Transition of multi-national clinical trials from the voluntary harmonisation procedure (VHP) to the Clinical Trial-Regulation (CTR 536/2014)

Hartmut Krafft, PhD
VHP-Administrator
Head, Clinical Trial Unit
Paul-Ehrlich-Institut
Paul-Ehrlich-Str. 55-59
63225 Langen
Germany

Fax: +49 (0)6103 771277
Phone: +49 (0)6103 771811
E-Mail: CT@pei.de
http://www.pei.de

Disclaimer

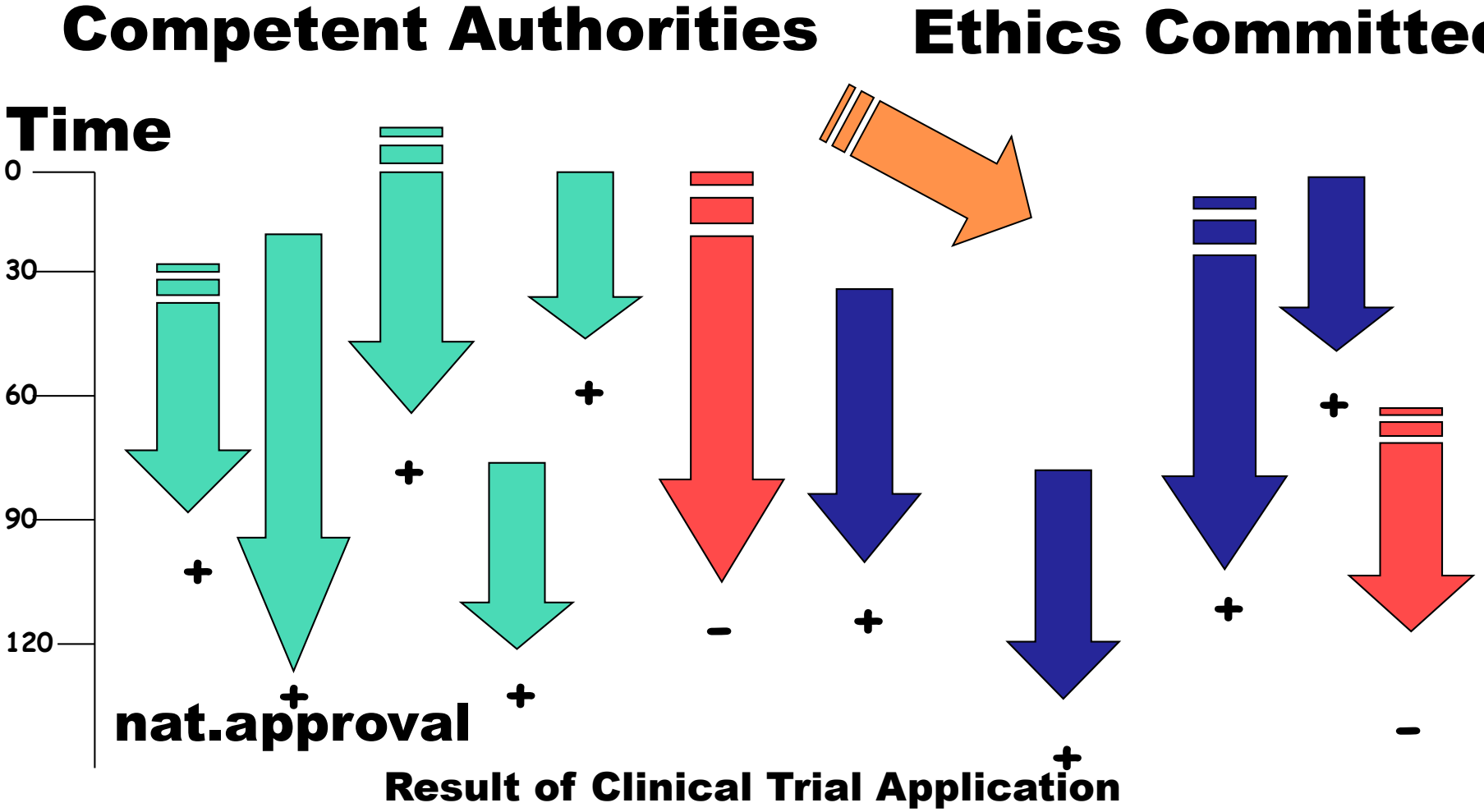
This presentation contains only my thoughts and not necessarily those of the Paul-Ehrlich Institut or other European Institutions!

