

Multinational Clinical trials in Europe and the Voluntary Harmonisation Procedure (VHP)

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Situation of clinical trials in Europe before the implementation of the Clinical Trials Directive in 2004

- 15 different national approaches of the Member States
- Differences between approval and notification systems
- Completely different documentation
- Different timelines
- Languages
-
-



Situation of clinical trials in Europe before CTD



Situation of clinical trials after the implementation of the Clinical Trials Directive in 2004

- 15/27 Member States working with the same english versions of documents like
 - Investigational Medicinal Product Dossier (IMPD)
 - Protocol
 - Investigators Brochure
 - SmPCs
- but



Situation of clinical trials after the implementation of the Clinical Trials Directive in 2004

- not harmonised are
 - Assessments
 - Treatment options and standards
 - Some documents related to the clinical trial applications due to different interpretations of guidance documents
 - Application times at the national Competent Authorities



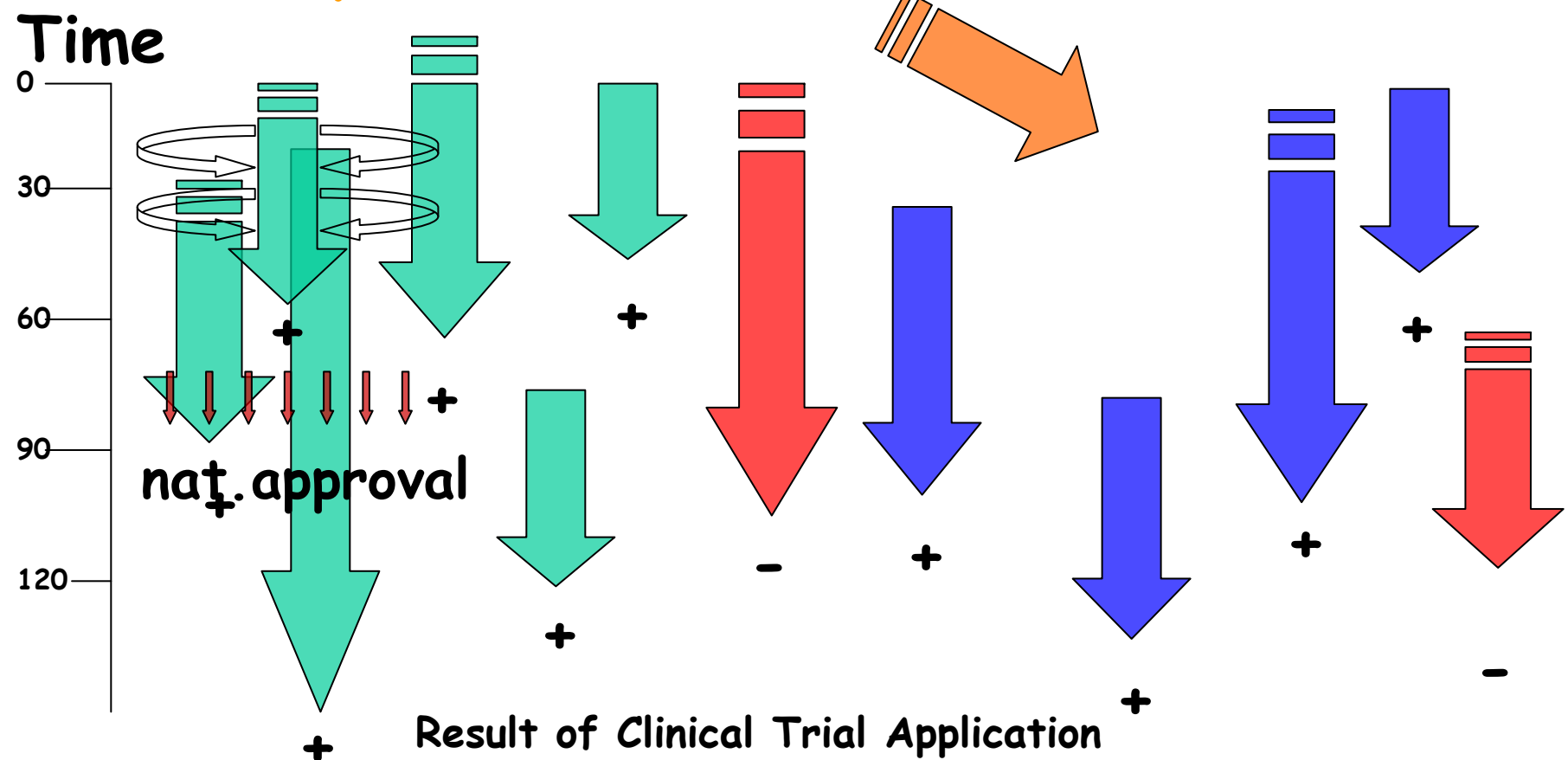
The Voluntary Harmonisation Procedure offers a solution to address these points within the existing European legal framework



