Clinical Trials Facilitation and Coordination Group

Guidance document for sponsors for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications

Version 5

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1 Abbreviations

ATMP	Advanced Therapy Medicinal Product
CA	competent authority
CT	clinical trial
CTFG	clinical trials facilitation and coordination group
CTA	clinical trial application
EC	ethics committee
EU	European Union
FIH	first in human
HMA	EU Heads of Medicines Agencies
MN-FIH	multinational first in human
GMO	medicinal products containing or consisting of genetically modified organisms
GNA	grounds for non-acceptance
IB	Investigator's Brochure
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
MA	marketing authorisation
MC-CT	multicentre clinical trial
MS	member state
MN-CT	multinational clinical trial
lead REF-NCA	REF-NCA leading the assessment of a SA applicable to several CT
NIMP	Non IMP
NCA	national competent authority
P-NCA	participating national competent authority
PIP	paediatric investigational plan
REF-NCA	reference – national competent authority
SR-VHP	second round VHP: introduction of one or more MS into a positive VHP
VHP	voluntary harmonisation procedure
VHP-A	VHP-Administrator (mail: VHP-CTFG@VHP-CTFG.eu)
VHP-C	VHP-Coordinator
VHP plus	A VHP involving Ethics Committees in the assessment of benefit/risk; IB and protocol in some Member States
VHP-SA	substantial amendment of a positive Voluntary Harmonisation Procedure

2 Introduction

The EU Heads of Medicines Agencies (HMA) agreed in 2004 to establish a clinical trials facilitation group (CTFG) to co-ordinate the implementation of the EU clinical trials directive 2001/20 EC across the member states.
This document is produced by the CTFG in order to propose VHP as a harmonised procedure for assessing multinational clinical trials by the National Competent Authorities (NCA) in EU. The changes of this new version of the guideline were approved by the HMA.
This document should be read in conjunction with other EU-published guidelines (see also Section References).

The main changes in v2 with respect to v1 refer to:

a) the acceptability of all CTs with at least 3 concerned MS
b) the deletion of the *"Pre-procedural step" or "Request for VHP"* phase in the procedure and
c) the inclusion of substantial amendments in the scope of the VHP

The main changes in v3 with respect to v2 refer to:

a) the introduction of a mandatory Reference NCA
b) the introduction of a second round to introduce one or more additional MS into a positive VHP
c) the procedural steps to address the fulfilment of conditions
d) the introduction of information requests in VHP-substantial amendment
e) VHP plus

The main changes in v4 with respect to v3 refer to:

a) Change of responsibilities from VHP-C to REF-NCA
b) minor clarifications

The main changes in v5 with respect to v4 refer to:

a) VHP also for CT on GMO MP

The CTFG is open for discussions on further improvements. Suggestions or feedback should be sent to VHP-CTFG@VHP-CTFG.eu indicating on the message reference "suggestion for improvement of VHP or feedback on VHP……".

3 Background/Rationale

The Directive 2001/20/EC, (the "EU Clinical Trials Directive")[I], relating to the implementation of good clinical practice in the conduct of clinical trials (CT) on medicinal products for human use, defines a multi-centre clinical trial (MC-CT) as a CT conducted according to a single protocol but at more than one site, and therefore by more than one investigator. The trial sites may be located in a single Member State (MS), in a number of MS, or in one or more MS and additionally in third countries. This document relates to a MC-CT with trial sites in several MS, referred to as multinational CTs (MN-CTs) throughout this document.
In the context of the implementation of Directive 2001/20/EC and with the aim to harmonise the conduct of CTs within EU MS, the EU-Commission has issued detailed guidances and information regarding major aspects of clinical trials, such as the format of requests to Competent Authorities (CA) and of CT information to be submitted to Ethics Committees (EC), the reporting of adverse reactions arising from CT, the documentation on the quality of the Investigational Medicinal Product (IMP) and the European clinical trial database EudraCT (EudraLex - Volume 10 Clinical trials guidelines).
To coordinate the implementation of Directive 2001/20/EC across the MS at an operational and national level, the EU Heads of Medicines Agencies have set up the Clinical Trials Facilitation and Coordination Group (CTFG). This is another major step for the achievement of harmonisation of CTs in Europe.