Voluntary Harmonisation Procedure

Started in 2009 as an Initiative of the Clinical Trials Facilitation Group to gain experience in the practical work within the ideas of a "CT- regulation" and

to offer an option for sponsors and Member States to achieve harmonised multi-national clinical trials and share workload

Present situation for the approval of a multi-national Clinical Trial without VHP



Present situation for the approval of a multinational Clinical Trial using VHP-plus

Competent Authorities

Ethics Committees

Time

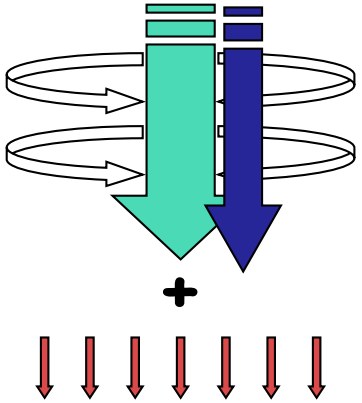
0

30

60

90

120



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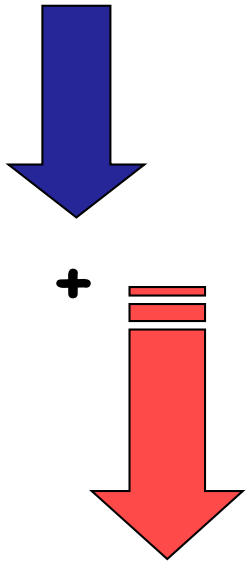
nat.approval



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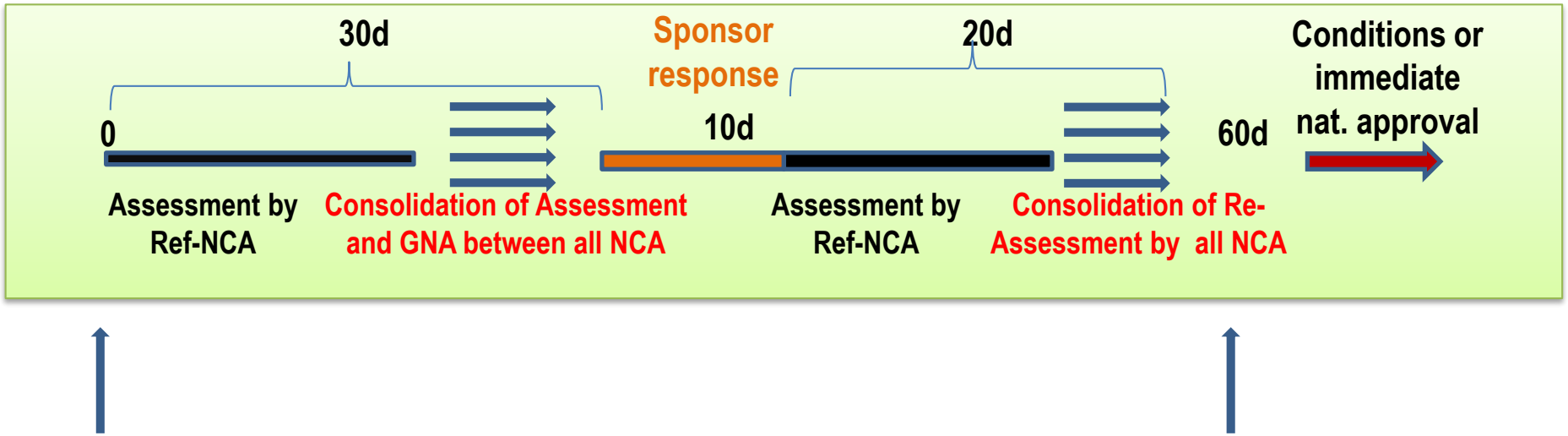
Result of Clinical Trial Application