Present situation for the approval of a (VHP) for a multinational Clinical Trials

Competent Authorities

Ethics Committees



**The HMAs Clinical Trials
Facilitation Group (CTFG)
voluntary harmonisation procedure
(VHP)**

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

Contact and submissions:

VHP-CTFG@VHP-CTFG.EU

or Tel.: + 49 6103 771811



Ideal situation of clinical trials in Europe after VHP?



Key features of the Voluntary Harmonisation Procedure

- Only electronic documents sent to one address (**one stop shop**)
- Only **general documents** required, which are part of any clinical trial application (Protocol, Investigators brochure, Investigational Med. Product Dossier)
- **Reliable timelines** for Sponsor and Member States
- Harmonised scientific discussion resulting in harmonised applications in the Member States
 - no tracking of Member States specific modifications necessary
 - consolidated lists of grounds for non-acceptance, if needed



The VHP consists of three phases

- VHP-Phase 1: Request for a VHP at any time
 - Request by sponsors including the identification of the participating NCAs and submission of a full dossier
 - Decision by Member States to participate in the VHP

Max.
5 Days

- VHP-Phase 2: the assessment phase
 - Review of the CTA by all the participating NCAs
 - 1st common position around D30, total period maximum 60 days
 - Administrative co-ordination by the VHP coordinator

Max.
60 Days

- VHP-Phase 3: the national Member States step
 - Formal CTA applications to NCAs.
 - CTA approval by NCAs within short timelines (after positive VHP)

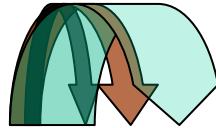
10 Days



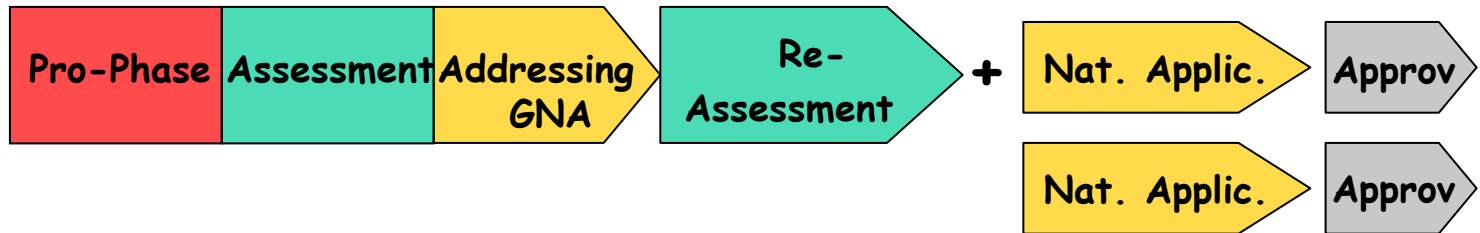
Development of VHP-versions and Substantial Amendments