With the translation of the Directive into national laws and regulations, divergent practices between the different MS remain in areas such as:

- Distribution of duties between the CAs and the ECs
- Content, format or language requirements
- Timelines for the review of a CT application
- Different application dates by the sponsor in the different MS
- Human resources and workload vs. the number of applications per NCA

Further to October 2007, CTs Conference, organised by the European Commission and EMA, and the experience in the Member States, the importance of maintaining the following general principles for the conduct of clinical research in the EU has been recognised:

- Protect clinical trials participants
- Ensure high-quality research in the EU
- Contribute to a favourable research environment in EU
- Bring innovative medicines to patients as quickly as possible

For these reasons, the need to harmonise MN-CTs in Europe in order to ensure the protection of participants as well as the scientific value of CTs by the means of harmonising NCAs' processes and practices relating to MN-CTs (about 25% of CTs in EU), has become a priority for the CTFG. Thus, the organisation of coordinated assessment of MN-CTs through the Voluntary Harmonisation Procedure (VHP) has been a major objective of the CTFG work plan after 2008. This procedure has been set up within the current legal frame-work for CTs.

With the new Regulation for CT (EU Regulation Nº 536/2014) the coordinated assessment of multinational trials will be addressed and this will limit the need for VHP, which will then be terminated when the Regulation comes into force for all clinical trials.

On the basis of the experience with the VHP from 2009 to 2016, the CTFG developed updated versions of the VHP guidance: the procedure has been modified in order to streamline the assessment, to shorten the timelines and now to establish a second round and to regulate a VHP with conditions. For each VHP, one of the participating NCA i.e. REF-NCA takes the lead in the scientific assessment and the consolidation of the grounds for non-acceptance.
Procedural steps such as internal assessment reports and rapporteurships (i.e. REF-NCA) have been included in the VHP since September 2011.

Before the implementation of the new EU Regulation Nº 536/2014 for CT the MS plan to reflect the situation of missing central organisation by transferring the coordination duties to the respective REF-NCA in order to gain experience.

4 Scope and general principles

On the one hand, a harmonisation procedure of the assessment occurring after the application of a CT in the different MS is foreseen difficult to achieve and may even be counterproductive by adding an additional step at the end of an already lengthy process. On the other hand, taking into account the current legal framework, each NCA remains responsible for the approval of a CTA in its own country. Therefore, a harmonisation procedure for the assessment of MN-CT applications is proposed i) before the initial phase of the national process, and ii) on a voluntary basis.

The main objectives of the assessment of the CT are to ensure the quality of the IMP and the safety of the trial subjects.

All MN-CTs involving 2 or more MS willing to participate are eligible to undergo the VHP.

Where a sponsor intends to run a MN-CT, the VHP application should include ALL those EU NCAs planned to be involved in the clinical trial (before and after a VHP submission). The list of MS participating in VHP is published in the HMA/CTFG web site[1].

In the case of CT on GMO, a standard VHP dossier should be provided, VHP assessment would be limited to that related to the CT legislation and timelines would be those indicated in section 9.1.2. However, sponsors should take into account that there are specific national requirements for this kind of CT to be accomplished before the CT start including the need for a MS authorisation taking into account the GMO environmental legislation[1,2]. In VHP on GMO CT applications the P-NCA should be limited to those having indicated agreement to participation in VHP for CT on GMO MP in the document "List of participating member states in VHP"[1].

The sponsor should not mix between the national route and VHP for a CT, unless parallel national applications to the NCA only refer to MS not participating in such VHP CTA or the sponsor is directed to do so by the VHP-A. However, parallel national submission to Ethic Committees should be considered by the sponsor too in order to save time (see also VHP plus below). If a mixture of national routes and VHP will be noticed, outside the previous acceptable exceptions, this will lead to the immediate stop of the VHP in all Member States. If, following a positive VHP, the sponsor wishes to include further NCAs, the "second round" approach can be used (see section 7).
In general no fees will be charged for VHPs or VHP-SA; the costs of the NCAs will be covered by the national applications to the NCAs. If the CT in the VHP is finally rejected, withdrawn by the applicant or finally not conducted in a MS as per sponsor´s decision, the applicant should contact the NCA in order to know how the payment should be made. In cases where these payments are refused the permanent exclusion of this sponsor from any further VHP will be considered.

VHP Plus

Some MS involve EC in the VHP applications (named as VHP plus). This procedure only requires submission of standard VHP content. No additional documents for EC have to be submitted in a VHP plus procedure.

A list of the NCA's participating in VHP plus and the specific conditions to do so is available on the CTFG website[1].

The sponsor needs to specifically request in the cover letter a VHP plus, indicating the name of the EC per MS participating in VHP plus unless different instructions are given related to VHP plus in the document "List of participating member states in VHP"[1], and

[1] Please consult "List of participating member states in VHP" in https://www.hma.eu/ctfg.html
[2] https://ec.europa.eu/health/human-use/advanced-therapies/gmo_investiganional_en

submit the VHP package to the VHP-A. VHP-A would circulate the documents to P-NCA and P-NCA would submit the cover letter, protocol, IB and documents on the benefit-risk to the EC.

