

# Clinical Trials Facilitation Group

## Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications Version Sponsor 1.1 Pilot Phase proposed by CTFG

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## 1 Abbreviations

CA: competent authority  
CT: clinical trial  
CTFG: clinical trial facilitation group  
CTA: clinical trial application  
EC: ethics committee  
EU: European Union  
FIH: first in human  
MN-FIH: multinational first in human  
GNA: grounds for non acceptance  
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  
NCA: national competent authority  
P-NCA: participating national competent authority  
PIP: Paediatric investigational Plan  
RFI: request for further information  
VHP: voluntary harmonisation procedure  
VHP-C: VHP-Coordinator

This document is produced by the CTFG in order to propose a harmonised procedure for assessing multinational CTs by the National Competent Authorities in EU.  
This document should be read in conjunction with other EU published guidelines (see also Section References).

## 2 Background/Rationale

The Directive 2001/20/EC, (the “EU Clinical Trials Directive”), relating to the implementation of good clinical practice in the conduct of clinical trials 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, in which the trial sites may be located in a single Member State (MS), in a number of MS, and/or in one or more MS and third countries. This document relates to 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 clinical trials 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 member states at an operational and national level, the EU Heads on Medicines Agencies (HMA) have set up the Clinical Trials Facilitation Group (CTFG). This is another major step for the achievement of harmonisation of CT 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

Regarding MN-CT for which an application is filed in several MS, since the authorisation of a clinical trial is subject to national legislations, the assessment of the same Clinical Trial Application (CTA) for a given MN-CT might result in varying final decisions. Country-specific modifications might occur due to changes requested by the different National Competent Authorities (NCAs) and Ethics Committees; a CT might even be approved in one MS and rejected in another. Such situations not only may jeopardize the scientific value of clinical trial results in the case of country-specific modifications but also are hardly understood by the public, since the levels of protection of clinical trials participants should be the same in all European countries.

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

- Protect clinical trials subjects,
- 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 clinical trials, by the means of harmonising NCAs' processes and practices relating to MN-CTs (about 60% of CTs in EU), has become a priority for the CTFG. Thus, the organisation of the coordinated assessment of multinational

CTA applications through the Voluntary Harmonisation Procedure (VHP) is a major objective of the CTFG work plan for 2008-2009.

### 3 Scope and general principles

A harmonisation procedure of the assessment occurring after the application of a CTA 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, each NCA remains competent for delivering a CTA in their 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 subjects' safety and IMP's quality and safety.

Due to the volume of MN-CTs to be assessed every year, and bearing in mind that CTA decisions remain a competence of each NCAs, an incremental process is proposed, with an initial pilot phase.

During the pilot phase, only MN-CTs with the following criteria would undergo the VHP:

- MN-CTs involving an IMP without MA in the EU

and any of the following :

- FIH MN-CTs and particularly with investigational medicinal products with known or anticipated risk factors as described in EMEA/CHMP/SWP/294648/2007.
- MN-CTs with "Critical" investigational medicinal products (limited community expertise e.g. IMP with novel modes of action, novel manufacturing process, novel administration and storage requirements, links to a class of medicinal product with recognised safety concerns, unresolved pre-clinical abnormal findings, for instance monoclonal interfering with immune regulation, advanced therapies) or "Critical" MN-CTs (e.g. for limited trial populations e.g. orphan diseases, less common types of cancer, paediatrics diseases with small numbers, adult diseases with small numbers or unmet medical needs), based on NCA's judgement, endorsed by the CTFG
- MN-CTs with very large population and where the sponsor indicates a need for harmonisation (e.g. large phase III CTs and several 5-10 MS concerned)

### 4 Definitions

- VHP-Coordinator (VHP-C): the CTFG representative of the National CA in charge of coordinating the VHP for CTAs.
- Participating NCAs (P-NCAs): the NCAs concerned by the CT and wishing to participate to the VHP, on a voluntary basis
- The "VHP applicant": a sponsor, whoever is submitting a request for VHP of a MN-CT to the CTFG.

- Letter of intention for VHP: letter from the VHP applicant, requesting a planned MN-CT to undergo the VHP. The applicant should describe the key features of the CT together with the CT protocol synopsis, the reason(s) why a VHP is warranted for this CTA and indicate which EU countries will be involved in the MN-CT.
- VHP application: documentation required for the assessment of a Draft CTA through the VHP; the content of the VHP Application is detailed under section “Format and content of the VHP application”

## 5 Outline of the proposed procedure

The VHP will comprise three phases:

Phase 1: a “pre-procedural” or “Request for a VHP” step: inclusion of a request for review of a planned MN-CT CTA into the VHP system

Phase 2: an assessment step: review of a draft CTA by the NCAs of the participating MS

Phase 3: a national step, with formal CTA applications to all concerned NCAs.

Phase 1 and 2 are actually composing the pre-submission phase to CTFG. Phase 3 is the formal application of a CTA to each NCA as described in the CT directive.