GNA

5th each
month only

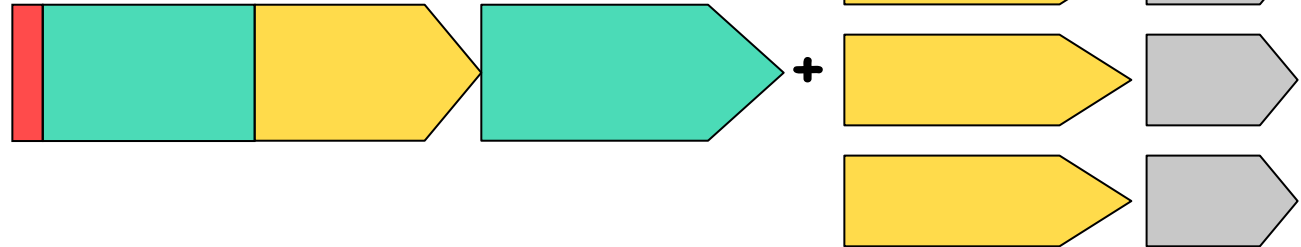
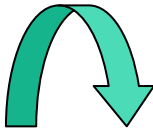


VHP Version 1

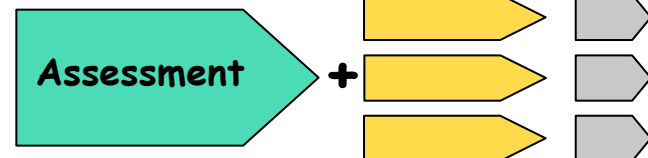


VHP Version 2

Any time



VHP Substantial Amendments



Documents to be submitted for the VHP

VHP Application dossier :

1. General Information

1.1 Covering Letter including EudraCT number

1.2 Application form, if available

1.3 List of NCAs concerned

2. Protocol related folder

2.1 Current Protocol (including the summary/synopsis)

3. IMP related folder

3.1 IB

3.2 IMPD (including viral safety data if applicable)

3.3 Scientific advises and PIP summary report (if applicable)

4. NIMP related folder, if applicable



Details of the of the VHP Guidance – Version 2



Criteria for application/selection

- During the pilot phase, only MN-CTs with the following criteria would undergo the VHP:
 - Applications involving not less than 3 MS^{*}

^{*} Exceptions for multinational FIH possible

effective from March 2010



Features of the VHP introduced with version 2

- Addition of substantial amendment for successful Voluntary Harmonisation Procedures
- Guidance for NIMPs Documentation

effective from March 2010



VHP phases

Phase 1	Request for VHP
Any time	Electronic submission of request and CTA documentation to VHP-C 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-C	Information to the applicant on the acceptance by NCAs 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-C and should be submitted within 3 days



VHP phase 2 (part 1)

Phase 2	VHP CTA assessment step I	
Day 1	Start of VHP	
Day 30	If no GNA or RFI: information (VHP-C) of the applicant on acceptance	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 (Response has to be submitted within 10 days)	
	Day 40 – Day 50 VHP assessment step II	
Day 40	Deadline for electronic submission of additional documentation and revised CTA to VHP-C by the applicant	



VHP phase 2 (part 2)

Day 50	If the revised CTA is considered approvable: information (by the VHP-C) of the applicant on acceptance	End of VHP and start of Phase 3 → National step
Day 60	If a revised CTA approvable after internal discussion :	
	- Information of the applicant by the VHP-C on acceptance	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	
	Disagreement between MS on GNAs: - List of MS that are ready to approve the CTA and list of MS with open points	



National phase after VHP

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 ^[1]	Procedure and decision according to national laws
After P-NCA's decision	Information of the VHP-C by the applicant on the outcome of the national CTAs (with respect to the VHP decisions)

^[1] 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.