Procedural steps of the Voluntary Harmonisation Procedure

Validation



Start Assessment

VHP Decision

Share of multi-national clinical trials and VHP of all clinical trial in Europe

- **Only approx. 28% of all clinical trials in Europe involve more than one Member State** (see backup)
- **Approx. 20% of the multi-national clinical trials in Europe underwent a VHP before they were submitted to the National competent authorities**

Voluntary Harmonisation Procedure
What have we achieved

- More than 1800 VHPs in the last 12 years
- More than 3500 substantial amendments (VHP-SA)
- More than 95% decisions in complete agreement between MS (see backup)
- Mean time used for initial VHPs ~60 days; for substantial amendment 35 days

- VHP will end 2 months before the CTR becomes fully active

Transition of VHP CT into CTR?

- **VHP-CTs even with many SA (>20) are completely harmonised between the Member States and have a REF-NCA / -> future rMS**
- **Many VHP-CTs run for many years and should remain harmonised when VHP has ended**
- **Transition of VHP-CTs will be a priority to maintain harmonisation and to keep these CTs going**

- HOW MANY VHP-CT ARE CANDIDATES FOR THE IMMEDIATE TRANSITION
- WHAT WILL BE THE WORKLOAD FOR THE MEMBER STATES

How many VHP-CTs candidates for immediate transition / Member States workload

Status 4.3.2021	
total VHP	1846
number of positive or open VHPs	1467
number of positive or open VHPs minus Sec Rounds and re-submissions / per EudraCT	1254
number of VHPs without global end / per EudraCT data warehouse	512*

REF-NCA / -> future rMS

AUSTRIA	12
BELGIUM	20
CZECH REPUBLIC	58
DENMARK	44
FINLAND	11
FRANCE	7
Germany BfArM	36
Germany PEI	76
HUNGARY	20
IRELAND	19
ITALY	79
LATVIA	2
NETHERLANDS	11
NORWAY	8
POLAND	6
PORTUGAL	8
ROMANIA	2
SPAIN	39
SWEDEN	15

*Some Procedures lost due to Brexit

Guidance for VHP Transition?

- **HMA website /CTFG**
  - **Best Practice Guide for sponsors of transition multinational clinical trials**
  - https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2018_05_CTFG_Best_Practice_Guide_for_sponsors_of_transition_multinational_clinical_trials.pdf
  - **Conclusion of the Voluntary Harmonization Procedure project**
  - https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2021_01_CTFG_Conclusion_of_the_Voluntary_Harmonization_Procedure_project.pdf
- **Eudralex Vol. 10**
  - **CLINICAL TRIALS REGULATION (EU) NO 536/2014 DRAFT QUESTIONS & ANSWERS VERSION 3 FEB.2021 (11.5 to 11.9)**
  - http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

CLINICAL TRIALS REGULATION (EU) NO 536/2014
DRAFT QUESTIONS & ANSWERS VERSION 3 FEB.2021

- **386. For clinical trials in the Voluntary Harmonisation Procedure (VHP), the Member State of the VHP Reference National Competent Authority (Ref-NCA) shall be indicated as the Reporting Member State. This applies also to trials that are partly in the VHP.**

11.9 Question: What will happen with the clinical trials included in the Voluntary Harmonisation Procedure (VHP)?

CLINICAL TRIALS REGULATION (EU) NO 536/2014 DRAFT QUESTIONS & ANSWERS VERSION 3 FEB. 2021

390. Answer: The Voluntary Harmonisation Procedure (VHP) will discontinue as of entry into application of the clinical trials Regulation.

The clinical trials included in the VHP will, in principle, qualify to transition as multinational clinical trials (see Q11.7). It is the sponsor's responsibility to assess however whether this is the case (as described in this document) and, in case a harmonised protocol does not exist,

to prepare one consolidated protocol reflecting acceptable differences in authorized national trials (please see CTFG Best Practice Guide for sponsors of multinational clinical trials with different protocol versions approved in different Member States under Directive 2001/20/EC that will transition to Regulation (EU) No. 536/201468).

