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### Addendum to the CTR pilot project guidance for participating parties

| Your letter from | Your reference | Our reference | Annex | Date       |
|------------------|----------------|---------------|-------|------------|
|                  |                | FAMHP/R&D     |       | 17.12.2020 |

## CTR pilot project VHP plus process Version 2.0

Dear Madam,  
Dear Sir

With this addendum to the CTR pilot project guidance for sponsors we would like to introduce the VHP plus process in the context of the CTR pilot project.

**Sponsors interested to participate to the VHP plus in the CTR pilot project are kindly requested to contact the national contact point via [CTRpilot@afmps-fagg.be](mailto:CTRpilot@afmps-fagg.be).**

## Document revision history

| Date of publication | Revision description   |
|---------------------|--|
| 25.02.2019, V1.0    | N/A  |
| 22.07.2019, V1.1    | 4. Table work process flow page 5.: alignment to the VHP timeline : answers from the sponsor on Part II to be provided for day 49 (instead of day 50 in the last version). |
| 17.12.2020, V2.0    | 7. Substantial modifications   |

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## 1. Definitions, conventions and abbreviations

**ATMP:** advanced therapy medicinal product

**BE:** Belgian

**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 main guidance on the CTR pilot project

**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. See: <http://www.ct-college.be>

**DAR:** draft assessment 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 Products

**GNA:** ground for non acceptance

**HMA:** Heads of Medicines Agencies

**ICF:** inform consent form

**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 national contact point will be the following e-mailbox: [CTRpilot@afmps-fagg.be](mailto:CTRpilot@afmps-fagg.be).**

**P-NCA:** participating national competent authority

**Ref.-NCA:** reference-national competent authority (as mentioned in the VHP guidance document)

**RFI:** request for additional information (following Regulation (EU) No 536/2014)

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

**TC:** teleconference

**VHP:** voluntary harmonisation procedure

**VHP-A:** VHP-administrator

**VHP guidance document:** guidance document for sponsors for a voluntary harmonisation procedure (VHP) for the assessment of multinational clinical trial applications, available on the HMA website:

[http://www.hma.eu/fileadmin/dateien/Human\\_Medicines/01](http://www.hma.eu/fileadmin/dateien/Human_Medicines/01)

[About HMA/Working Groups/CTFG/2016\\_06\\_CTFG\\_VHP\\_guidance\\_for\\_sponsor\\_v4.pdf](http://www.hma.eu/fileadmin/dateien/Human_Medicines/01/About_HMA/Working_Groups/CTFG/2016_06_CTFG_VHP_guidance_for_sponsor_v4.pdf)

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

## 2. What is the VHP plus in the CTR pilot project?

The VHP plus process in the Belgium CTR pilot project is the combination of the VHP plus process as described in the VHP guidance document (with participation of the evaluating EC in the assessment of the VHP package) with the parallel submission of the Part II of the CTA dossier to the FAMHP (NCP) in the Belgium CTR pilot project.

The independent and volunteer evaluating EC will be selected by the College in accordance with the CTR pilot project process.



### 3. How to participate to the VHP plus in the CTR pilot project?

The sponsors that are interested to participate to the VHP plus are referred to §4.1. and §8.1 (information on Part II only) of the CTR pilot project guidance for sponsors.

The new version of the letter of intent "form" available on the FAMHP website, introduces the VHP plus option ([https://www.famhp.be/en/human\\_use/medicines/medicines/research\\_development/clinical\\_trials](https://www.famhp.be/en/human_use/medicines/medicines/research_development/clinical_trials)).

The sponsor is also asked to indicate whether Belgium is selected as P-NCA in the VHP procedure or as Ref.-NCA.

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

The NCP and the College will decide on a case by case basis whether the proposed CTA dossier can be processed in the CTR pilot project and if Belgium can play the role of Ref-NCA in the VHP procedure.

### 4. Practical procedure

Assessment of Part II will run in parallel of the VHP process, with some adaptations as there are no exchanges with other member states during assessment of Part II. However the Part II process will begin and end at the same moment as the VHP (Part I) process.

Both processes will be pre-submission processes as national legal submission of Part I (with BE EU application form and BE labels) and Part II (with statements of suitability of the sites) will be performed after the end of the VHP process. At the moment of the national submission of Part I and Part II, a word document listing all documents has to be submitted with the cover letter.

