Assessment of Multinational Clinical Trial Application within the European Union: Experience and Expectation of the Voluntary Harmonization Procedure

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List of Abbreviation

AR	Assessment Report
CA	Competent Authority
CT	Clinical Trial
CTA	Clinical Trial Application
CTD	Clinical Trial Directive
CTFG	Clinical Trial Facilitation Group
CTGA	Clinical Trials Coordination and Advisory Group
EC	Ethics Committee
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
EU-CTR	European Clinical Trial Regulation
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GNA	Grounds of Non-Acceptance
HMA	Heads of Medicines Agencies
IMP	Investigational Medicinal Product
MSc	Concerned Member State
NCA	National Competent Authority
P-NCA	Participating National Competent Authority
REF-NCA	Reference National Competent Authority
rMS	Reporting Member State
VHP	Voluntary Harmonisation Procedure
VHP-C	Voluntary Harmonisation Procedure Coordinator

A Introduction

Before the implementation of the European Clinical Trial Directive 2001/20/CE in 2004, obtaining approval for a multinational study in Europe was an enormous complexity. The conduct of clinical trials in Europe varied from one country to another; there were different national approaches to many of the procedures involved.

Sponsors had to submit an application to each European Member State in which they wish to conduct the study. Each country had different requirements concerning:

- Regulatory notification/approval process
- Documentation requirements
- Rules for submitting the application
- Timelines
- Language

Additionally, to this administrative burden each single country responded with scientific questions - diverse or duplicated by other member states, and Sponsors had to respond to each country separately [9; 13].

In April 2001, Directive 2001/20/EC (the “Clinical Trials Directive”) came into force with the objective of detailing the legal provisions for Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) for clinical trial products across the EU. The aim of the Clinical Trials Directive was to harmonise the processes for application and approval of clinical trials in Europe, and to increase and standardize the protection afforded to clinical trial participants. EU Member States were required to integrate these provisions into national legislation. Since May 2004, all EU clinical trials have been required to be conducted in accordance with GCP principles [9; 10].

To co-ordinate the implementation of the Clinical Trials Directive across member states the Clinical Trial Facilitation Group (CTFG) were set up in 2004 by the Heads of Medicines Agencies (HMA) [9].

To address difficulties due to the implementation of the Clinical Trials Directive into national laws and regulations, which led to divergent review processes especially for multi-national clinical trial applications in the member states, the Voluntary

Harmonisation Procedure (VHP) was established by the Clinical Trials Facilitation Group and introduced in Marche 2009 [14]. In Table 1 an overview is presented over the regulatory framework for approval of Clinical Trial Applications within the European Union and its past and expected changings.

2001	Directive 2001/20/EC
2004	Directive 2001/20/EC became effective
2004	Clinical Trial Facilitation Group (CTFG) was established by HMA
2009	VHP was initialised
2010	Revised Commission guideline 'CT-1' 2010/C82/01 relating to Clinical Trial Applications
2010	VHP Updated Guidance (v2)
2011	Commission guideline on the definition of an IMP/NIMP
2012	Proposal for a 'Clinical Trials Regulation'
2013	VHP Updated Guidance (v3 / 3.1)
2014	Clinical Trial Regulation EU/536/2014
2014	VHP Updated Guidance (v3.2)
2016	Clinical Trials Regulation will come into force (only if EU-Database is fully functional, otherwise 6 months after functionality has been formally confirmed)
3 years	CTD is still in force; the sponsor can choose the legislation for his trial
2019	Clinical Trials Regulation's final coming into force as sole CT legislation or later if database functionality is delayed

Table 1: Development of European regulatory framework for Clinical Trials Applications

Since no adequate harmonization has been achieved, 2014 the new Clinical Trial Regulation (EU) 536/2014 was enacted and will come into force in 2016 and as sole clinical trial legislation in 2019 at the earliest. In the meantime the VHP will be provided as alternative to single national clinical trial applications in all member states planned to be involved in a clinical trial.

In this Master Thesis, a brief description of the approval process of clinical trial applications in Europe is described. Then, a placement of the Voluntary Harmonisation Procedure should be undertaken as well as development, advantages and its value for future regulatory adaptations should be highlighted.

B Multi-National Clinical Trials Application

As outlined in the introduction, most of the EU countries already had their own legislation and practice before the adoption of the Directive 2001/20/EC. Some countries developed legislation centred on the patients, with an equivalent level of protection in any type of biomedical research. Whereas other countries adopted legislation centred on the product, focusing on the credibility of data used for registration purposes, and in which the protection of participants is restricted to clinical trials on medicinal products. The type of clinical research covered by these laws and the nature of the protection widely varied between the countries. This resulted in major challenges for commercial as well as academic applicants involved in multi-national studies within the European Union [15]. This pointed up the need for harmonisation of the legislative framework for clinical research in the European Union, with the objective of harmonising the regulatory systems, of improving the protection of participants, of optimising the use of safety information, and of ensuring the quality of studies and the credibility of data [15].

1 Current Regulatory Environment for the Approval of Clinical Trial Applications within the European Union

The “Clinical Trials Directive” 2001/20/EC, the “GCP-Directive” 2005/28/EC and the “Detailed guidance 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/C82/01, which had been implemented according to Article 9(8) of the Clinical Trial Directive, represent the legal and regulatory framework for application, assessment and authorisation of clinical trials by competent authorities in the European Union [1; 2; 4]. In addition the “Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use” (ENTR/CT-2) ruled out general aspects of the requirements and the procedure for requesting the opinion of the ethics committee according to Article 3(2a) and Article 6 of the Clinical Trials Directive [3]. A further

number of guidance documents presented in the “EudraLex” database under “Notice to Applicants, Volume 10” completed the legislative environment for the preparation, approval, performance and reporting of clinical trials.