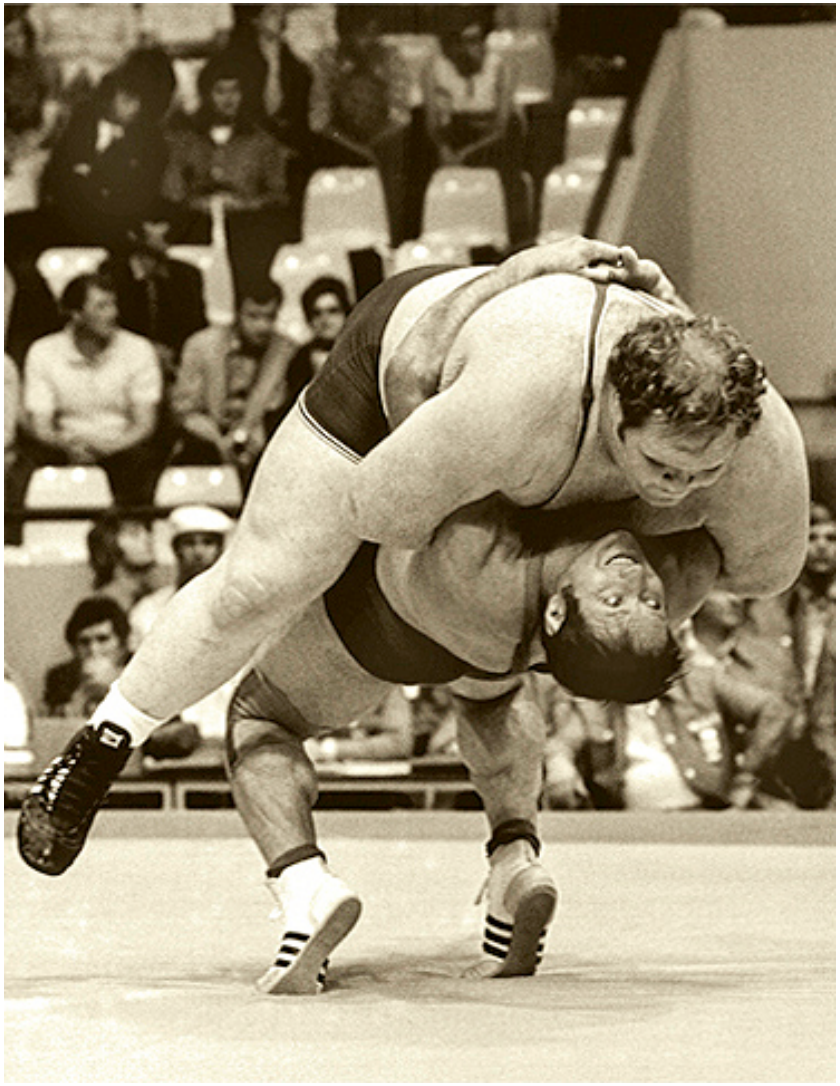
In order to benefit from the advantages of harmonisation a sponsor should transition those trials as soon as possible after the entry into application of the Regulation, and at the latest before any new submission concerning a trial

Practical tips for transition

- **Prioritise your clinical trials according the need for transition and substantial amendments**
- **Use the time prior to the 2 month gap between VHP and CTR application for urgent VHP-SA.**
- **Use the 2 month gap for preparing missing documents for the CTR application**
- **Make sure that you as a sponsor or applicant are known to EMA as users of the CTIS to establish your users and user roles when CTR application is possible**