### 5.1 *“Pre-procedural step” or “Request for VHP”*

In a letter of intention, the applicant should describe the key features of the CT together with the CT protocol synopsis, the reason(s) why a VHP is warranted for this CTA and indicate which EU countries will be involved in the MN-CT.

5.1.1 The applicant informs the VHP-C by sending electronically to [VHP-CTFG@VHP-CTFG.EU](mailto:VHP-CTFG@VHP-CTFG.EU) via E-mail/Eudralink a letter of intention for VHP, highlighting important features of the MN-CT together with the CT protocol synopsis, at fixed dates, i.e. every 5th of each month.

5.1.2 Upon receipt of the letter of intention and the protocol synopsis, the VHP-C creates a new file in the VHP database and allocates a VHP number (the EudraCT number with the Prefix VHP/plus an ongoing number).

Within 5 days after the TC (3<sup>rd</sup> Thursday of the month), the VHP-C informs the applicant of the CTFG decision regarding the acceptance of the CTA in the VHP.

### 5.2 *VHP CTA assessment step*

Of note, the time lines proposed hereby are maximum timelines. Whenever possible for the P-NCA, the timelines can be shorter.

Important: during the entire VHP, any contact from the applicant to the P-NCA should be avoided, and the VHP-C being the sole contact with the applicant.

#### 5.2.1 The VHP application

The VHP application should be made by the sponsor within 15 days after the notification of the CTFG’s decision to accept the MN-CT for VHP.

All the documents should be submitted electronically to the VHP-C (Contact E-Mail for VHP Submissions: [VHP-CTFG@VHP-CTFG.EU](mailto:VHP-CTFG@VHP-CTFG.EU)) via E-mail/Eudralink in the format and structure defined by the CTFG in section 7.3.

#### 5.2.2 Validation of the content (Day 1-Day 3)

Upon receipt (Day 1), the VHP-C checks the dossier for completeness. If the application is not complete, e.g. missing information, the applicant will be contacted by the VHP-C. If deficiencies are minor, missing information will be requested. If the deficiencies are major or if the requested documentation is not provided within 10 days, the sponsor may be required to resubmit a complete application.

When the application is considered valid, an electronic acknowledgement mail will be sent to the applicant. Documents will be forwarded electronically to the other P-NCAs and the assessment period can start (Day 3).

#### 5.2.3 VHP Assessment Step I (Day 3-Day 29)

- In the absence of GNA/RFI,
  - a statement will be sent by the VHP-C to the applicant (copy to all P-NCAs), between Day 26 and Day 29, signed by the VHP-C stating that no GNA/RFI have been expressed by any P-NCA during the VHP assessment phase and that the P-NCAs unanimously consider the draft CTA (with date & version #) acceptable for this MN-CT.
  - The final step, i.e. submission of a CTA in each participating MS, can then start (See Section 5.3 National step).
- In case of GNA or RFI:
  - The VHP-C compiles all GNA and RFI received by the P-NCAs. The document is forwarded to the applicant by the VHP-C via E-mail/Eudralink on Day 29, with a request for response to the GNA/RFI and/or revised CT documentation, by E-Mail/Eudralink by Day 40.
  - If the applicant decides to proceed, the VHP assessment step II starts on receipt of the responses with a revised CT documentation by the VHP-C.
  - The VHP file will be closed without notice if no response from the applicant is received within the allotted time

#### 5.2.4 VHP Assessment Step II (Day 40-Day 60)

The applicant's response document is immediately dispatched by the VHP-C to the all P-NCAs for review. After a 7-day period, the VHP-C compiles the P-NCAs assessments.

➤ If consensus is reached, i.e. the revised version of the Draft CTA is considered approvable by all P-NCAs, on Day 50, the VHP-C sends to the applicant a signed statement by electronic mail (copy to all P-NCAs), mentioning that all GNA/RFI have been resolved and that the P-NCAs unanimously consider the revised draft CTA (with date & version #) as approvable. The final step, i.e. submission of a CTA in each participating MS, can start (See Section 5.3 National step).

➤ If consensus is not reached among the P-NCAs, or if the MN-CT revised Draft CTA is unani- mously considered as not approvable, the VHP-C sets up a TC (between Day 50 and Day 57), chaired by the VHP-C, during which all P-NCAs are invited to express their views and possible solutions to the remaining issues so that a final response can be given at the end of the meet- ing:

- Revised version of the Draft CTA approvable: electronic letter to the applicant on Day 60, mentioning that all GNA/RFI have been resolved and that the P-NCAs unanimously consider the revised draft CTA (with date & version #) as approvable. The final step, i.e. submission of a CTA in each participating MS, can start (See Section 5.3 National step).
- Revised version of the Draft CTA not approvable: electronic letter to the applicant on Day 60, listing, by P-NCAs, the remaining GNAs and/or proposed solutions (See Section 5.3 National step).

### **5.3 “National step”/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 draft 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 the Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (ENTR/F2/BL D 2003. Rev 2).