Part II of the dossier is to be structured as described in the CTR pilot project guidance for sponsors. An empty structure zipped file is available on the FAMHP website from which the empty structure for Part II can be taken.

In order to ease the submission of the Part II of the dossier to the NCP via CESP at the same moment as the submission of the VHP package to the VHP administrator it will be accepted that ICFs and other patient documents are only submitted in the language of the evaluating EC. For this, the list of involved sites in Belgium will have to be sent as soon as possible to the NCP so that the College can select the evaluating EC. As soon as the evaluating EC is selected, the sponsor will be informed by the NCP of the selected EC and of the requested language for patient documents.

Questions on Part II will be sent to the sponsor by the NCP at day 32 of the VHP process (Part I), so that the sponsor receives the questions on Part I (from the ref.-NCA) and the questions on Part II (from the NCP) at the same moment.

The sponsor can thus modify the ICFs (if applicable) taking into account:

- the modifications of the protocol as asked in the VHP (if applicable)
- the questions from the evaluating EC on patient documents.

Updated ICFs (if applicable) should be provided at the moment the sponsor answers the questions on Part II and at the latest at day 49 of the process.

ICFs submitted at the moment of the national official submission will be the updated ones provided at the moment of the submission of the answers on Part II (maximum at day 49) and approved by the EC at day sixty during the parallel Part II process.

The following table presents the work process flow for the VHP plus process for initial trials.

| VHP Step   | DAY       | Part II process with NCP   |
|--|-----------|--|
| Submission of VHP package to VHP-A and confirmation of receipt sent to Sponsor   | <b>-5</b> | submission of Part II via CESP to NCP  |
| Date informing NCAs on VHP/VHP-Dossier location in VHP area                      | -5        | beginning validation of Part II by NCP   |
| Final acknowledgement of receipt to sponsor                                      | <b>0</b>  | Part II dossier should be complete at day 0 of VHP (except written statements), ICFs and other patients documents included <b>in the language of the evaluating EC</b>                         |
| DAR/GNAs to be stored in VHP-area/VHP-Database by Ref.-NCA                       | 20        |  |
| Statement on ASR/GNAs by P-NCAs and additional GNA to be entered in VHP-database | 25        |  |
| Date of consolidated List of GNAs by Ref-NCA in VHP-Database due by              | 28        |  |
| Date acceptance P-NCA of consolidated list of GNA                                | 29        |  |
| TC on GNA before   | 30        |  |
| Info of sponsor on GNAs by   | <b>32</b> | questions on part II (RFIs) sent to the sponsor  |
| Response on GNA by sponsor due by  | 42        |  |
| Assessment of response by Ref.-NCA in VHP-area/VHP-database by                   | 49        | answers from the sponsor on Part II to be provided for <b>day 49 (17 days timeline to answer)</b>  |
| Response of P-NCAs on assessment by Ref.-NCA in VHP-database by                  | 56        |  |
| Final ASR by Ref-NCA to be stored in VHP-area by                                 | 57        |  |
| TC on unsolved GNA before  | 58        |  |
| End of VHP/final info to sponsor   | <b>60</b> | final info to the sponsor on Part II by NCP  |
| National applications by sponsor   | <b>80</b> | mandatory submission of written statements (sites suitability statements and translations of participant's documents in all languages of the participants) with official submission of Part II |
| National approval by NCA   | <b>90</b> | EC approval letter to the sponsor at the latest for day 90   |

Sponsors are kindly requested to provide a word list of documents submitted with dates and/or version of each document and to update this word list of submitted documents with the answers to the validation questions (if applicable), the answers to the Request For Information (RFI, if applicable) and with the answers to the condition(s) (if applicable) in case new documents are submitted or in case some documents have been updated.

A template for this word list of submitted document is available in the initial dossier zipped structure available on the FAMHP website.

## 5. National legal submission and approval of the CTA dossier

As foreseen in the VHP guidance for sponsors, the national legal submission of the CTA to the FAMHP (NCP) by the applicant/sponsor should normally not be later than twenty days after receipt of the VHP acceptability statement or statement on the fulfilment of conditions.