1.1 European Clinical Trials Directive 2001/20/EC

Clinical trials on one or more investigational medicinal products for human use with the object of ascertaining their safety and/or efficacy are governed currently by Directive 2001/20/EC, defining the requirements for the conduct of clinical trials for medicinal products for use in humans in the European Union [1]. Issued in 2001, this Clinical Trials Directive signified a milestone for the performance of clinical trials within the European Union. Approval of clinical trials is under the responsibility of individual Member States and involves a thorough evaluation of the products used in the clinical study. The so called “Clinical Trials Directive” 2001/20/EC became effective in 2004, but its required implementation in the different EU Member States, occurred by transposition into national laws of each member state, was only completed in 2006 [8].

Its main objectives were [15]:

- protection of human subjects in clinical research
- implementation of the Good Clinical Practice (GCP) standard in all clinical trials with medicinal products
- harmonised procedures for clinical trial authorisation from competent authorities and ethics committees
- central collection of information on clinical trial activities and safety results

After adoption of the Clinical Trials Directive 2001/20/EC, the interpretation and the changes brought to the national legislation due to the now established Clinical Trials Directive were highly dependent on this pre-existing framework. Generally, transposition of an EU Directive left considerable room for interpretation at national level, especially in practical aspects. Several EU Member States choose to implement the Clinical Trials Directive in their new clinical research legislation with a wider scope and, consequently, this process resulted in divergent systems [15]. In this context Germany’s competent authorities, *Bundesinsitut für Arzneimittel und Medinzinprodukte* (BfArM) and *Paul-Ehrlich-Insitut* (PEI), confirmed that complete

harmonisation between the member states was not reached by the Clinical Trials Directive but one has to regard the different diagnostic, medical and therapeutic standards in the different member states which might be the reason for diverse evaluations of clinical trial applications [35].

Nevertheless, the Clinical Trials Directive has definitely had their immediate benefits to the Sponsors. In the opinion of different stakeholders, like commercial and non-commercial sponsors, ethics committees and competent authorities, the safety, the ethical soundness and the reliability of data were improved. A major achievement regarding harmonisation of the approval process was that competent authorities start working with same versions of clinical research documents. Furthermore, as a big advantage over the former regulatory situation up from now all documents were submitted in one language. Hence, the same English version of the core document of a clinical trial application, Clinical Trial Protocol, the Investigator's Brochure and the Investigational Medicinal Product Dossier, for instance, could be submitted to all competent authorities of all member states in which the Sponsor plan to conduct the clinical trial within the European Union [15].

1.2 Submission and Approval of a clinical trial application according to the CT-1-Guidance 2010/C82/01

For all clinical trials the request is submitted to the national competent authority of every member state concerned (Article 9(1) Clinical Trials Directive and Article 13 CT-1 Guidance 2010/C82/01). Member states are obliged to introduce requested procedures. In accordance with Article 9(4) of the Clinical Trials Directive and Article 15 of the CT-1 Guidance 2010/C82/01, the assessment of the clinical trial application by the national competent authority shall be done as rapidly as possible. According to this guidance submission to competent authorities can be handled both in parallel to ethics committee submission and sequentially. Sponsor needs one favourable opinion from ethics committee per member state before he can start the clinical trial. Change of submission based on request for additional information is possible once. A clinical trial is approved by implicit authorisation if by day 60 no grounds for non-acceptance (GNA) have been emerged. Member states are allowed to decide on shorter timelines, thus, explicit approval can be given faster. Also, explicit approval is necessary for substances falling under obligatory Central Procedure (biological

products or components, products in oncology, HIV, diabetes mellitus, neurodegenerative diseases), and is required for gene therapy, somatic and xenogenic cell therapy. For complex products like gene or somatic cell therapy or genetically modified organisms an approval time of 90 days is given. If external experts need to be consulted the authorisation period is extended to 180 days. There is no time limit for xenogenic cell therapy. All parties are requested to maintain the English language in their communication and for documentation but the member states are not obliged to do so. Of course, documents that are provided to subjects should be translated in the respective local language [2].

The guideline presents a list of documentation to be provided to the national competent authority of the Member State concerned as followed [2]:

- Cover letter with the contents set out in Section 2.3,
- Clinical trial application form, standardised in all member stated
- Clinical trial protocol with all current amendments
- Investigator's Brochure or document replacing the IB
- IMPD/simplified IMPD, with data on quality, pharmacology/toxicology, clinical results and risk/benefit analysis
- NIMP dossier
- The additional pieces of documentation as set out in Section 2.9, which are ethics committee opinion, Scientific Advice and PIP decision if available, content of the labelling of the IMP as well as proof of payment of fees.

Additional information, according to section 2.10, may only be requested by member states if instead of the ethics committee the competent authority reviews, for instance, indemnity/insurance, compensation of subjects or investigator contract, or if member states have more comprehensive provisions to protect the subject than requested by the Clinical Trials Directive.

Obviously, these additional national requirements on the content of a clinical trial application lead to diverse contents of a clinical trial application for multi-national clinical trials throughout the community and as a consequence to a lack of harmonisation between involved member states.

1.3 Raising Concerns about the Clinical Trials Directive due to differences in national legislation

Apparently, the scientific community has raised concerns whether the objectives of the European Clinical Trials Directive 2001/20/EC in its current form have been achieved [11]. Some problems turned out, as one might expect in a region made up of so many cultures [13]. This Directive was established to advance innovation and research, raise the level of competitiveness of clinical research and improve patient protection by streamlining the scientific assessment of Clinical Trials Applications [11].

