essentially, the pilot follows as expected the **law of 7th May 2004**, but follows the **spirit of CTR and the text of the new Belgian Law of 7 May 2017**, with the selection of the EC by the College and the joint assessment (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).

The CTR pilot project has started after publication of the new law on clinical trials.

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

As one of the principles of the present project is a learning by doing approach, some flexibility will be accepted from all parties involved. The CTA dossiers and SM dossiers will not be automatically rejected if the sponsor cannot answer the questions within the CTR deadlines (12 days). As much as possible, this timeline, as foreseen in the CTR, should be respected but exceeding the time of maximum 20% will be accepted in practice.

This pilot is limited in time. It will not continue after the CTR regulation has come into place. 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 with the following E-mail title : **CTR pilot – Letter of intent to participate to the CTR pilot procedure – CTA dossier 20xx-xxxxxx-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 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 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 College.

In case the dossier is accepted within the pilot an acceptance 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 as soon as possible. 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 (CTRpilot@afmps-fagg.be) and the sponsor will stay in close contact in order to refine the submission date if necessary.

For a submission of a CTA dossier following the 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. 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.

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

Important points for the constitution of the CTR pilot dossier:

- 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 file for submission: Curriculum Vitae of the investigator (section M. of part II) and written statement of the site (section N. of part II),
- The informed consent procedure has to be provided in section L. of part II of the submission dossier.
- Protocol:
 - ⇒ following Helsinki declaration art.34 Post trial provisions : "In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial". As far as possible this should be foreseen in the protocol.
 - ⇒ the first act of recruitment (e.g. advertising) should be specified in the protocol as according to the clinical regulation 536/2014 it defines the official start of the trial.

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: PCHQBEBBIBAN 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 section Q. of the submission dossier.

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

For each file a separate payment should be made.

The invoicing details of the sponsor must be part of section Q of part II of the submission dossier.

Once the EC responsible for the assessment of the dossier will be identified by the College, a bill with the unique fee of 1280.23 EUR will be sent to the sponsor by the EC using the provided invoicing details.

4.2.3. Validation phase

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

At the end of the **validation phase** which will last a maximum of **ten days (except for phases I mono-national 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, Eudralink if possible) 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 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 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 Part II of the CTA pursuant to the CTR are assessed in parallel by the Ethics committee. Questions and/or requests for additional information regarding these aspects are sent to the sponsor by the national contact point at the same time with the list of questions related to part I of the dossier.

Informed Consent Forms (ICFs) are reviewed by the EC in one language. The correct translation into all other languages remains the responsibility of the sponsor. 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 deficiency letter and these comments/remarks have to be taken into account by the sponsor when providing the answers to the questions. However, the sponsor remains responsible for the translation of the updated ICF into the other ICF's languages.

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

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

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

4.2.5. Approval

After evaluation of the sponsor's response to questions related to part I and part II of the dossier by the national contact point and the Ethics committee, the NCP compiles their final decisions on the basis of the Assessment Reports on Part I and Part II of the CTA and the final and unique conclusion is provided to the sponsor by the national contact point.

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

If the CTA is "Authorized subject to conditions", the clinical trial can be started after fulfilment of the conditions by the sponsor.

If the CTA is "Refused", the clinical trial cannot be started.

5. Procedure for sponsors Substantial Modifications

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

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 section G. of the substantial modification dossier. 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 proof of payment of the fee to the EC is provided by the sponsor to the national contact point together with the SM submission dossier.

5.3. Validation phase

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

At the end of the **validation phase** which will last a maximum of **six days (except for phases I mono-national 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 (CTRpilot@afmps-fagg.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 Part II of the CTA pursuant to the CTR are assessed in parallel by the Ethics committee. Questions and/or requests for additional information regarding these aspects are sent to the sponsor by the national contact point at the same time with the list of questions related to part I of the SM dossier.

If the substantial modification is related to an update of the Inform Consent Form (ICF), the ICF is reviewed by the EC in only one language. The correct translation into all other languages remains the responsibility of the sponsor. 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 deficiency letter and these comments/remarks have to be taken into account by the sponsor when providing the answers to the questions. However, the sponsor remains responsible for the translation of the updated ICF into the other ICF's languages.

