

An Overview to Voluntary Harmonization Procedure (VHP) - Approach to Clinical Trial Application (CTA)

Article Review by Anil Eknath Khedkar
Ph.D in Clinical Research, Texila American University
Email: - anil.khedkar@live.co.uk

Abstract

The clinical trial application (CTA) approval in the European Union (EU) member state has been subject to national legislation. Due to this the assessment of a CTA that was filed simultaneously in several EU member states often resulted in varying final decisions and unnecessary delays. Sometimes country-specific modifications to the application often occurred due to changes requested by the different regulatory/competent authorities (RA/CA) and ethics committees (EC). Sometimes a clinical trial might even be approved in one member state and rejected in another. The whole procedure could be extremely time-consuming and the country-specific modifications risk the scientific value of clinical trial results. The Voluntary Harmonisation Procedure (VHP) offers sponsors of multinational clinical trials involving three or more EU member states a harmonised procedure for the regulatory assessment of clinical trial authorisation applications. The Voluntary Harmonisation Procedure makes it possible to obtain a coordinated assessment of an application for a clinical trial that is to take place in several European countries.

Keywords: *Clinical trials, Voluntary Harmonisation Procedure (VHP), Clinical trial application (CTA), Regulatory authority approval, European Union (EU)*

Introduction

The clinical trial application (CTA) process to perform a clinical trial in Europe takes place on a country-by-country basis. Therefore, a sponsor must apply for approval in each country in which it intends to have study sites. While the processes are similar in most countries, there are slight differences and in some cases, additional material must be submitted in many European countries, a sponsor must submit a copy of the insurance coverage obtained to cover the clinical study. E.g. the regulatory authority that governs therapeutics in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA). To file a clinical trial application in the UK, a sponsor must reside or have a legal representative in the EU. The specific requirements for each country in the EU are outlined in a guidance document published by the European Commission.

Traditional Clinical Trial Application (CTA);

The guidance for CTA is outlined by European commission (EC), the detailed guidance is based on Article 9(8) of 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.

Major parts of a clinical trial application (CTA)

A clinical trial application consists of several major parts:

- Covering letter: This should contain EudraCT (European Clinical Trials Database) number, the title and number of the study protocol, and information on any special issues such as first-time use in humans, use of special populations, or unusual trial design.
- Clinical trial application form: The form is available from the EudraCT website.

- Protocol: The protocol should include an evaluation of the anticipated benefits and risks, a justification for including any subjects who may not be able to provide informed consent (if applicable), and a description of the plan to provide additional care once patients leave the study, if different from normal medical care.
- Investigator's Brochure (IB) or Summary of Product Characteristics (SmPC)- provide the SmPC when a drug has been commercialized. The IB should be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and safe use of the investigational product.
- Investigational Medicinal Product-related data: Include the Investigational Medicinal Product Dossier (IMPD). This contains summaries of information related to the quality, manufacture and control of the investigational product. It should include chemical, pharmaceutical and biological data, non-clinical pharmacology and toxicology data, previous clinical trial and human experience data, and overall risk and benefit assessment. In cases where the investigational product has a marketing authorization in another EU member state or it has been approved in another pharmaceutical form, the sponsor can provide an abbreviated IMPD.
- XML file of the application form: Provide the complete data set.
- Applicable fee.

The specific requirements for each country in the EU are outlined in a guidance document published by the European Commission.

Country-specific modifications to the application often occurred due to changes requested by the different CA and EC. In some cases, a clinical trial might even be approved in one member state and rejected in another. The entire procedure could be extremely time-consuming and the country-specific modifications risk jeopardising the scientific value of clinical trial results. In response, a requirement was identified for harmonisation of the assessment of multinational clinical trial applications in the EU. This requirement was guided by the need to protect clinical trial participants, ensure high quality research and bring innovative medicines to patients as quickly as possible.