Each year ~4,000–6,000 randomized clinical trial protocols are submitted for assessment by either commercial or academic sponsors to the national competent authorities within the European Union and numerous local or central ethics committees. Divergent decisions by national competent authorities on the same clinical trials or various content, format or language requirements, in combination with different assessments made by central and local ethics committees, make it more and more complex to conduct innovative clinical research [11]. Various sponsors have experienced first-hand that scientific evaluation of multinational clinical trial applications in the European Union has led to the unwanted situation of divergent assessments due to inconsistencies in interpretations of application documents. Although the procedures are almost identical, each participating country's Competent Authorities and/or Ethics Committees still had to review and approve the study in detail according to their local regulations [11; 13]. In addition, response times varied widely, while the potential for duplication of questions and parallel discussions with multiple authorities remained [13]. The same situation applies not only for first submission but als for regulatory follow-up procedures regarding the already approved clinica trial protocoll. It is completely separated from one another and does not provide any kind of cooperation or exchange of information [24]. Subsequently, the administrative burden and the costs especially for the conduct of multinational trials have increased significantly since the entry into force of the Clincial Trials Directive [15].

In addition to the differences due to the clinical trial application process there are numerous other issues resulting from the different translation and interpretation of the Clinical Trials Directive into the legislation of the member states. A frequently given

example of substantial heterogeneity is the interpretation of what could be defined as investigational medicinal product (IMP). The Directive 2001/20/EC gives the following definition of the IMP: “a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form or when used for an unauthorised indication or when used to gain further information about the authorised form“[1].

Table 2 demonstrates diversity of the definition of investigational medicinal products of ten different competent authorities within the European Union [18]. Only Austria adopted the definition from the Clinical Trials Directive. The other countries adopted definitions that were similar but not identical. In multi-national clinical trials this could lead to difficulties regarding labelling or safety reporting, for instance, if a product is considered as IMP in one country but not in others. To address this issue, in March 2011 the EU Commission published a guidance on IMPs and non-IMPs (NIMP) for clarification and further harmonisation [18].

Further areas of heterogeneity are identified as, for instance, the definition of interventional and observational studies, the variability of insurance requirements, differences for adverse event reporting and what could be interpreted as substantial amendment. Significant is also the variability in number and role of competent authorities, the number and role of ethics committees, the process leading to one single ethical opinion per member state as well as the interaction between competent authorities and ethics committees. Varying practice in competent authorities and their dialogue with the ethics committee resulted in significant differences in clinical trial application procedures. One example is the parallel submission by the sponsor as the rule in most countries, in contrast to use of a one-stop shop approach in Hungary in which the competent authority, not the sponsor, interacts with the central ethics committee [15; 17].

Countries	Definition of investigational medicinal product
Austria	The definition is that of the Directive 2001/20/EC.
Denmark, France, Hungary, Ireland, Italy, Spain, Sweden, UK	The investigational medicinal product is the study drug and the comparator including the placebo or active drug.
Denmark	The rescue drug and all background treatment that directly influences the main efficacy outcomes of the study are also considered investigational medicinal products.
France	The background treatment is also considered an investigational medicinal product if collecting information on it is one of the objectives of the study.
Germany	The investigational medicinal product is a pharmaceutical form of active pharmaceutical substances and placebos that is tested in a clinical trial on humans or used as a comparator or that is applied to induce specific reactions in humans. This includes EU authorised drugs if they are investigated within a clinical trial, EU authorised drugs if they will be used as comparator, and EU non-authorised drugs.
Italy	The drugs which are not the direct subject of the experimental design, but their use is considered in the protocol, are also considered investigational medicinal products: 1. Drugs with market authorisation, used according to the indications, included in the protocol as needed to the success of the trial, such as drugs to prevent or treat side effects of the investigational medicinal product. 2. Drugs with market authorisation, used outside the approved indication. 3. Drugs without market authorisation, but with market authorisation in other countries of the EC, used within or without the approved indication. 4. Challenge agents, i.e., drugs that are used to induce physiological reactions needed to evaluate the effect of the investigational medicinal product. The rescue drug, and background treatments are not investigational medicinal products.
Spain	Background treatment, the rescue drug, the challenge agent and the medicine used to assess the primary endpoint, if not authorised in any EU country, or when authorised and used for non-authorised indications are also considered investigational medicinal product.
Sweden	The drugs used to assess outcome measures are also considered investigational medicinal products. This includes already approved drugs, which have been formulated differently or are used outside their approved indication, or used to gain additional knowledge about the approved indication.

Table 2: National definition of an investigational medicinal product (modified according to [17])

To sum up the criticism for the Clinical Trials Directive, there are some barriers identified to the conduct of clinical trials in Europe. It allows Member States to introduce additional requirements, and both costs for conducting clinical trials in the EU and delay for launching clinical trials are increased. The regulatory approval procedure for multi-national clinical trials are hampered by numerous localising submissions which creates more bureaucracy with high resource needs, differing timelines for approval (but usually 60 days plus clock-stops - delays), assessment by several competent authorities and ethics committees who may reach divergent decisions for the same trial as well as fees to be applied separately in all Member States.

Thus, at least one main aim of the Clinical Trials Directive - the reduction of administrative burden in preparing and performing clinical trials - has not been achieved. Concerns were raised that this administrative complexity is not only hindering clinical research in Europe but even leads to a decreased attractiveness and competitiveness of clinical research in Europe, especially in the non-commercial sponsor sector [15]. In summary one can say that a great common purpose should be improvement of harmonisation of the approval processes and practices across European member states beside intensification of communication and a system of sharing expertise and information. That would be strengthen the attractiveness of Europe for clinical research.

2 Clinical Trial Facilitation Group (CTFG)

As a major step to address these issues and for achievement of harmonization of clinical trials in Europe, in 2004 the EU Heads of Medicines Agencies established the Clinical Trials Facilitation Group (CTFG) as a working group to coordinate the implementation of the EU Directive 2001/20/EC. The CTFG acts as a forum for discussion to agree on common principles and processes, and promotes harmonization of clinical trial assessment decisions and administrative processes across the national competent authorities of the member states [19; 33]. Members and Representatives are from the national competent authorities of each member state, the European Commission (EC) and the European Medicines Agency (EMA).