In the case of a deficiency letter, the sponsor is called upon to remedy the deficiencies noted or to supply the requested information within **12 days at the most** in order to comply with the deadlines specified in the CTR. As before, the answer here should also be as a single response sent by E-mail to the national contact point (CTRpilot@afmps-fagg.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 national contact point and the Ethics committee, the NCP compiles their final decisions on the basis of the Assessment Reports on Part I and Part II of the SM and the final and unique conclusion is provided to the sponsor by the national contact point.

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

If the SM is "Authorized subject to conditions", the substantial modification can be implemented after fulfilment of the conditions by the sponsor.

If the SM is "Refused", the substantial modification cannot be implemented.

6. Survey

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

7. Annex I

Timetables for the CTR pilot project process

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

Maximum duration of the process: 28 days (timeline as foreseen in the law of 7 May 2004) + 10 days for validation + max. 15 additional days if questions during validation + max. 12 days if list(s) of questions during assessment => max. 65 days

Step	DAY
Confirmation of receipt to Sponsor/beginning of validation	Date submission = T0 - 10
Notification of the validation status to the sponsor: <ul style="list-style-type: none"> - Dossier complete => beginning of assessment - Dossier still not complete after max. 15 additional days (10 for the sponsor to answer the request for additional info + 5 for the national contact point to verify if the dossier is complete after answer from the sponsor) => dossier refused 	T0 (+ max. 10 + max. 5 if validation questions)
Compiled assessment report for part I and assessment for part II available : <ul style="list-style-type: none"> ⇒ Direct approval at T28 at the latest if no questions from FAMHP or EC ⇒ List(s) of questions provided by the national contact point to the sponsor 	T23
Response on questions by sponsor due by (maximum 12 days clock stop if list of questions)	T23 (+ max. 12 days)
Review of the answers by FAMHP and/or ethics Committee and final coordinated decision sent by the national competent authority by	T28

2) National initial phase I mono-national dossier

Maximum duration of the process: 15 days (timeline as foreseen in the law of 7 May 2004) + 5 days for validation (+ max. 15 additional days if questions during validation) + max. 12 days if list(s) of questions during assessment => max. 47 days

Step	DAY
Confirmation of receipt to Sponsor (dossier + payment)/beginning of validation	Date submission = T0 - 10
Notification of the validation status to the sponsor: <ul style="list-style-type: none"> - Dossier complete => beginning of assessment - Dossier still not complete after max. 15 additional days (10 for the sponsor to answer the request for additional info + 5 for the national contact point to verify if the dossier is complete after answer from the sponsor). => dossier refused 	T0 (+ max. 10 + max. 5 if validation questions)
Compiled assessment report for part I and assessment for part II available : <ul style="list-style-type: none"> ⇒ Direct approval at T15 at the latest if no questions from FAMHP or EC ⇒ List(s) of questions provided by the national contact point to the sponsor 	T10
Response on questions by sponsor due by (maximum 12 days clock stop if list of questions)	T10 (+ max. 12 days)
Review of the answers by FAMHP and/or ethics Committee and final coordinated decision sent by the national competent authority by	T15

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

Maximum duration of the process: 28 days (timeline as foreseen in the law of 7 May 2004) + 6 days for validation (+ max. 10 + max. 5 days if questions during validation)+ max. 12 additional days if list of questions => max. 61 days

Step	DAY
Confirmation of receipt to Sponsor (dossier + payment)/beginning of validation	Date submission = T0 - 6
Notification of the validation status to the sponsor: <ul style="list-style-type: none"> - Dossier complete => beginning of assessment - Dossier still not complete after max. 15 additional days (10 for the sponsor to answer the request for additional info + 5 for the national contact point to verify if the dossier is complete after answer from the sponsor). => dossier refused 	T0 (+ max. 10 + max. 5 if questions during validation)
Compiled assessment report for part I and/or assessment for part II available (depending from the scope of the substantial amendment) : <ul style="list-style-type: none"> ⇒ Direct approval at T28 at the latest if no questions from FAMHP or EC ⇒ List(s) of questions provided by the national contact point to the sponsor 	T23
Response on questions by sponsor due by (Clock stop of maximum 12 days if list of questions)	T23 (+ max. 12 days)
Review of the answers by FAMHP and/or ethics Committee and final coordinated decision sent by the national competent authority by	T28