Note:

1. VHP plus is not to be confused with pilot procedures of EU Regulation 536/2014/EC of some MS to involve EC in the assessment of complete national Clinical Trial Applications[3]

2. VHP plus documents should only be submitted to the VHP-A (i.e. not direct submission to the EC).

5 Definitions

- VHP-Administrator (VHP-A: the CFTG representative of the NCA in charge of transfer of requests, responses and further information submitted by the applicant to the member states, maintenance of the VHP area and VHP database.

- Participating NCAs (P-NCAs): the NCAs concerned by the CT and wishing to participate to the VHP on a voluntary basis.

- REF-NCA: the NCA responsible in collaboration with the concerned P-NCAs for the principal scientific assessment, the consolidation of the grounds for non-acceptance, and the reassessment of the response of the sponsor to the GNA and for communication with the VHP applicant.

- The “VHP applicant”: a sponsor, whoever is submitting a request for VHP of a MN-CT to the CTFG.

- Request for VHP: the letter from the VHP applicant, requesting a planned MN-CT to undergo the VHP. The applicant should describe the key features of the CT and indicate which EU countries will be involved in the MN-CT. The request for VHP should also contain all the documentation required for the assessment of the CTA through the VHP. The content of the VHP application is detailed under section “Format and content of the VHP application”.

6 Outline of the VH procedure

The VHP comprises three phases:

- Phase 1: Request for VHP and validation of the application
- Phase 2: Assessment step: review of a CTA by the NCAs of the participating MS,
- Phase 3: National step, with formal CTAs to all concerned NCAs

Phase 1 and 2 are actually composing the submission phase to the CTFG. Phase 3 is the formal submission of a CT to each NCA according to the national regulations.

6.1 Request for VHP and validation of the application

In the request for VHP, the applicant should provide the documents indicated in section 9.2. The sponsor is requested to propose one of the P-NCAs as REF-NCA. This proposal is not binding for the NCAs and might be internally overruled by the decision of the P-NCAs.

The following points should be noted:

A. If the proposed REF-NCA refuses to be the REF-NCA and no other P-NCA volunteers for REF-NCA, the VHP application will be rejected. The decision will be given to the applicant within 5 working days after receipt at VHP-A.
B. If no REF-NCA is proposed in the initial VHP application, a REF-NCA proposal will be requested by the VHP-A. If the proposed P-NCA refuses to be the REF-NCA and no other P-NCA volunteers for REF-NCA, the VHP application will be rejected. The decision will be given to the applicant after the validation step via the VHP-A.
C. The numbers of REF-NCA ships/rejections of REF-NCA ships per MS will be published according the rules agreed by HMA in the section Clinical Trials Facilitation and Coordination Group (HMA web site).

At any time, the applicant informs the VHP-A by sending the request for VHP to VHP-CTFG@VHP-CTFG.eu via e-mail/Eudralink, highlighting important features of the MN-CT and the documentation required for the assessment of the CTA.

Upon receipt of the request and VHP-documentation, the VHP-A creates a new file in the VHP database and allocates a VHP number.

The complete VHP-documentation is forwarded electronically, if applicable, by VHP-A to the P-NCAs immediately after receipt.

A CT is eligible for VHP if a CTA is not already submitted or approved in a European Member State prior or during VHP.
During a VHP only parallel national CTA in those countries, who have rejected to participate in VHP, are acceptable. After a VHP, a second round submission in VHP is recommended in order to add new participating MS (see section 7).

Within 5 working days after receipt, the VHP-A informs the applicant whether all requested NCA will participate and which NCA will take over the REF-NCAship. Validation of the dossier will also be performed and the applicant will be informed of any deficiencies or, if complete, the starting date of the VHP.

All timelines in the VHP are calendar days with one exception: the 5 working days between initial submission and confirmation by the VHP-A (day 1) and the 5 working days when submitting VHP-substantial amendment (VHP-SA) (8.1).
If applications/responses etc from applicants arrive outside normal business hours, the next working day will be assumed as reception date.

6.2 VHP CTA assessment step

Of note, the timelines of 60 days proposed hereby are maximum timelines. Whenever possible for the P-NCAs, the timelines will be shorter. The timelines for CT with ATMPs

can be extended to a total of 90 days when requested by the majority of the participating MS.
Important: After acceptance of the VHP procedure by P-NCA, communication will take place between the designated REF-NCA and the applicant only.