Representatives from other interested parties may be invited to attend the CTFG meetings.

In order to achieve and to implement this mandate CTFG the working plan contains the aims of sharing of scientific assessment of multinational clinical trials, of harmonizing processes and practices relating to clinical trials mainly in the fields of clinical trial applications, clinical trial amendments and safety procedures, of developing data sharing and participating in the improvement of information systems as well as developing communication channels with stakeholders and co-operating with other European working groups [19; 20].

The main objectives of the assessment of the clinical trial are to ensure subjects' safety and IMP's quality and safety. To further harmonize the review and assessment process of multi-national clinical trials by Competent Authorities within the European Union, the CTFG proposed a procedure before the initial phase of the national process and on the voluntary basis, which combines the disseminated review of a clinical trial application with a joint assessment [19].

In 2009 the CTFG started the Voluntary Harmonization Procedure (VHP) as an alternative to the current national clinical trial application submission procedures within the current legal framework plus production of a “Guidance document for Sponsors for a Voluntary Harmonization Procedure (VHP) for the Assessment of multi-national Clinical Trial Applications”. Thus, by VHP a programme was supplied that allows a sponsor to obtain a consolidated assessment for multinational CTAs or substantial amendments by avoidance of submitting clinical trial applications to national competent authorities of any participating country - a so called “one-stop-shop” was generated.

3 VHP and its impact on CTA

3.1 Development of the VHP

Between April and August 2009 a pilot study of the VHP, as first proposed by the CTFG, was conducted. It translated the idea of a process for streamlining the process of submission, review and approval of Clinical Trial Applications in the European Union into action. The first version of the guidance described and invited

applications for multi-national clinical trials involving more than three member states, investigational medicinal products without a marketing authorisation in any European member state, or special clinical trials (for example large Phase III trials, first-in-human trials, or trials on orphan drug). This first version started with a 'pre-procedural step'. A letter of intention to participate had to be submitted before the fifth day of the month, wherein the qualification of the clinical trial for the VHP was exposed. The acceptance amongst the sponsors was not as initially expected. In 2009 only fifteen applications were submitted including eleven procedures from the pandemic influenza situation in 2009 (see Fig. 1). Following this, a revised version of the VHP (v2) was presented in March 2010. Essentially, the scope of the VHP was enlarged and the timelines shortened. The main changes in version 2 with respect to version 1 were the acceptance of all clinical trials with all IMPs/NIMPs in the VHP if at least three member states were involved, the cancellation of the 'pre-procedural-step' to shorten timelines by several weeks, as well as the inclusion of substantial amendments to clinical trial applications. Generally, VHP requests should have priority in the daily national competent authorities work. Hence, in 2010 the CTFG had received 26 applications to participate in the VHP (see Fig. 1). From the perspective of the authorities or the CTFG respectively, one of the biggest improvement of version 2 was the implementation of an internal leading member state. Its tasks were to consolidate the list of questions from the single member states arising during assessment. This avoided redundancy of questions and reduction of initial questions by around 50 %. In the next years the assessment of the multinational Clinical Trial Applications underwent the VHP has been improved. In 2011 the leading member state was replaced by a reference-national competent authority (REF-NCA) from which the other participating national competent authorities (P-NCA) receive the preliminary internal assessment report. Based on this report they decide if they have further questions to the applicant to produce a higher consolidated list of grounds for non-

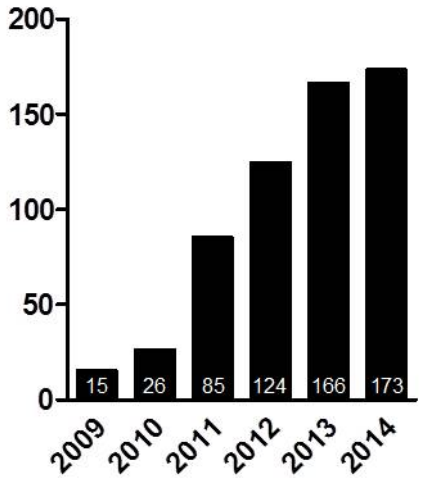

Fig. 1: Number of VHPs per submission year (source: VHP-Coordinator, PEI, results of VHP, status 20.1.2015)

acceptance (GNA). Up from version 3.2 (December 2014), the designation of a REF-NCA is mandatory for the applicant but not binding for the NCAs. Consequently as the VHP is a voluntary process, if no other P-NCA volunteers for REF-NCA the application will be rejected. Further modifications in version 3 of the VHP guidance, launched in April 2013, were placed in order to streamline the assessment, to shorten the timelines and to regulate a VHP or substantial amendment submission with conditions beside the introduction of a second round for the inclusion of additional member states after a positive VHP opinion. The increasing number over the years as shown in figure 1 is indicating the sponsor's acceptance of the VHP - 173 VHPs were submitted in 2014. Since 2015 the NCAs communicate via an internal portal for the member states, makes it much easier and therefore faster to come to a consolidated list of GNAs. As one may recognize, the VHP adapts more and more to the demands of the coming regulation, and certainly the Voluntary Harmonisation Procedure will be terminated when the Clinical Trials Regulation comes into force for all clinical trials. [5; 9; 14; 20]

3.2 Rational, Key Features and Main Advantages of the VHP

As lay down in chapter 1.3, concerns came up whether the targets of the Clinical Trials Directive have been reached. There is still a lack of harmonisation in some areas such as documentation requirements on content, format or language in combination with different assessment procedures. Accordingly, scientific evaluation of multinational clinical trials submitted for assessment by both commercial or academic sponsors to different 28 European national competent authorities as well as many local and central ethics committees has led to the unwanted situation of divergent decisions in dissimilar timelines (see Fig. 2A), causing costly delays in the overall clinical trial procedure [9; 11]. Also, diverse opinions may lead to changes to the protocol after the trial has been initiated in other countries, resulting in a non-uniform clinical trial design [10]. This situation makes it highly complex to conduct innovative clinical research in the European Union.