However, if during the VHP assessment process, a NCA has expressed strong GNA in its own MS or if the solutions proposed in that MS are not acceptable by the sponsor, the sponsor may decide to exclude that MS from the project.

On the other hand, if the sponsor decides to consider a MS that was not initially part of the VHP, the NCA of the new MS may accept the decisions taken by the VHP, without additional requests allowed.

In his covering letter to the NCAs for the CTA, the sponsor should remind the NCAs that this MN-CT has undergone the VHP and indicate where in the application a copy of the VHP approvability statement can be found. Generally, no changes between the final CTA and the draft CTA approved during the VHP will be accepted.

Submissions of the CTA at the National levels should be no later than 20 days after receipt of the VHP acceptability statement by the applicant

The applicant should notify a list of the dates of authorisations of the MN-CT i to the VHP-C, when available.

## **6 References**

- 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
- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial . ENTR/F2/BL D (2003) Rev 2.
- Detailed guidance on the European clinical trials database (EUDRACT Database) as required by Article 11 and Article 17 of Directive 2001/20/EC, CT 5.1 Amendment describing the development of EudraCT Lot 1 for 1 May 2004 and CT 5.2 EudraCT core dataset. April 2004.
- Guideline on strategies to identify and mitigate risks for first-in-man human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/294648/2007.

## 7 Appendices

### 7.1 Flow-chart

#### 7.1.1 Flow chart VHP at the sponsor's request

<b>Phase 1</b>		<b>Request for VHP</b>	
Before 5th of each Month	Electronic submission of request to VHP-C		
Around the 3rd Thursday	Information of the applicant, If MN-CT was chosen/rejected for VHP		
Within 15 days after CT was chosen for VHP	If elected, Submission of the VHP dossier to the VHP-C via Eudralink		
<b>Phase 2</b>		<b>VHP Draft CTA assessment step 1</b>	
Upon receipt Day 1	Checking the completeness of the VHP dossier by the VHP-C (if need the missing information will be requested by the VHP-C and should be submitted within 10 days)		
Day 3	if a valid VHP dossier exists: information of the applicant on the start of the VHP		
Day 29-30	If no GNA or RFI: information (VHP-C) of the applicant	End of VHP and start of phase 3 →National step	
Day 30	In case of GNA and/or RFI: transfer of GNA/RFI by VHP-C to the applicant and the P-NCAs.		

<b>Day 40 – Day 50 VHP assessment step II</b>			
Day 40	Deadline for electronic submission of additional documentation and revised draft CTA to VHP-C by the applicant		
Day 50	If the revised draft CTA is considered approvable: information (by the VHP-C) of the applicant	End of VHP and start of Phase 3 →National step	
Day 60	If a revised CTA approvable with changes : - Information of the applicant by the VHP-C	End of VHP and start of Phase 3 → National step	
	Revised CTA not approvable : - End of the VHP: Letter to the applicant with details of GNAs by NCAs		
<b>Phase 3</b>		<b>National step</b>	
Within 20 days of receipt of approvability statement	Submission of formal CTA to each P-NCA with the letter of decision on VHP		
Within 10	Procedure and decision according to national laws		

days of valid CTA <sup>1</sup> After P-NCA's decision	Information of the VHP-C on the outcome of the national CTAs (with respect to the VHP decisions)
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## 7.2 Content of a “Request for VHP”

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

- 1.1. Covering Letter
- 1.2. Letter of intention describing the key features of the CT and the reason(s) why a VHP is warranted
- 1.3. List of the CA the applicant intends to submit a CTA in the national phase
- 1.4. Summary/synopsis of the current protocol

## 7.3 Content of the VHP-Dossier

(when the CT is accepted for VHP)

The application for a VHP should include the following:

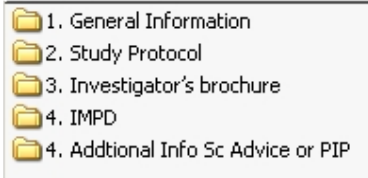
1. General information
  - Covering letter including the EudraCT number
  - Notification of acceptance in the VHP
  - List of NCAs to which the final CTA will be submitted
  - CTA form, if available
2. Protocol related folder
  - Protocol including synopsis
3. Investigator's brochure
4. IMP related folder
  - IMP dossier, as defined in Volume 10 (including viral safety if applicable)
  - IMP additional information (if not included in IMPD): manufacturing authorisation, GMP compliance certificate, Importation authorisation, certificate of analysis if applicable, authorisation for special characteristic products e.g. GMO or radioelements.
5. 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 (EMA/CHMP/SWP/294648/2007), or justification provided as to why the points have not to be addressed in the CT documentation.

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<sup>1</sup> 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.

Electronic structure of the VHP application:

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- 1. General Information
  - 2. Study Protocol
  - 3. Investigator's brochure
  - 4. IMPD
  - 4. Additional Info Sc Advice or PIP