6.2.1 VHP Assessment Step I (Day 1-Day 32)

- In the absence of grounds for non-acceptance (GNA)
  - a statement will be sent by the REF-NCA to the applicant (copy to all P-NCAs), not later than day 32, stating that no GNA have been expressed by any P-NCA during the VHP assessment phase and that the P-NCAs unanimously consider the CTA acceptable for this MN-CT. Comments to facilitate the national submission in the MS might be added. The final step, i.e. submission of a CTA in each P-NCA, can then start (See Section 6.3 National step).

- In case of GNA:

  - A consolidated list of GNA will be forwarded to the applicant by the REF-NCA via e-mail on day 32 with a request for response to the GNA and provision of the revised CT documentation when applicable via e-mail/Eudralink by day 42 at the latest.
  - If the applicant decides to proceed, the VHP assessment step II starts on receipt of the responses together with a revised CT documentation by the VHP-A. These response documents (e.g. protocol, IMPD or IB) affected by the GNA should contain not only responses to the GNA but preferably final draft versions of the modified documents including track changes and a clean version. The version should be final in terms of version number and text but not necessarily signatures.
  - If no response from the applicant is received within the allotted time or the applicant withdraws the application, the VHP file will be closed with a notice from the REF-NCA to the applicant and the P-NCAs/VHP-A. In this case a resubmission via a new VHP is possible.

6.2.2 VHP Assessment Step II (Day 42-Day 60)

The applicant's response document is immediately dispatched by the VHP-A to all P-NCAs for review.

➢ If consensus is achieved, i.e. the revised version of the CTA is considered approvable by all P-NCAs around day 56, the REF-NCA sends to the applicant a statement by e-mail, mentioning that all GNA have been resolved and that the P-NCAs unanimously consider the revised CTA as approvable.
The final step, i.e. submission of a CTA at each participating NCA, can start (See Section 6.3 National step).
➢ If no consensus is among the P-NCAs on day 56, all P-NCAs are invited to express their views and possible solutions to the remaining issues so that a final decision can be given. Possible outcome of the procedures are:

- Unanimous decision of the NCA that the original or the revised version of the CTA is approvable: an e-mail to the applicant will be sent on day 60, mentioning that all GNA have been resolved and that the P-NCAs unanimously consider the revised CTA as approvable. Comments to facilitate the national submission in the MS might be added. The final step, i.e. submission of a CTA in each participating MS can start (See Section 6.3 National step).

- Unanimous decision of the MS that revised documents have to be submitted and agreed before the CTA can be submitted and approved nationally (conditional approval): Questions or clarification on conditions shall be provided by the REF-NCA.
- The revised documentation including track changes and a clean version should be submitted to the VHP-A within 10 days after a positive VHP with conditions. The response whether the documentation is acceptable will be given by the REF-NCA within 8 days after the submission. Before a response from the REF-NCA direct submissions of documents to the national NCA only are excluded as this could lead to non-harmonised documentation and documents. After the confirmation by the REF-NCA that all documentation is acceptable and the conditions are completely fulfilled, national applications to the NCAs should be filed (See Section 6.3 National step).

- Unanimous decision of the NCA that the revised version of the CTA is not approvable: an e-mail will be sent from the REF-NCA to the applicant on day 60 with the remaining GNAs and proposed solutions for a VHP-resubmission. Comments to facilitate national submissions in the MS or a VHP-resubmission might be added (See Section 6.3 National step). A VHP-resubmission is considered the better alternative to the submission of non-harmonised national applications to the individual MS.

- In the case that the P-NCA are not in agreement, that all GNA have been resolved i.e. divergent decision, the open points and the names of NCA, which consider GNA as unsolved, will be forwarded to the applicant. The open points have to be resolved before or in the national procedure, the timelines for the submission of the CTA (20 days, see Section 6.3) and the approval by the NCA (10 days, see Section 6.3) do not apply for the MS with unsolved GNA. Also the list of NCAs, which consider all GNA as resolved, will be forwarded. For these NCAs national CTA submission within 20 days and approval within 10 days timelines apply. (See Section 6.3) As a consequence of the divergent decision, VHP-SAs are only possible in those MS that considered the VHP as approvable.

6.3 "National step" Formal CTA

The acceptability statement following the VHP does not imply that the MN-CT is authorised by the P-NCAs. Once the applicant has been notified that the CTA is considered acceptable (at the end of the VHP assessment Step I or II), a CTA has to be submitted in each participating MS as outlined in the Clinical Trial Directive (2001/20/EC), and in information of the Commission CT-1[II], and according to national regulations of the MS.