As a specific step to resolve challenges surrounding clinical trial application management in the individual countries and to streamline the assessment process for clinical trials conducted in more than one member state, the CTFG introduced the

“Voluntary Harmonisation Procedure”. They produced a guidance document in order to propose a harmonised procedure for assessing multi-national clinical trials by the national competent authorities in the European Union. The VHP respects the need for national competent authorities to make their own decisions on clinical trial applications, as required by the Clinical Trials Directive [5; 10; 38]. Therefore and in order to achieve timely solutions without waiting for time consuming changes in European legislation, the VHP has been set up within the current legal framework for clinical trials [13].

The basis for the VHP forms a coordinating process that takes place prior to national review of the formal Clinical Trial Application by which, as a first step, the sponsors submit the application to a coordinating institution and, at the same time, name all the countries in which they would like to perform the clinical trials. By this means, a parallel discussion and collaborative assessment of the application could take place.

The coordination institution is the CTFG and the Paul-Ehrlich-Institute (PEI) acts as the VHP-Coordinator (VHP-C). [16]

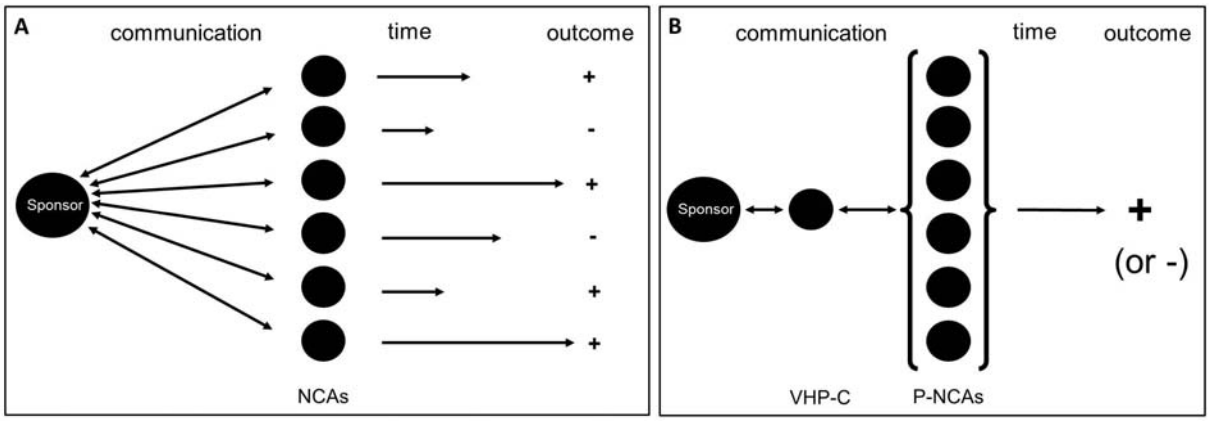

Fig. 2: EU multinational Clinical Trials - (A) Current Situation and (B) VHP (NCAs = National Competent Authorities; VHP-C = VHP-Coordinator; P-NCAs = participating National Competent Authorities; modified according to [39])

As schematically shown in figure 2B, via this way VHP would have made applicants enable to send all clinical trial submissions for a study to be conducted in multiple European countries to a single email address, to submit a harmonised set of documents for any kind of study and to get a response in pre-defined accelerated

timelines in a harmonised manner that could be an approval, rejection or request for further information on the clinical trial documentation [13].

Here it is clearly demonstrate, that the main advantage of the VHP for the sponsor is the provision of a ‘one-stop-shop’ to gain one decision for a multinational clinical trial. This includes a single highly consolidated list of questions rising during the scientific assessment. Thereby, the number of questions was decreased by about 50 % resulting in significant savings in time and resources. For the participating national competent authorities a great advantage is that the assessment of a multinational clinical trial application is done in a coordinated way. As a result, there is a significant reduction in the number of substantial amendments. Member states may profit from the operating experience of others which offers the opportunity of work-sharing and leads, as a result, to a higher consolidated list of questions for the sponsor just as well as to a clear and brief list of answers.

3.3 The Process Sequences of the VHP

The VHP is appropriate for all multinational clinical trials. The only restriction is that the application has to be intended for two or more member states which agree to participate, beside the precondition that the clinical trial application is not already submitted or approved in a European member state prior or during VHP [5].

The cause of VHP involves three phases:
1) Request for VHP / Validation
2) VHP Assessment
3) Formal national CTA approval

In general and according to the Clinical Trial Directive 2001/20/EC, each member state remains responsible for the approval of a clinical trial application on its territory, which is phase three in the work-flow of the VHP. The national phase is prefaces by a harmonized process on a voluntary basis for both the applicant and the national competent authority, realized by CTFG. Annex 2 discloses all Member states of the European Union whose competent authority confirmed their participation in the moment this master thesis was generated. Subsequently, this allows a coordinated parallel assessment resulting in a consistent decision. The VHP-Coordinator (VHP-C) is, according to the guidance document, a CTFG representative who is responsible for the coordination of all VHPs. The VHP-C is provided by the Paul-Ehrlich-Institute

(PEI), Germany, and is the only contact for the applicant during the VHP in order to guarantee that all NCAs receive identical information. The applicant for his part is not allowed to contact the NCAs as well as to submit any documents to P-NCA directly before the VHP-C directed to do so as this could lead to non-harmonised documentation. [5]