Summary of VHP-Substantial Amendments (VHP-SA)

- Offered for successful VHPs after national approval of the initial Clinical Trial Applications
- One-stop-shop for submission
- VHP-SA accepts electronic submissions only
- Approval after 20 days, if none of participating Member State raises internally GNAs
- Approval after 35 days, if GNAs are resolved after the final internal discussion
- Rejection after 35 days giving reasons for GNA to the applicant
- Resubmission after rejection in shorter time lines possible



VHP for substantial amendments

Phase 1	Request for VHP-SA	
Any time	Electronic submission of request and substantial amendment documentation to VHP-C 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-C	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-C and should be submitted within 3 days)	
Phase 2	VHP-SA CTA assessment step	
Day 1	Start of the VHP for substantial amendments	
Day 20	If no GNA within the assessment of the VHP-SA were raised by the P-NCA: information (via VHP-C) 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 VHP-C) 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 VHP-C to the applicant and the P-NCAs.	



VHP for substantial amendments

national step

Phase 3	National step
Within 10 days 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 ^[1]	Procedure and decision on SA according to national laws
After P-NCA's decision	Information of the VHP-C on the outcome of the national CTAs (with respect to the VHP SA decisions)

Shorter timelines are possible for resubmissions

^[1] 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.



Points of the VHP I tend to forget to mention

- In those MS declining participation in the VHP, a national CTA in parallel to the VHP or after the VHP is possible
- During the pilot phase no fees will be charged for VHPs or VHP-SAs; the costs of the NCAs will be covered by the national applications to the NCAs
- All timelines in the VHP are calendar days with one exception: the 5 working days between initial submission and confirmation by the VHP-C (0) and the 5 working days when submitting VHP-substantial amendment (VHP-SA)
- Please give a list of the leading Ethics Committees of the suggested Member States (some assessments of the NCA are performed by the Ethics Committees, therefore this information is crucial for these countries. **This does not mean that an Ethics Committees approval is included!**)



Experience with VHP



Participating Member States in 28 VHPs

Country	No. of VHP
Germany	20
France	16
Spain	16
Belgium	9
UK	8
Austria	7
Sweden	7
Czech Republic	7
Portugal	6
Hungary	6
Romania	5
Greece	4
Finland	4
Denmark	4
Italy	2
Norway	2
Ireland	2
The Netherlands	1
Bulgaria	1
Latvia	1
Iceland	1

Country reject joining VHP

Poland
(The Netherlands until 2010)

The following MS weren't selected for a VHP:

Estonia
Malta
Cyprus
Luxemburg
Slovenia
Lithuania



VHP numbers (March 2009–April 2010)

- **30 applications**
 - 19 standard VHP
 - 11 accelerated VHP (Pandemic Influenza Vaccines)
- **23 finished positive**
 - 1 negative (GNA not addressed)
 - 2 withdrawals (before dossier subm.)
 - 4 ongoing