In the covering letter for the CTA to the NCAs, the sponsor should remind the NCAs that this MN-CT has undergone the VHP and add the e-mail with the VHP approval. Generally, no changes between the final CTA and the CTA approved during the VHP (except all modifications in response to GNA) will be accepted.
This letter should indicate the versions of documents that were accepted at VHP and a statement ensuring that those versions are the ones approved in the VHP.
However, if at the end of the VHP process, a NCA has considered GNA as unsolved or if the solutions proposed by that NCA are not acceptable for the sponsor, the sponsor may decide not to file a CTA in that MS. In this case the rules for compensations are applicable (see section 4).

Submissions of the CTA to the NCAs by the applicant should normally not be later than 20 days after receipt of the VHP acceptability statement or statement on the fulfilment of conditions.

It is agreed by the MS, that after a positive VHP a decision of the NCA should be issued within 10 days and that no scientific discussion on the agreed documents of the VHP (e.g. Protocol, IB, IMPD) will be started again. In Member States where the approval of the Ethics Committees is mandatory for an approval of the NCA, the sponsor should ensure the timely application to the Ethics Committees. In cases when the Ethics Committees approval is not applied for in time/ in parallel to VHP, the 10 day obligation for NCA lapses in case of mandatory Ethics Committees approvals.

In case of unanimous decision that the trial is not approvable, it is strongly recommended that resubmission of the CTA is done via VHP.

In case the sponsor wants to add new MS to a CT that underwent a VHP the following rules for a second round VHP will apply.

7 Second Rounds of VHPs

SR-VHP is the addition of MS to a VHP after the end of a VHP (including national steps, exceptions for MS with mandatory EC approval apply; 10 days after a valid application to the NCA of such MS, SR-VHP will be accepted) and provided there is no VHP-SA under assessment.

7.1 Addition of new Member States to an ongoing Clinical trial after a VHP

In general all MS, where it is proposed that the CT will take place, should be nominated in the initial VHP by the sponsor. In exceptional cases, the addition of MS may be warranted but an addition outside a VHP is discouraged as this would lead to disharmonized CT.

If additional MS are planned to be added to an ongoing CT after a VHP, a second round of VHP should be requested. A restriction is that the number of additional MS must not exceed the number of MS in the initial VHP. The initial VHP has been completed and the CT has already been authorized by the P-NCAs (exceptions for Member States with mandatory EC approval apply; 10 days after a valid application to the NCA of such Member States, SR-VHP will be accepted) and any VHP-SA have to be finalized before a SR-VHP can be filed to the VHP-A. If one or further rounds of VHPs should be performed during an ongoing CT a justification should be given, why this is necessary.

As the function of a REF-NCA and the preparation of internal assessment reports has been started in September 2011, SR-VHPs can only be accepted for initial VHPs filed after the 01.09.2011. The addition of new MS to VHPs that were filed before 01.09.2011 should be done nationally only.

The request should contain a list of the additional MS, an updated version of the CTA including all further SA finally accepted by the initial VHP, the e-mail of the former VHP-C or the REF-NCA on final decision of the initial CTA and any other e-mails related to

VHP decisions on SA, if applicable, and the confirmation that the documentation submitted is identical to the dossier agreed through the VHP/ and following VHP-SA. Note that one or more rounds of VHP are only accepted when all substantial amendments have been submitted via VHP.

The VHP-A will forward the request for SR-VHP to the new P-NCA and the initial REF-NCA. Within 5 working days after receipt, the VHP-A informs the applicant whether all requested new P-NCA will participate. Validation of the dossier will also be performed within this time and the applicant will be informed of start of the SR-VHP and whether additional documents are required, if necessary.

7.1.1 SR-VHP Assessment Step I (Day 1-Day 32)

- Assessment by the new P-NCA will be done and a statement will be sent by the REF-NCA to the applicant not later than day 32, stating that no GNA have been expressed by the new P-NCA during the VHP assessment phase and that the CTA is considered acceptable for this MN-CT.
- The final step, i.e. submission of a CTA in each P-NCA, can then start (See Section 6.3 National step).

In case of additional GNA raised by the new P-NCA, the REF-NCA and the new P-NCA will discuss the necessity of the GNA until day 30.
If the concerns of the new P-NCA can be solved, the REF-NCA will inform the applicant not later than day 32 stating that the new P-NCAs unanimously consider the CTA acceptable.
The final step, i.e. submission of a CTA in each new P-NCA can start (See 6.3).

If the GNA are retained by the new P-NCA after the discussion, the GNA are forwarded by the REF-NCA to the applicant at day 32 and an answer is requested within 10 days according to the VHP timelines. A subsequent VHP-SA may be warranted to the MS of the first round VHP to introduce the changes of the SR-VHP.