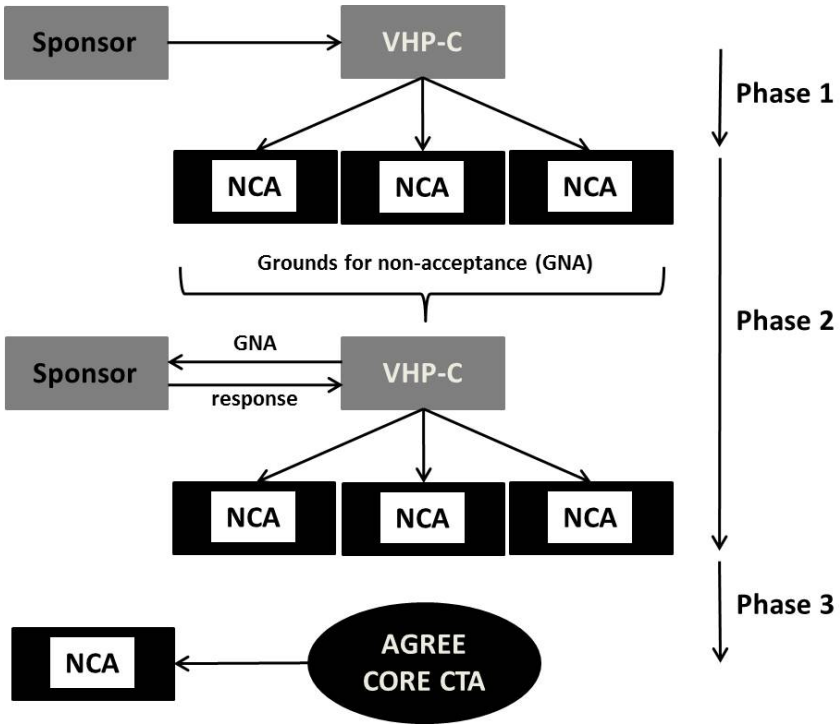

Fig. 3: Summary of the authorisation procedure under VHP (NCA = National Competent Authority, VHP-C = VHP-Coordinator, GNA = Grounds for non-acceptance, CTA = Clinical Trial Application; modified according to [42])

3.3.1 Phase 1: Request for VHP and CTA Validation

The sponsor, commercial or non-commercial, makes a written application to the CTFG and VHP-C, respectively, via e-mail or EudraLink in a defined electronic structure requesting participation in the VHP. In this electronic letter the VHP-applicant should describe the key features of the clinical trial and indicate all member states planned to be involved in the project. One of them should be proposed as Reference-NCA (REF-NCA) who would be responsible, according to the guidance document, for the principle scientific assessment, the consolidation of the grounds for non-acceptance (GNA), and the re-assessment of the response to the GNAs in collaboration with the participating NCAs (P-NCA). If no proposal for a REF-NCA is

made by the VHP-applicant, the proposed P-NCA refused to be the REF-NCA and no other P-NCA volunteers for REF-NCA, the VHP application will be rejected. As mentioned before, this proposal is not binding for the NCAs. Within the “Request for VHP” the sponsor has to provide all the documentation required for the assessment of the CTA (for details see Table 3 and Annex 1) [5].

Content of a “Request for VHP”
• Covering Letter (with EudraCT number)
• List of all competent authorities to which the applicant intends to submit a CTA
• Proposal of a REF-NCA
• CTA EudraCT form
• Protocol including synopsis
• Investigator’s Brochure
• IMP Dossier / NIMPs Dossier (if applicable)
• Manufacturing or import authorisation
• Good Manufacturing Practice compliance certificate
• Certificate of analysis (if applicable)
• Authorisation for special products (eg. genetically modified organisms)
• Copy of summary of any scientific advice
• Paediatric investigational plan (if applicable)

Table 3: Content of the “Request for VHP” (modified according to [5])

After receipt the VHP-C, immediately, will create a VHP file, assign a VHP number (EudraCT number with VHP prefix), and forward the documentation to the P-NCAs. Within five working days the applicant will be informed whether the application is valid and to be considered for the VHP, about the starting date of the VHP, and if all requested NCAs agree to participate. Any missing information should be submitted within three days. If NCAs refuse to participate a parallel national application to these member states would be possible on the recommendation of the VHP-C [5]. Also, a parallel submission to Ethics Commissions should be taken into account in order to save time.

3.3.2 Phase 2: VHP CTA Assessment

Day one of phase 2 is the start of VHP. Phase 2 is for its part divided into two steps (see Fig. 4). In the first assessment step within about 30 days the NCAs may accept the application unanimously, request further information or present a list of grounds for non-acceptance (GNAs) consolidated by the REF-NCA. If no objection is raised by any P-NCA the VHP ends and the process moves to phase 3. If any GNAs rose during this step the applicant is requested to address these questions within 10 days. Any response will then be assessed by the P-NCAs and after another 20 days a common final decision is issued that is positive, negative or positive with conditions. As shown in figure 4 this leads either to the end of VHP and subsequent continuation with phase 3, or to the fulfilment of the conditions by submitting the revised documents within 10 days, response if the documentation is acceptable after 8 days and, again, subsequent continuation with phase 3. In case of a negative decision, which requires a resubmission, the remaining GNAs and commends to facilitate the resubmission are send to the applicant. CTFG recommend VHP-resubmission strongly as the better alternative to single non-harmonised national applications. If there is no consensus reached between the P-NCAs of the VHP, the unsolved GNAs with the particular P-NCAs will be disclosed to the applicant. In this case, as respects to timelines and substantial amendments (VHP-SA), VHP continued solely for p-NCAs which consider all GNAs as resolved. [5]