Voluntary Harmonization Procedure (VHP)

In 2004, the EU Heads of Medicines Agencies (HMA) established a Clinical Trials Facilitation Group (CTFG) to coordinate the implementation of the EU clinical trials directive 2001/20 EC across the member states. In 2009, the CTFG proposed a voluntary harmonisation procedure (VHP) for assessing multinational CTAs. The latest version of this procedure streamlines the assessment of multinational CTAs to be conducted in the EU in order to enlarge the scope of the pilot phase and shorten the timelines. To date, all EU member states have accepted and are implementing the VHP except Poland, where there are some country-specific requirements that need to be fulfilled to facilitate successful clinical trial applications. The VHP committees composed of representatives of the different national agencies.

The Voluntary Harmonisation Procedure is a procedure which makes it possible to obtain a coordinated assessment of an application for a clinical trial that is to take place in several European countries.

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 a harmonised procedure for assessing multinational clinical trials (CT) by the National Competent Authorities (NCA) in EU.

When the clinical trials directive came into force in the European Union (EU) in 2004, the Heads of Medicines Agencies established the Clinical Trials Facilitation Group (CTFG) to support the authorization of clinical trials across the member states. One important request to the European Medicines Agency was to issue alerts to national competent authorities (NCAs) — the agencies that assess clinical trial applications in each member state; for example, the Medical Products Agency in Sweden and the Paul-Ehrlich-Institut (PEI) in Germany — from the clinical trials database EudraCT which was

established through the directive and is not currently publicly accessible] whenever there was a negative decision or withdrawal about a clinical trial in any of the member states. Through the alerting system we found that there were divergent decisions being made about the same clinical trials in different member states.

The assessment is conducted and coordinated between the national competent authorities (medicines agencies) of the countries in which the trial is to take place following which the application is submitted to the countries involved. It is an offer through which sponsors can obtain a harmonised assessment of an application. The actual trial must still be authorised at national level, and it is therefore not a centralised authorisation. Provided that the VHP assessment reaches consensus, the scientific content of the application must not be changed when submitted to the national competent authorities. However, it may be adapted to meet national requirements.

VHP steps

The VHP will comprise 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.

Request for VHP and validation of the application

In the request for VHP, the applicant should shortly 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 by the MS.

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

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

2.1.3 The complete VHP-documentation is forwarded electronically by VHP-C to the P-NCAs immediately after receipt

Within 5 working days after receipt, the VHP-C informs the applicant whether all re-requested MS will participate. Validation of the dossier will also be performed and the applicant will be informed of any deficiencies or, if complete, the start date of the VHP.

All timelines in the VHP are calendar days with one exception: the 5 working days between initial 4 submission and confirmation by the VHP-C (0) and the 5 working days when submitting VHP-substantial amendment (VHP-SA)(7.1).

In those MS declining participation in the VHP, a national CTA in parallel to the VHP or after the VHP is possible.

VHP CTA assessment step

Of note, the timelines proposed hereby are maximum timelines. Whenever possible for the P-NCAs, 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 only contact for the applicant to ensure that all P-NCA receive identical information.

VHP Assessment Step I (Day 1-Day 30)

• In the absence of grounds for non-acceptance (GNA)/ request for further information (RFI), a statement will be sent by the VHP-C to the applicant (copy to all P-NCAs), not later than day 30, 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 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 6.3 National step)

In case of GNA/RFI:

- A consolidated list of GNA will be forwarded to the applicant by the VHP-C via E-mail/Eudralink on day 30 with a request for response to the GNA/RFI and/or for the revised CT documentation by E-Mail/Eudralink by day 40 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-C.
- The VHP file will be closed with a notice to the applicant and the P-NCAs if no response from the applicant is received within the allotted time

VHP Assessment Step II (Day 40-Day 60)

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

- If consensus is achieved, i.e. the revised version of the CTA is considered approvable by all P-NCAs on day 50, the VHP-C sends to the applicant a 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 CTA (with date & version #) 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 a teleconference will be organised (between day 50 and day 57), during which all P-NCAs are invited to express their views and possible solutions to the remaining issues so that a final decision can be given at the end of the meeting:

Unanimous decision of the MS that the revised version of the CTA is approvable: an electronic letter to the applicant will be sent on day 60, mentioning that all GNA/RFI have been resolved and that the P-NCAs unanimously consider the revised CTA (with date & version #) 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 the revised version of the CTA is not approvable: an electronic letter will be sent to the applicant on day 60 with the remaining GNAs and proposed solutions for national submissions or a VHP-resubmission. Comments to facilitate national submissions in the MS or a VHP-resubmission might be added

- In the case that not all P-NCA agree, that all GNA/RFI have been resolved, the open points and the names of MS, which consider GNA/RFI as unsolved, will be forwarded to the applicant. Also the list of MS, which consider all GNA/RFI as re-solved, will be forwarded. The open points have to be resolved before or in the national procedure, the timelines for the submission of the CTA (20 days) and the approval by the NCA (10 days) do not apply for the MS with unsolved GNA.

“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 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. current version)*. In his 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 will be accepted.

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 to skip the filing of a CTA in that MS Or if the sponsor decides to apply in a MS that was initially not part of the VHP, the NCA of the new MS may accept the decisions taken in the VHP, without changes by the sponsor to the documents that have been agreed in the VHP.

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

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.

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

VHP application

Any clinical trial sponsor, commercial or non-commercial, can apply for a VHP if they are planning to submit a clinical trial application to at least three EU member states. When we first offered the procedure, we stated that the multinational clinical trial had to be either a first-in-human clinical trial or a trial for a critical product (that is, an investigational medicinal product with a novel mode of action, a novel manufacturing process or novel administration). However, the only restriction we now have is that the application has to be destined for at least three EU countries.

We decided not to charge application fees for participating in the VHP because we were concerned that this would discourage sponsors to use the process. As the assessment of the trial will be done once, we came to the conclusion that a sponsor should be charged by the NCAs only.

The Pharmaceutical approach and the VHP

Despite the fact that all members of the EU (excluding Poland) have accepted the VHP as a valid approach to gaining clinical trial approval, there are still many sponsors and contract research organisations (CROs) that have yet to use it. Prior to the introduction of the VHP two years ago, it was expected that the new procedure would be immediately accepted and used across the pharmaceutical industry. While there is evidence that the VHP is being increasingly adopted, some companies have shown reluctance due to a number Firstly, there is a perceived risk associated with the fact it is a new procedure.

Sponsors are not familiar with the process and are afraid that it might not be as effective as expected. As a result, they prefer to use established processes that have been more commonly used. Another factor that has resulted in limited adoption of the VHP to date is that it is free of charge. Many sponsors believe that non-paid approval procedures are of low value compared to submissions which are subject to a fee.

Results of the Voluntary Harmonisation Procedure 2009 – 1/2013(HMAs Clinical Trials Facilitation Group Status 30.1.2013)

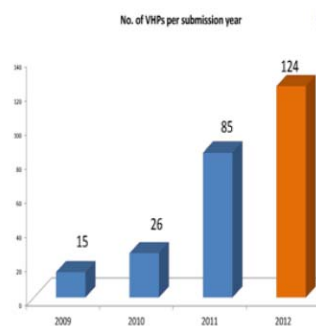


Figure 1: Number of VHP submission per year in EU

(<http://www.hma.eu/77.html>)

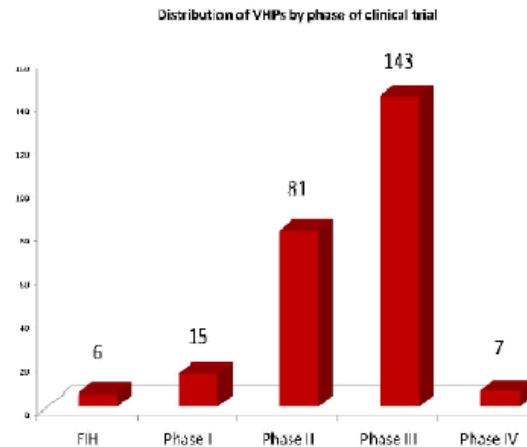


Figure 2: Distribution of VHP by Clinical trial phase
(<http://www.hma.eu/77.html>)