4) National Substantial Modification for a phase I mono-national trial

Maximum duration of process: 15 days (timeline as foreseen in the law of 7 May 2004) + 5 days for validation (+ max. 10 + max. 5 days if questions during validation) + max. 12 additional days if list of questions => max. 47 days

Step	DAY
Confirmation of receipt to Sponsor (dossier + payment)/beginning of validation	Submission date = T0 - 5
Notification of the validation status to the sponsor: <ul style="list-style-type: none"> - Dossier complete => beginning of assessment - Dossier still not complete after max. 15 additional days (10 for the sponsor to answer the request for additional info + 5 for the national contact point to verify if the dossier is complete after answer from the sponsor). => dossier refused 	T0 (+ max. 10 + max. 5 if validation questions)
Compiled assessment report for part I and/or assessment for part II available (depending from the scope of the substantial amendment) : <ul style="list-style-type: none"> ⇒ Direct approval at T15 at the latest if no questions from FAMHP or EC ⇒ List(s) of questions provided by the national contact point to the sponsor 	T10
Response on questions by sponsor due by (clock stop of maximum 12 days if list of questions)	T10 (+ max. 12 days)
Review of the answers by FAMHP and/or ethics Committee and final coordinated decision sent by the national competent authority by	T15

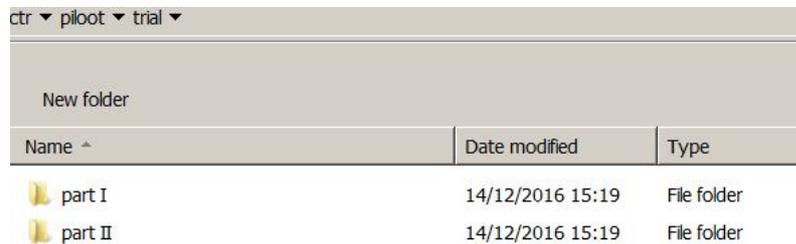
8. Annex II

Dossier structure as per Regulation 536

INITIAL APPLICATION

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

1. Please use a folder structure with part I and part II



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

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

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

APPLICATION DOSSIER FOR THE INITIAL APPLICATION

part I

A. Fulfilment of INTRODUCTION AND GENERAL PRINCIPLES

B. COVER LETTER

C. EU APPLICATION FORM

D. PROTOCOL

E. INVESTIGATORS BROCHURE (IB)

F. DOCUMENTATION RELATING TO COMPLIANCE WITH GOOD MANUFACTURING PRACTICE (GMP) FOR THE INVESTIGATIONAL MEDICINAL PRODUCT

G. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)

1.1. Data relating to the investigational medicinal product

1.2. Simplified IMPD by referring to other documentation

1.3. IMPD in cases of placebo

H. AUXILIARY MEDICINAL PRODUCT DOSSIER

I. SCIENTIFIC ADVICE AND PAEDIATRIC INVESTIGATION PLAN (PIP)

J. CONTENT OF THE LABELLING OF THE INVESTIGATIONAL MEDICINAL PRODUCTS

part II (INFORMATION PER MEMBER STATE CONCERNED)

K. RECRUITMENT ARRANGEMENTS

L. SUBJECT INFORMATION, INFORMED CONSENT FORM AND INFORMED CONSENT PROCEDURE

M. SUITABILITY OF THE INVESTIGATOR

N. SUITABILITY OF THE FACILITIES

O. PROOF OF INSURANCE COVER OR INDEMNIFICATION

P. FINANCIAL AND OTHER ARRANGEMENTS

Q. PROOF OF PAYMENT OF FEE

R. PROOF THAT DATA WILL BE PROCESSED IN COMPLIANCE WITH UNION LAW ON DATA PROTECTION

3. File format

Please apply the PDF file format except for the EudraCT application form, which in addition to the PDF format, must be in XML format.

Some requirements for the preparation of these PDF files:

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

4. File names

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

Example:

EudraCT Number-Name of file.pdf
2010-090094-00-Cover-Letter.pdf

Special cases:

1) To name the scanned pages of the documents with signatures we ask you to add "signature" in the name.