The sponsor is requested to submit the entire CTA dossier (Part I and Part II) at that moment.

Both official letters (from the EC and from the FAMHP) will be provided to the sponsor maximum ten days after the national legal submission of the CTA dossier.

In case a conditional approval is issued by the evaluating EC on Part II and an approval of Part I by the ref.-NCA in VHP, the sponsor is requested to submit the entire CTA dossier (Part I and Part II) within twenty days after conditions on Part II are met.

## 6. Payment of the fee

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

## 7. Substantial modifications (SMs)

Sponsors are kindly requested to provide a word list of documents submitted with dates and/or version of each document and to update this word list of submitted documents with the answers to the validation questions (if applicable), the answers to the Request For Information (RFI, if applicable) and with the answers to the condition(s) (if applicable) in case new documents are submitted or in case some documents have been updated. A template for this word list of submitted document is available in the SMs dossier zipped structure available on the FAMHP website.

### 7.1. General principles

There are three possible situations.

- 1 **Substantial modifications (SMs) only related on Part I** are evaluated within the VHP amendment process (involving an evaluation by a Ref.-NCA). This is a pre-submission process. Official national submission is to be performed after VHP approval.
- 2 **SMs only related on Part II** are evaluated within the usual Belgian pilot project process as described in the CTR pilot project guidance for sponsors. This is a direct national official submission. A direct national decision is given at the end of the process.
- 3 The assessment of **SMs related on both Part I and Part II** will run in parallel: assessment of Part I by a Ref.-NCA and assessment within the Belgian pilot project process following the same principle as for the initial CTR pilot project VHP plus dossiers. Therefore part II questions can be provided by the evaluating ethics committee and sent to the sponsor by the NPC if applicable. Both processes (on Part I and on Part II) will be pre-submission processes as national legal submission of Part I and Part II will be performed after the end of the VHP process. In case questions on part II of the SMs are issued the sponsor is asked to provide answers at the moment of the national official submission of the SMs.

Depending on the Part of the dossier which is subject to SMs (SMs Part I/SMs Part II/SMs Part I and Part II), the three types of processes to be followed are described here below.

### 7.2. SMs only related to Part I

The VHP process for SMs will be followed (with evaluating EC involved if applicable).

We refer you to the [VHP guidance for sponsors](#) available on the HMA's website for details on the process and timelines.

The SM application has to be submitted to the VHP-A.

In this process, no questions can be sent to the sponsor during the procedure: after evaluation by the Ref.-NCA and exchanges between the P-NCAs, a final decision is directly provided to the sponsor at maximum day 35. The SM is approved, approved with conditions or refused.

After the VHP process is finalised the SM is submitted nationally by the sponsor within ten days. The official FAMHP approval letter and EC approval letter (if applicable) will be provided by the NCP within seven days after national submission to the sponsor.

### 7.3. SMs only related to Part II

The usual Belgian pilot project process for SMs will be followed, as described in the CTR pilot project guidance for sponsors.

The SM application has to be submitted to the NCP (FAHMP) via CESP (see CTR pilot project guidance for sponsors available on the [FAMHP website](#)).

### 7.4. SMs related to Part I and Part II

The SM application on Part I has to be submitted to the VHP-A and the SM application on Part II has to be submitted directly to the NCP via CESP. When submitting the Part II to the NCP, indicate clearly to which VHP number and VHP SM number this submission should be linked.

In this case, both VHP amendment process for Part I and Belgian pilot project process for Part II will run in parallel and an e-mail with the decision on the modification of Part II will be sent to the sponsor by the NCP at day 35 at the latest.



Both processes will be pre-submission processes as national legal submission of Part I and Part II will be performed after the end of the VHP process.

For the Part I, no round of questions is foreseen at European level.

For Part II, questions from EC can be sent to the sponsor by the NCP at day twenty if Belgium is Ref-NCA or at day 27 if Belgium is P-NCA.

The answer of the sponsor to the questions related to Part II has to be provided at the moment of the national legal submission of Part II together with the national legal submission of Part I, at the latest ten days after VHP approval following the VHP guidance for sponsors.

Decision on part II pre-submission can be approval or approval on condition that questions sent at day 20 or day 27 are answered and provided with the national legal submission of part II.