7.1.2 SR-VHP Assessment Step II (Day 42-Day 60)

Starting at day 42, the assessment of the response will be performed by the new P-NCAs with the support of the REF-NCA.

- If consensus between the P-NCAs and the REF-NCA is achieved i.e. GNA are addressed sufficiently, the REF-NCA informs the applicant of acceptance no later than day 56.
- The final step, i.e. submission of a CTA in each new P-NCA can start (See Section 6.3 National step).

- If no consensus between new P-NCA and REF-NCA is achieved, the statement of the P-NCAs is forwarded to all P-NCAs (first and second round). All P-NCAs are invited to express their views and possible solutions to the remaining issues so that a final decision can be taken.
The possible outcome of discussions is treated as described in 6.2.2.

After a positive SR-VHP, national application of the CTA and VHP approvals should be filed by the applicant to the new P-NCAs and approved by the NCAs according to the timelines and procedures of the first round of VHP.

8 Substantial amendments

Substantial amendments (SA) related to the documents of CTAs that have undergone a VHP can be submitted, to the VHP-A, at any time, under the condition, that the CTAs have already been approved by the P-NCAs (exceptions for Member States with mandatory EC approval apply; 10 days after a valid application to the NCA of such Member States, VHPSA will be accepted). If no REF-NCA exists (as for "some old" VHPs or as for Ref-NCAs dropped out during the procedure), a volunteer for Ref-NCA for this VHP-SA will be searched by VHP-A. If no volunteer can be found this is the final stop of VHP. The decision will be given to the applicant within 5 working days after receipt at VHP-A. In this case, a resubmission is not possible.

The date of the national approvals should be given in the cover letter together with summary information on the content of the SA including information if the RSI (Reference Safety Information) has been changed, where applicable.

The notification should be made in accordance with the current version of the *Communication from the Commission - (CT-1) (2010/C 82/01)*[II] and national Guidances of the Member States should be used and appropriate documents to assess the changes of the CT should be added. The substantial amendment should be identified by a unique code number and a date.

To facilitate the assessment, all changes should be justified and the changed documents (e.g. IMPD, IB and Protocol) should be submitted with the changes highlighted or with a comparative table highlighting the before/after. When changes are complex and affecting several parts of the document, the complete document with track changes as well as a clean copy with the final version should also be submitted.

Like the documents of the original VHP, SAs should be submitted via E-Mail only to the VHP-A.

8.1 Timelines of substantial amendments

The submission of SAs to the VHP-A is possible at any time. Within the 5 working days after the submission, the submitted documentation will be validated and the applicant will be notified via e-mail of any deficiencies or of the start of the VHP-SA. If the dossier is not complete, additional information will be requested by the VHP-A and this should be submitted by the applicant within 3 days.

The result of the assessment will be communicated to the applicant within 35 days after a valid request.

Requests for limited additional explanations or clarifications may be addressed during VHP-SA. For this, the request will be forwarded to the sponsor at day 21 and a response is awaited before day 24. The decision on VHP-SA will be forwarded on day 35 at the latest.

In case of a positive statement by the REF-NCA on the VHP-SA, the applications to the P-NCA should be filed according to the national regulations within 10 days. The approval by the NCA should be issued within 7 days after the valid request (see the flow chart on VHP-SA for detailed timelines).

In case the sponsor decides to submit a SA outside the VHP-SA procedure and directly to P-NCAs further VHP-SA or SR-VHP are excluded as the documentation and/or the CT are not longer harmonised.

Generally, no changes between the SA approved during the VHP and the final national SA will be accepted.
At the time of national submission the sponsor should explicitly state in the covering letter that the information provided is the same as that has been approved by the VHP.

In case of GNA a rejection will be forwarded and the GNA will be sent to the applicant. GNA cannot be addressed during the VHP-SA by the applicant, but a resubmission of the complete SA including the proposed resolution of the GNA is endorsed.

In case of conditional approvals of VHP-SA, answers to any questions on the conditions or clarification shall be provided by the REF-NCA.

A VHP-SA resubmission should have a new substantial amendment code number and date. However, the sponsor should refer in the cover letter to the previous VHP-SA to which it relates and should explain the changes made to solve the refusal. The e-mail with the VHP conclusions for the previous SA should be provided.