Example: 2010-090094-00-Application-Form-Signature.pdf

2) In case the document refers to a particular medicinal product (investigational medicinal product or authorized medicinal product) we ask you to add the name of this medicinal product in the filename.

Example: EudraCT Number-Manufacturing-Authorisation-Name of the medicinal product.pdf

PART I

Document	Name	Annex I Regulation No 536/2014	References
Cover Letter	Cover-Letter.pdf	B	Pilot project number
EU application Form	Application-form.pdf	C	EU Application Form (the current EU Application Form should be used during the pilot as a new CTR Application Form is not yet available)
Protocol	Protocol.pdf	D D 24.	See also ICH E6 GCP The protocol shall be accompanied by a synopsis of the protocol. The first act of recruitment (e.g. advertising) should be specified.
Investigator's Brochure	Investigators_Brochure.pdf	E	See also ICH E6 GCP
Documentation relating to GMP for the IMP <ul style="list-style-type: none"> • Copy of the manufacturing authorisation • Certification by the Qualified Person • ... 	<ul style="list-style-type: none"> • Manufacturing-Authorisation.pdf • QP-Declaration.pdf • ... 	F	GMP certificates not accepted, only GMP manufacturing authorisations EU template strongly recommended for QP declaration
Investigational Medicinal Product Dossier	Impd.pdf	G	See also Eudralex volume 10 chapter III for content and Common Technical Document (CTD) format. GLP statement has to be part of the IMPD (see: point 44. Of annex I of the CTR and http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/QAs_document_on_GLP_-_2017.pdf)

Simplified Investigational Medicinal Product Dossier	Simplified-Impd	G	See CTR (annex I points 50 to 53) to see cases when a simplified IMPD is accepted
Summary of product characteristics	Smpc.pdf	G	If applicable
Auxiliary Medicinal product Dossier	Ampd.pdf	H	AMPD or SmPC if applicable
Copy of the summary of scientific advice	Scientific-Advice.pdf	I 56	If applicable
Copy on the agreement on the PIP	PIP.pdf	I 57	If applicable
Content of the labelling	Labels.pdf	J	Example of the planned label in accordance with annex 13 of the GMP
Proof of payment of fee Part I	Proof-of-Payment-PartI.pdf	Q	Mandatory

PART II (no specific cover letter for part II)

Document	Name	Annex I Regulation No 536/2014	References
Recruitment arrangements, unless described in the protocol	Recruitment-arrangements.pdf	K 59	
Advertising material	Advertising-material-name.pdf	K 60	
Subject (and legally designated representative) information and informed consent	ICF-language-target group.pdf	L 61&63	<p>Use of the existing template strongly recommended – possible update in 2017 To be submitted in all languages that will be used in Belgium.</p> <p>Sponsor is responsible for appropriate translations. The EC only reviews the ICFs in one language.</p>
Informed consent Procedure	ICF-procedure.pdf	L 62	Has to be provided.
List of the planned sites, name and position of PI and planned number of subjects at the sites	Planning.pdf	M 64	
CV and declaration of interest of the investigators	CV-name.pdf & DOI-name.pdf	M 65&66	<p><u>CV</u>: diplomas have to be listed.</p> <p>GCP training should be documented (in the CV or by a GCP certificate)</p> <p>Proposed template (not mandatory): TransCelerate template (available in the structure zip file on the FAMHP website)</p> <p><u>Declaration of interest</u>: The FAMHP recommends to use the following form https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048310.pdf</p>

			<p>With the following explanation</p> <p>https://www.ecfr.gov/cgi-bin/text-idx?SID=c6ab674f8ec325be440c8b408bc55e4a&mc=true&node=pt21.1.54&rqn=div5</p>
Statement on the suitability of the sites	Suitability-statement-namesite.pdf	N	<p>Most recent version of the written statement issued by the site.</p> <p>Template available in the structure zip file in on the FAMHP website.</p> <p>It is advised to contact the sites as soon as possible when identified in order to have the written statements ready at the time of submission</p> <p>.</p>
Proof of insurance cover or indemnification	Proof of Insurance Cover.pdf	O	<p>Certificate with specification of the amount insured and reference to the Belgian law (7/5/4)</p>
Brief description of the financing of the CT	Financing.pdf	P 69	
Information on financial transactions and compensation paid to subjects and investigator/site	Budget-namesite.pdf	P 70	<p>Draft version with (draft) amounts is currently accepted</p> <p>It is advised to contact as soon as possible the CTCs of the concerned sites in order to gain time in the evaluation of the financial agreements.</p>

