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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		25.02.2019

CTR pilot VHP plus process
Version 1.0

Dear Madam,
Dear Sir

With this addendum to the CTR pilot 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: CTRpilot@afmps-fagg.be.

Document Revision History

Date of publication	Revision description
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Contents

1. Definitions, conventions and abbreviations

ATMP: Advanced Therapy Medicinal Products

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

CESP: Common European Submission Portal – see procedure for submission via CESP in annex III of the 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. Website: http://www.ct-college.be

DAR: Draft Assessment Report

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.

GNA: Ground for Non Acceptance

HMA: Heads of Medicines Agencies

National contact point (NCP): the FAMHP is the national contact point as defined in article 83 of the CTR. This means that for the purpose of the present project, the FAMHP will be the single contact point for the sponsor (for Part I and Part II of the dossier), without prejudice of the organisation between the competent authority and the College at the time all functionalities of the portal will be available.
From a practical point of view, for the sponsor the national contact point will be the following mailbox: CTRpilot@afmps-fagg.be

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.

VHP: voluntary harmonised procedure.

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 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 BE 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).

The independent and volunteer evaluating EC will be selected by the College in accordance with the CTR pilot 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 guidance for sponsors.

The new version of the letter of intent “form” available on the FAMHP website introduces the VHP plus option.

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 VHP plus process is to be provided by E-mail to the specific E-mail address for the pilot: 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 and if Belgium can play the role of RMS 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.

Part II of the dossier is to be structured as described in the CTR pilot 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 50 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 (max. at day 50) and approved by the EC at day 60 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
Confirmation of receipt to Sponsor	**-5**	submission of Part II 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 dossier should be complete at day 0 of VHP (except written statements), ICFs and other patients documents included **in the language of the evaluating EC.**
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-DB	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	**32**	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 **day 50 (18 days timeline to answer).**
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	**60**	Info to the sponsor on Part II by NCP
National applications by Sponsor	**80**	Mandatory submission of written statements (sites suitability statements) with official submission of Part II
National approval by NCA	**90**	EC approval letter to the sponsor at the latest for day 90

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

5. 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 20 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 10 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 20 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 (nor to the FAMHP, nor to the evaluating Ethics Committee).

7. Substantial modifications

The VHP plus process for substantial modifications will be presented in the next version of this addendum.

8. Survey

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