9 Appendices

9.1 Flow-charts

9.1.1 Flow chart Voluntary Harmonisation Procedure and SR-VHP

Phase 1	Request for VHP	
Anytime	Electronic submission of request and CTA documentation to VHP-A via e-Mail/Eudralink (VHP-CTFG@VHP-CTFG.eu) Forwarding of the CTA documentation to the P-NCA Or immediate information of the applicant that no REF-NCA exist and CTA should be filed nationally to the NCAs	
Within 5 working days after receipt at VHP-A	Information to the applicant on the acceptance by NCAs, REF-NCAship and on the date of start (Day 1) of the VHP phase 2 Or, Compilation of formal deficiencies of the VHP dossier, if applicable: if needed, the missing information will be requested by the VHP-A and should be submitted within 3 days If no REF-NCA is found within the list of the P-NCA the VHP will be rejected and the applicant will be informed accordingly	
Phase 2	VHP CTA assessment step I	
Day 1	Start of VHP	
Day 32	If no GNA: information (REF-NCA) of the applicant on acceptance	End of VHP and start of phase 3 →National step
Day 32	In case of GNA: transfer of GNA by REF-NCA to the applicant (Response has to be submitted within 10 days)	
	Day 42 – Day 60 VHP assessment step II	
Day 42	Deadline for electronic submission of additional documentation and re-	

	vised CTA to VHP-A by the applicant	
Around Day 56	If the revised CTA is considered approvable: information (by the REF-NCA) of the applicant on acceptance	End of VHP and start of Phase 3 →National step
Day 60	If a revised CTA is approvable after internal discussion - Information of the applicant by the REF-NCA on acceptance	End of VHP and start of Phase 3 → National step
	Revised CTA is not approvable : - End of the VHP: Letter to the applicant with details of GNAs	
	Disagreement between MS on GNAs: - List of MS that are ready to approve the CTA and list of MS with open points	
	In case of approval with requested revision of documents	
Day 70	Submission of the requested revised documentation including track changes and a clean version to the VHP-A	
Day 78	Information of the applicant via REF-NCA that the requested revised documentation is acceptable and that the revised CTA is considered approvable	End of VHP conditions and start of Phase 3 → National step
Phase 3	National step	
Within 20 days of receipt of approvability statement	Submission of the formal CTA (as agreed during the VHP with the requested changes, where applicable) to each P-NCA with the letter of decision on VHP	
Within 10 days of valid CTA[3]	Procedure and decision according to national laws	

9.1.2 Flow chart Voluntary Harmonisation Procedure with ATMP or GMO MP

Phase 1	Request for VHP
Any time	Electronic submission of request and CTA documentation to VHP-A via e-Mail/Eudralink (VHP-CTFG@VHP-CTFG.eu) Forwarding of the CTA documentation to the P-NCA
Within 5 working days after receipt at VHP-A	Information to the applicant on the acceptance by NCAs, REF-NCAship and on the date of start (Day 1) of the VHP phase 2 Or, Compilation of formal deficiencies of the VHP dossier, if applicable: if needed, the missing information will be requested by the VHP-A and should be submitted within 3 days If no REF-NCA is found within the list of the P-NCA the VHP will be rejected and the applicant will be informed accordingly
Phase 2	VHP CTA assessment step I
Day 1	Start of VHP

[3] The 10 days can relate to CA decisions only. In MS where the CAs have to forward the CTA to EC or other committees different timelines for the decisions might result.

Day 55 Day 55	If no GNA: information (REF-NCA) of the applicant on acceptance	End of VHP and start of phase 3 →National step
	In case of GNA : transfer of GNA by REF-NCA to the applicant and the P-NCAs (Response has to be submitted within 10 days)	
	Day 65 – Day 90 VHP assessment step II	
Day 65	Deadline for electronic submission of additional documentation and revised CTA to VHP-A by the applicant	
Around Day 82	If the revised CTA is considered approvable: information (by the REF-NCA) of the applicant on acceptance	End of VHP and start of Phase 3 →National step
Day 90	If a revised CTA is approvable after internal discussion - Information of the applicant by the REF-NCA on acceptance	End of VHP and start of Phase 3 → National step
	Revised CTA is not approvable : - End of the VHP: Letter to the applicant with details of GNAs	
	Disagreement between MS on GNAs: - List of MS that are ready to approve the CTA and list of MS with open points	
	In case of approval with requested revision of documents	
Day 100	Submission of requested revised documentation including track changes and a clean version to the VHP-A	
Day 108	Information of the applicant via REF-NCA that the requested revised documentation is acceptable and that the revised CTA is considered approvable	End of VHP conditions and start of Phase 3 → National step
Phase 3	National step	
Within 20 days of receipt of approvability statement	Submission of the formal CTA (as agreed during the VHP with the requested changes, where applicable) to each P-NCA with the letter of decision on VHP	
Within 10 days of valid CTA[4]	Procedure and decision according to national laws	