Description of any other agreement	Agreement-namesite.pdf	P 71	Clinical trial agreements and others with relation to the trial
Proof of payment of fee Part II	Invoicing-details.pdf	Q	During pilot, EC to be paid directly, invoicing details to be added to submission file
Statement that data will be collected and processed in accordance with Directive 95/46/EEC	Data-Protection-Statement.pdf	R	

SUBSTANTIAL MODIFICATIONS

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

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

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

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

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

APPLICATION DOSSIER FOR SUBSTANTIAL MODIFICATIONS

- A. Fulfilment of 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
- G. PROOF OF PAYMENT OF FEE for part I/II (INFORMATION PER MEMBER STATE CONCERNED)

2. File format

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

Some requirements for the preparation of these PDF files:

1. The files must allow "copy/paste" and other changes. If the source file is no longer available, the applicant can provide a scanned copy. However he must provide readable documents.
2. Certificates, licenses, authorizations and other documents with a signature must be scanned.
3. The layout should be as clear as possible. If possible a detailed table of contents must be included in order to find quickly specific sections of text.
4. Files should not be locked by a password.
5. Each part of the application dossier for the substantial modification should be a separate file.
6. The names of these files must follow the syntax described below.
7. The PDF version of the Modification Application Form must be saved twice: a first part corresponding to the entire form and the second part with only the signed page that has been scanned.
8. An extract from the amended documents or the amended document itself showing previous and new wording in track changes, as well as the extract/document only showing the new wording must be provided. A summary of changes must also be provided. If the summary of changes and the track changes version(s) of the updated documents are not present, this will be a validation question.
9. Regarding modifications to the Reference Safety Information:
in view of the upcoming update of the CTFG Q&A document on RSI (Q1 2017), the sponsor should fully comply with the Q&A during the IB updates that follow its publication. This will in particular concern the format of the RSI.

3. Filenames

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

Example:

EudraCT Number-Name of file. pdf
2010-090094-00-Cover-Letter. pdf

Special cases:

1) To name the scanned pages of the documents with signatures we ask you to add "signature" in the name.

Example: 2010-090094-00-Modification-Application-Form-Signature. pdf

2) In case the document refers to a particular medicinal product (investigational medicinal product or authorized medicinal product) we ask you to add the name of this medicinal product in the filename.

Example: EudraCT Number-Manufacturing-Authorisation-Name of the medicinal product.pdf

Document	Name	Annex II Regulation No 536/2014	References
Cover Letter	Cover-Letter.pdf	B	Pilot project number
Modification Application Form	Modification-Application-Form.pdf	C	Modification Application Form (the current Substantial Amendment Notification Form should be used during the pilot as a new CTR Modification Application Form is not yet available)
Description of the modification	e.g. Protocol-edition-date.pdf Protocol-edition-date-TC version.pdf Investigators-Brochure-edition-date.pdf Investigators-Brochure-edition-date-TC version.pdf Impd-edition-date.pdf Impd-edition-date-TC version.pdf Summary-of-changes.pdf ICF-language-target group-edition-date.pdf ICF-language-target group-edition-date-TC version.pdf ...	D	See ICH E6 GCP/EudraLex volume 10 Track changes version(s) must be provided! A summary of changes must be provided! Use of the existing template strongly recommended – possible update in 2017 To be submitted in all languages that will be used in Belgium.
Supporting information	e.g. Benefit-Risk.pdf, Justification-of changes.pdf...	E	
Update of the EU Application Form	Application-form.pdf	F	Revised version of the EU Application Form (with changes clearly highlighted)
Proof of payment of fee for part I/II	Proof-of-Payment-PartI.pdf Invoicing-details.pdf	G	Mandatory During pilot, EC to be paid directly, invoicing details to be added to submission file.