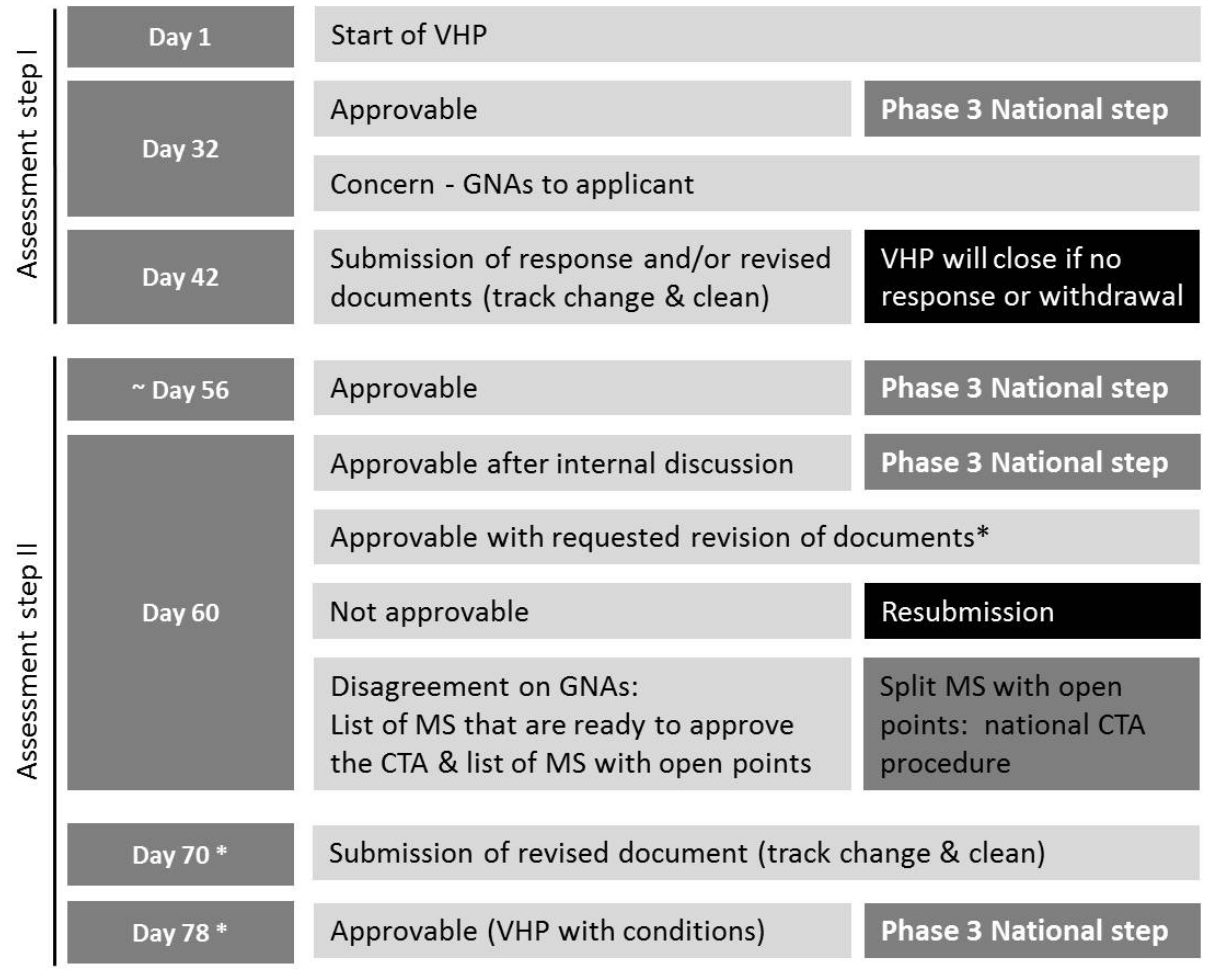

Fig. 4: **Phase 2 - VHP CTA Assessment Step** (modified according to [5])

3.3.3 Phase 3: Formal national CTA approval

Once the VHP assessment has been completed, within 20 days the applicant has to submit a formal clinical trial application to each P-NCA (see Fig. 5) according to the Clinical Trial Directive 2001/20/EC, the CT1-Guidance and the national regulations of the member state, respectively. The national clinical trial application should be accompanied by the VHP decision letter indicating the outcome of the procedure and the versions of the core documents already approved in the VHP [5]. After a positive VHP the decision of the NCAs should be provided within 10 days, but due to specific national issues (an ethics committee opinion required prior to approval of the clinical trial application, for instance) could extend the national approval time.

Within 20 days of approval	Submission of formal CTA to each P-NCA letter of decision on VHP + country-specific documentation
Within 10 days* of valid CTA	Procedure and decision according to national laws * The 10 days relate to NCA decicions only. In MS where NCAs have to forward the CTA to EC or other committees different timelines for decisions might result.
After P-NCA's decision	Information of VHP-C by applicant on outcome of national CTAs (with respect to VHP decisions)

Fig. 5: **Phase 3 - VHP CTA National Step** (modified according to [5])

3.3.4 Second Round (SR-VHP) and Substantial Amendments (VHP-SA)

One precondition of the approval process of a multinational clinical trial via VHP is that the clinical trial application is not already submitted or approved in a European member state prior or during VHP. Additionally, in the initial request of VHP the sponsor should indicate all member states planned to be involved in the project. It is permitted to mix between single national clinical trial application and application by VHP. An exception is the instruction to do so by the VHP-C after a nominated member state has been declined its participation. To avoid dis-harmonisation in an ongoing clinical trial while the sponsor wishes to include further NCAs after a positive VHP, the second round of VHP (SR-VHP) can be requested. Requirements for a SR-VHP are termination of initial VHP including all national steps as well as no ongoing

substantial amendments (VHP-SA); moreover, all substantial amendments had to be submitted via VHP to ensure harmonisation over all P-NCAs. The number of member states nominated in the SR-VHP should be less than in the initial VHP of the clinical trial. The course of the SR-VHP includes, as the initial VHP, a request and validation, two assessment steps followed by the national approval. The initial REF-NCA will remain the same in the SR-VHP as well. The request should contain a justification of the necessity, a list of additional member states, updated versions of the core documents approved by VHP / VHP-SA as well as all e-mails related to initial VHP or VHP-SA decisions. [5]