If the VHP Part I process ends earlier than at day 35, the Part II national process will continue until the assessment of the evaluating EC on part II is available. In this case, the full approval of the EC on Part II or the questions of the EC on Part II could be provided after approval of the amendment on Part I in VHP.

After the VHP Part I process and the Part II process are finalised the SM is submitted nationally by the sponsor within ten days. The official FAMHP and EC approval letters will be provided to the sponsor by the NCP within seven days after national submission.

See table below for the timelines.

| Step  | DAY | Part II process with NCP   |
|---|-----|--|
| Confirmation of receipt to sponsor  | -5  | submission of Part II (if applicable) via CESP to NCP  |
| Date informing NCA on VHP/VHP-dossier location in VHP area  | -5  | beginning validation of part II by NCP   |
| Final acknowledgement of receipt to sponsor   | 0   | Part II (if applicable) should be complete at day 0 of VHP (except written statements if applicable), ICFs and patients questionnaires included (if applicable) in language of evaluating EC   |
| Decision on amendment (accepted, conditions proposed or refused) to be stored in VHP- area/VHP-database by Ref.-NCA | 20  | if Belgium is Ref-NCA, questions on part II sent to the sponsor if applicable  |
|   | 27  | if Belgium is P-NCA, questions on part II sent to the sponsor if applicable  |
| Decision sent to the sponsor by the Ref-NCA due by  | 35  | info to the sponsor on part II by NCP: approval or approval on condition that questions sent at day 20 or at day27 are answered and provided with the national legal submission of part II   |
| National applications by Sponsor (within ten days after VHP) approval   | 45  | official submission of part II, including mandatory submission of written statements and participants' documents in all languages of the participants and, if applicable, of answers to the questions sent at day 20 (if Belgium is Ref-NCA) or at day27 (if Belgium is P-NCA) |
| National approvals by NCA (within seven days after reception)   | 52  | EC approval letter sent to the sponsor by the NCP at the latest for day 52   |

## 7.5. Nomenclature

Independently of the VHP amendment numbers, the following pilot project VHP plus SM nomenclature is proposed in order to insure a good follow up of the different type of substantial modifications submitted after approval of the pilot project VHP plus initial dossier in Belgium.

Pilot project XXX\_SMYZ.ZZ

In this SM denomination, the YY characters are related to modifications of the Part I of the dossier and the ZZ characters are related to modifications of the Part II of the dossier.

When a new SM is submitted, the characters related to the part of the dossier concerned by the modification are incremented by 1. If the modification is **only** related to the quality aspects of the dossier, the YY characters are incremented by 1 and a "q" extension is added at the end of the SM denomination. If the quality modification is submitted together with other Part I modifications and or Part II modifications, the "q" extension is not added at the end of the SM denomination.

A table with the history of the submitted SMs, related part(s) of the dossier and approval dates will be provided in the final decision e-mail for each national SM submission.

The applicant of the next SM is asked to provide this table updated with the information and denomination related to the new modification at the end of the word list of submitted documents.

The table corresponding to the current situation for each already submitted pilot project VHP plus dossier will be provided by the NCP to each applicant at the occasion of the next SM in the final conclusion e-mail for the national submission.

Example of a SM history table

| <b>Substantial modifications history table for Pilot777_VHP plus_20XX-00XXXX-XX</b> |                                     |   |
|---|-------------------------------------|---|
| <b>Final decision date</b>  | <b>Modified part of the dossier</b> | <b>SM denomination</b>                              |
| 21.01.2021  | Part II only                        | Pilot project 777_VHP plus_20XX-00XXXX-XX_SM00.01   |
| 02.03.2021  | Part I only                         | Pilot project 777_VHP plus_20XX-00XXXX-XX_SM01.01   |
| 18.05.2021  | Part I and Part II                  | Pilot project 777_VHP plus_20XX-00XXXX-XX_SM02.02   |
| 04.07.2021  | Part II only                        | Pilot project 777_VHP plus_20XX-00XXXX-XX_SM02.03   |
| 22.09.2021  | Part I_quality only                 | Pilot project 777_VHP plus_20XX-00XXXX-XX_SM03.03.q |
| 21.11.2021  | Part I only                         | Pilot project 777_VHP plus_20XX-00XXXX-XX_SM04.03   |

## 8. Survey

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