9.1.3 Flow chart VHP of substantial amendments (VHP-SA)

Phase 1	Request for VHP-SA
Any time	Electronic submission of request and substantial amendment documentation to VHP-A via E-mail/Eudralink (VHP-CTFG@VHP-CTFG.eu) Forwarding of the SA to the P-NCA
Within 5 working days after receipt at VHP-A	Information to the applicant on the date of start of the VHP-SA phase 2,. Or, Compilation of formal deficiencies of the VHP-SA dossier, if applicable (if needed the missing information will be requested by the VHP-A and

[4] The 10 days can relate to CA decisions only. In MS where the CAs have to forward the CTA to EC or other committees different timelines for the decisions might result.

	should be submitted within 3 days)	
Phase 2	VHP-SA CTA assessment step	
Day 1	Start of the VHP for substantial amendments	
Day 21	Requests for limited additional explanations or clarifications by REF-NCA to the sponsor, if applicable	
Day 24	Response of sponsor to requests of limited further information or very limited requests for minor changes	
Day 28	If no GNA within the assessment of the VHP-SA were raised by the P-NCA: information (via REF-NCA) of the applicant on positive decision	End of VHP SA and start of phase 3 →National step
Day 35	If GNA existed, but were resolved after internal discussion: information (via REF-NCA) of the applicant on positive decision	End of VHP SA and start of phase 3 →National step
Day 35	In case of rejection: transfer of reasons (GNA) by REF-NCA to the applicant	
	In case of approval with requested revision of documents	
Day 45	Submission of requested revised documentation including track changes and a clean version to the VHP-A	
Day 53	Information of the applicant via REF-NCA that the requested revised documentation is acceptable and that the revised CTA is considered approvable	End of VHP SA and start of phase 3 →National step
Phase 3	National step	
Within 10 d of receipt of approvability statement	Submission of the formal substantial amendment to every P-NCA including the letter of decision on VHP SA	
Within 7 days of valid SA[5]	Procedure and decision on SA according to national laws	

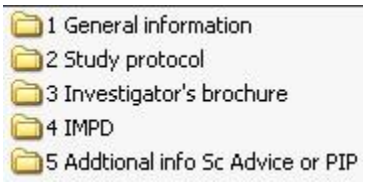
[5] The 7 days can relate to CA decisions only. In MS where the CAs have to forward the CTA to EC or other committees different timelines for the decisions might result.

9.2 Content of a "Request for VHP"

The following information should be contained in a request for VHP:

1. Covering letter including the EudraCT number and a short description of the key features of the CT. Where a previous CTA on the same IMP has been submitted through VHP, the parts of the IMPD or IB that have been updated with respect to the previous version provided to the VHP should be highlighted.
2. (For all VHPs involving Belgium, Spain and the Netherlands the EC responsible for the single opinion in that MS, for all VHPs involving The Netherlands the ABR number should be given).List of the NCAs the applicant intends to submit a CTA in the national phase. A REF-NCA has to be proposed (not binding)
3. Core CTA EudraCT form (general information for all MS), no country specific information
4. Protocol related folder with study protocol including synopsis
5. Investigator's brochure
6. IMP dossier, as defined in EudraLex - Volume 10 (including viral safety and IMPD on the Placebo, if applicable)
7. IMP additional information (if not included in IMPD): manufacturing authorisation; GMP compliance certificate; importation authorisation; certificate of analysis, if applicable; authorisation for special characteristics of products e.g. GMO or radioelements
8. NIMPs Dossier according to EU guidance [III], if applicable
9. Copy/summary of any scientific advice from any competent authority or EMEA and PIP summary, if applicable

For FIH MN-CTs, all applicable clinical and non-clinical aspects specific to the product under investigation and their potential impact on the study design and/or on the conduct of the clinical trial should be discussed, as outlined in the Guideline on strategies to identify and mitigate risks for FIH-CTs with IMP (EMEA/CHMP/SWP/294648/2007), or justification should be provided as to why the points have not to be addressed in the CT documentation.
Electronic structure of the VHP application:



If more than 3 documents are submitted via a Eudralink mail, all documents should be attached in a compressed folder i.e. a zip folder or a 7z folder without any passwords (winzip or 7zip)
The eudralink should have the maximum expiry date (90 days) and no password of the eudralink is preferred.

References:

[I] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal L 121, 01/05/2001. p34 – 44

[II] Information of the Commission on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)(2010/C 82/01)

[III] Guidance on investigational medicinal products (IMPS) and 'non investigational medicinal products' (NIMPS) (rev. 1,march 2011) SANCO/c/8/sf/cg/a.5.001(2011) 332855