THANK YOU FOR YOUR ATTENTION

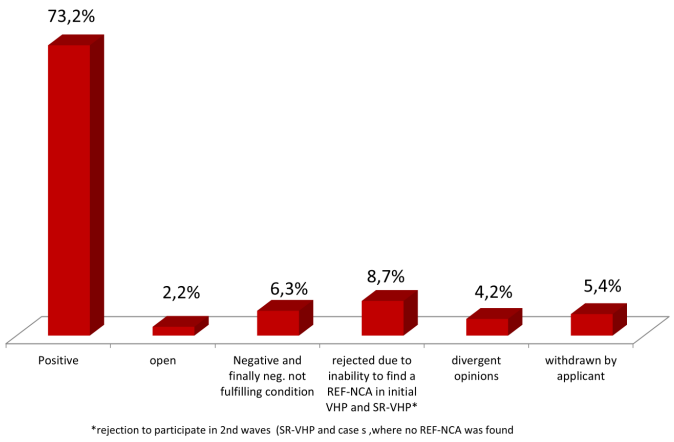
TRANSITION IS POSSIBLE, BUT NOT NECESSARILY EASY



Results of VHP

- **HMA website /CTFG**
  - **Results of the Voluntary Harmonisation Procedure 2009 - 2020, February 2021**
  - https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2021_02_CTFG_Results_of_the_Voluntary_Harmonisation_Procedure_2009-2020.pdf

Percentages of VHP decisions from 3/2009 to 1.1.2021



*rejection to participate in 2nd waves (SR-VHP and case s ,where no REF-NCA was found

Distribution of regions/countries of VHP sponsors

Country of Sponsor	Number of Voluntary Harmonisation Procedures
United States of America	640
SWITZERLAND	248
Germany	205
UNITED KINGDOM	115
FRANCE	105
DENMARK	71
BELGIUM	63
SWEDEN	40
SPAIN	22
ITALY	12
AUSTRIA	13
NETHERLANDS	13
IRELAND	14
CANADA	11
JAPAN	7
ISRAEL	5
AUSTRALIA	4
CZECH REPUBLIC/Norway	6
SINGAPORE	3
LUXEMBOURG	2
l, Taiwan, Ukraine, Iceland; Korea, Iceland	1

The total number of different sponsors is 365

Status 15.1.2020

Applicants with 10 to more than 100 VHP submissions

F.Hoffmann-La Roche
AbbVie Deutschland GmbH & Co. KG
Amgen Inc
Pfizer Inc
Gilead Sciences Inc.
Eli Lilly and Company
Incyte Corporation
Merck KGaA
Actelion Pharmaceuticals Ltd
AstraZeneca AB
Genentech, Inc.
Novo Nordisk A/S
Regeneron Pharmaceuticals, Inc.
Novartis Pharma Services AG
Eisai Ltd.
Gilead Sciences, Inc.
EORTC
Bristol-Myers Squibb International Corporation
GlaxoSmithKline Research & Development Ltd.
MedImmune, LLC
F. Hoffman-La Roche Ltd.
Millennium Pharmaceuticals, Inc
Laboratoires Thea
Allergan Ltd
Janssen-Cilag International N.V.
Sanofi-aventis recherche et développement
Idorsia Pharmaceuticals Ltd
Institut de Recherches Internationales Servier
Ferring Pharmaceuticals A/S
Alcon Research Ltd.

Status 15.

Approximately 28% of the Clinical Trial Applications involve more than one MS

Year	Total CTA	Mono-Nat.	Multi-Nat.	% Multi
2004	991	531	460	46,42%
2005	3.975	2.965	1.010	25,41%
2006	4.336	3.286	1.050	24,22%
2007	5.028	3.833	1.195	23,77%
2008	4.627	3.510	1.117	24,14%
2009	4.619	3.543	1.076	23,30%
2010	4.400	3.294	1.106	25,14%
2011	3.766	2.706	1.060	28,15%
2012	4.016	2.970	1.046	26,05%
2013	3.391	2.361	1.030	30,37%
2014	3.343	2.292	1.051	31,44%
2015	4.297	3.154	1.143	26,60%
2016	3.409	2.320	1.089	31,94%
2017	3.261	2.184	1.077	33,03%
2018	3.305	2.182	1.123	33,98%
2019	3.100	2.089	1.011	32,61%
2020	3.738	2.679	1.059	28,33%
SUM	**63.602**	**45.899**	**17.703**	**27,83%**

Co-ordinated assessment etc. involving several Member States will be required in approx. 1000 CTAs per year

If you used VHP for many substantial amendments of your clinical trials it should be worthwhile to keep it harmonised between Member States, when entered into CTIS