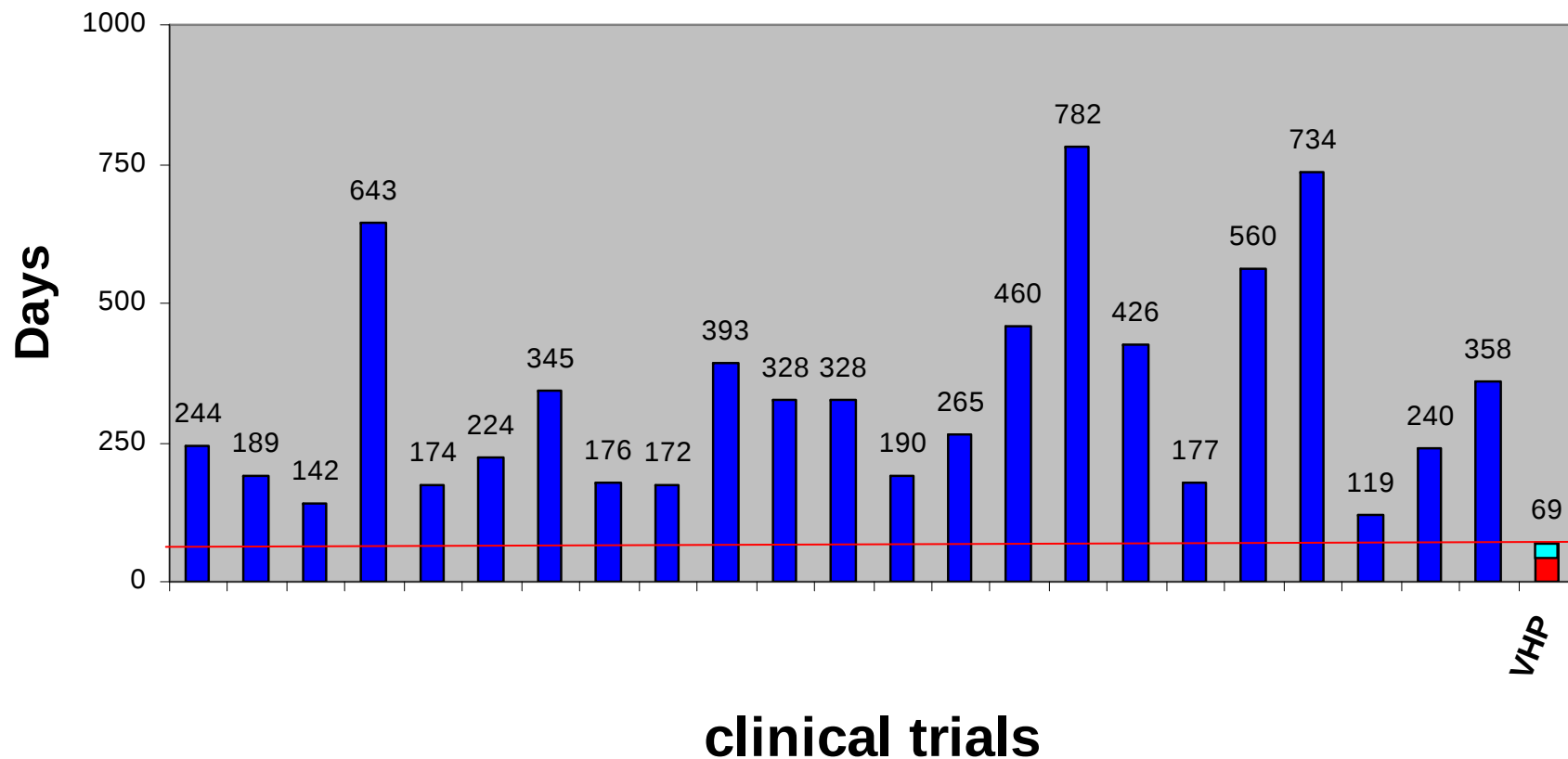
Summary results of the standard VHP

- Average time used for a VHP: **52 days**
- Mean of **8** Member States per standard VHP
 - Range **2-18** Member States
- Time until national CTA by applicant: mean **~18d**
 - Range 1-45 days
- Time for national approval by NCAs: mean **~12d**
 - Range 1-80 days
- Commercial applicants 80%,
- Non-commercial applicants 20%
- Biologicals 20%
- Chemicals 80%



Comparison of approval times of multinational clinical trials with 18 Member States

from the first application date to the last approval date by the national Competent Authorities



Conclusions on VHP

- The Voluntary Harmonisation Procedure is an efficient tool to achieve harmonised and quick approvals of clinical trials in many Member States of the EU in one procedure
- VHP offers a one-stop-shop for CTAs
- VHP accepts electronic submissions only
- Time lines for applicants and Competent Authorities are reliable and are met
- Substantial Amendments are now included in the VHP



Thanks to all the Sponsors, who dared to jump in the cold water!

Thanks to all the Clinical Trials Facilitation Group members, the HMAs, and especially the assessors, who do the scientific work and finally the VHP-coordinator, who keeps us all in line



Clinical Trials Facilitation Groups

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

Version 2

*Doc. Ref.: CTFG//VHP/2010/Rev1
March 2010*



Might VHP reduce the Work-load?



Paul Ehrlich in his study

Thank you for your attention!