VHP for challenges with Europe’s clinical trial directive

VHP offers what many stakeholders have requested: a ‘one stop shop’ to gain a positive decision for a multinational clinical trial. The current legal framework does still require the sponsors to apply to each NCA for national authorization of their clinical trials. However, we think that we have used the current framework in a pragmatic way to solve many of the problems that sponsors have with the clinical trials directive. We are now confident that we offer a highly attractive alternative to the system of separately applying to each member state. The process needs to more efficiently use our resources. But, as this is a voluntary procedure for both the sponsors and the member states, it can be improved very quickly by the agreement of all. We do not have to change laws to change the way we conduct the VHP.

One of the major issues of the clinical trials directive that the VHP does not solve is the fact that as well as applying to the NCA in each member state to gain approval of a clinical trial, sponsors also have to apply to the respective ethics committees. It may be a good idea to submit applications to the VHP and the ethics committees at the same time. But we are only just starting to have discussions with some of the relevant organizations in the member states to determine whether ethics committees would be involved in the VHP assessments as well.

Disadvantages of VHP

Guidance document outlining the Voluntary Harmonisation Procedure was published in February 2009 by the Clinical Trials Facilitation Group, set up by the Heads of Medicines Agencies in the European Union to co-ordinate the implementation of the clinical trials Directive, 2001/20/EC.

One effect of the Directive’s translation into national law has been divergence in the national assessment of multinational clinical trials (MN-CTs), with protocol changes and the subsequent amendments required in other member states making some applications a —“never-ending story”, as Professor Heiko von der Leyen of the Hannover Clinical Trial Centre in Germany described it at the TOPR symposium.

Reasoning that harmonising procedures for CTA assessment after the applications had been filed would be difficult and perhaps even counterproductive, coming at the end of an already lengthy process, the CTFG’s guidance proposed a Voluntary Harmonisation Procedure that would occur before the initial phase of national assessment.

The VHP is an incremental process whereby Phase 1 constitutes a ‘pre-procedural’ or ‘request for a VHP’ step; Phase 2 is an assessment step, involving the review of the draft CTA by the national

competent authorities (NCAs) of participating member states; and Phase 3 occurs at national level, with formal clinical trial applications to all of the concerned NCAs.

The procedure is also completely electronic, which helps to speed up the evaluations. In a best-case scenario, von der Leyen noted, the VHP should mean approval of the CTA in multiple member states within two months.

Conclusion

VHP has been positive and the process to operate in accordance with version 2 of the CTFG's guideline. Efficiencies have been realised, particularly with respect to the resolution of GNA from multiple MS at a single well defined time in the procedure. It is not possible to say whether fewer questions were received than if separate national procedures had been followed. However, the CTFG has indicated that some consolidation of questions can occur prior to sponsors receiving questions. We have found the impact on study start-up timelines to be neutral. We anticipate that greater efficiencies and scientific benefits may be obtained when seeking authorisation of large studies involving more countries than in the three case studies described, such as for large Phase III studies.

A co-ordinated assessment procedure for clinical trials in the EU is one of the key options on the table in the European Commission's ongoing revision of Directive 2001/20/EC, which is expected to produce a concrete legislative proposal next year.

Between 2007 and 2010, there was a 15% decline both in the number of MN-CTs with EU sites and the number of EU subjects participating in those studies, he noted. More specifically, there were 5,028 clinical trial applications across the EU in 2007 and only 4,193 in 2010.

The VHP would perhaps have been more widely and readily accepted if more efficient promotional activities had been conducted. However, many cases have proven that the VHP is a low-risk and highly beneficial procedure, with more than 50 successful applications completed to date. As more concrete results come to light demonstrating the usability of the procedure and a greater understanding of its benefits and use are communicated, it can be expected that the VHP will become increasingly adopted by the industry.

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