To keep the core documentation of the multinational clinical trial harmonised during the ongoing clinical trial substantial amendments in all P-NCAs are indispensable. For this purpose and under the condition the CTAs have already been approved in all P-NCAs substantial amendments (VHP-SA) can be submitted to the VHP-C. The rules of VHP-SA follow in principle the CT1-Guidance (2010/C82/01) and national guidances of the P-NCAs as well as the course of initial VHP with shortened timelines. Submission of substantial amendments outside the VHP-SA procedure lead to exclusion from further VHP-SA or SR-VHP because harmonisation is not guaranteed anymore. [5]

3.4 Results of the VHP / Main Advantages

VHP has been available for seven years now. As illustrated in figure 6, the VHP has received increasing acceptance since its implementation in 2009 although the initial uptake was slower than anticipated. The number of VHP submissions has increased annually for both clinical trial applications and substantial amendments, with almost 20% of all multinational clinical trials in Europe undergoing the VHP before being

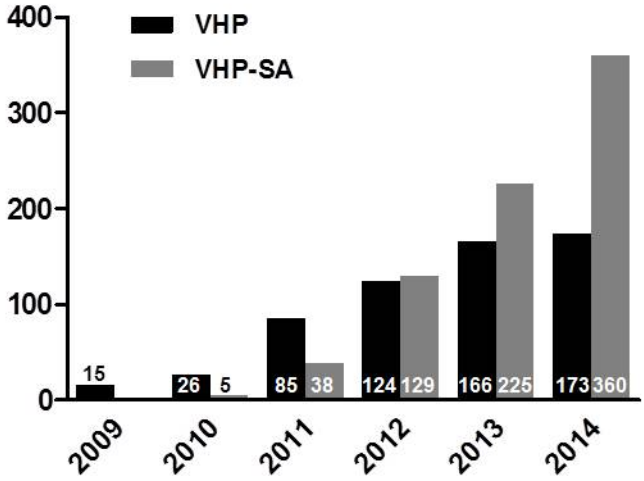

Fig. 6: Numbers of VHP and VHP-SA per submission year (source: VHP-Coordinator, PEI, results of VHP, status 20.1.2015)

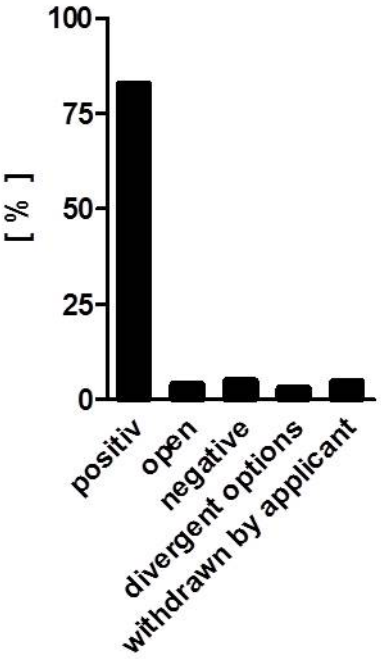

Fig. 7: Percentage of VHP decisions 2009 - 2014 (source: VHP-Coordinator, PEI, results of VHP, status 20.1.2015)

submitted to national competent authorities in 2014. As of December 2014, most of the EU national competent authorities had joined the VHP, although not all authorities had actually taken part at that time. Annex 2 presents a List of Member States participating in VHP by first of January in 2015. Up to the end of 2014, 82.9% of VHPs had a positive outcome, with only 5.0% not being approved. The remaining applications were either open (4.1%), subject to divergent opinions (3.1%) or withdrawn by the applicant (4.8%) (see Fig. 7). [20]

Multinational clinical trials for all phases have been filed for VHP (see Fig 8). Over the period of evaluation the VHP has been used most commonly for Phase II and III trials although initially intended for first in men studies among other special clinical trials like very large Phase III trials or trials on orphan drug [20].

On average, six Member States are involved in each VHP (minimum two P-NCAs, maximum 16 P-NCAs). For the period under evaluation, the mean duration of a VHP submission (excluding open, withdraw, ATMPs and accelerated VHPs but including the additional time required for submissions with grounds for non-acceptance) was 52.5 days (minimum 0 days, maximum 75 days) for a VHP decision [20].

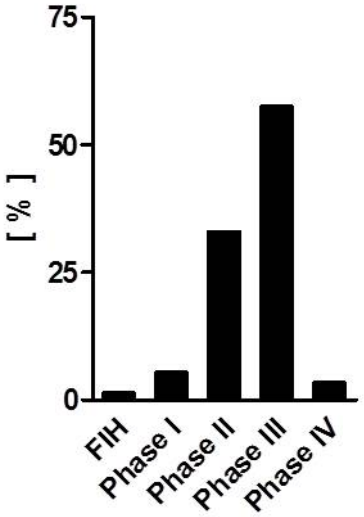

Fig. 8: Distribution of trial phases CTAs were filed for from 2009 to 2014 (source: VHP-Coordinator, PEI, results of VHP, status 20.1.2015)

The total numbers of 165 different sponsors (2009-2014) have used the VHP. Overall, 91% of VHP submissions were made by commercial sponsors (Fig. 9A). Notably, the greatest acceptance came from the United States with almost two times as many submissions being made (216) as any other country, followed by Switzerland (106), Germany (73), France

(45) and the United Kingdom (42). Remarkably, the distribution of the investigational medicinal product (IMP) regarding the nature of the IMP is almost equally between chemical entities and biologics (Fig. 9B). With respect to the status of the marketing authorisation approximately 16% of IMPs are authorised versus 83% non-authorised (Fig. 9C). [20]

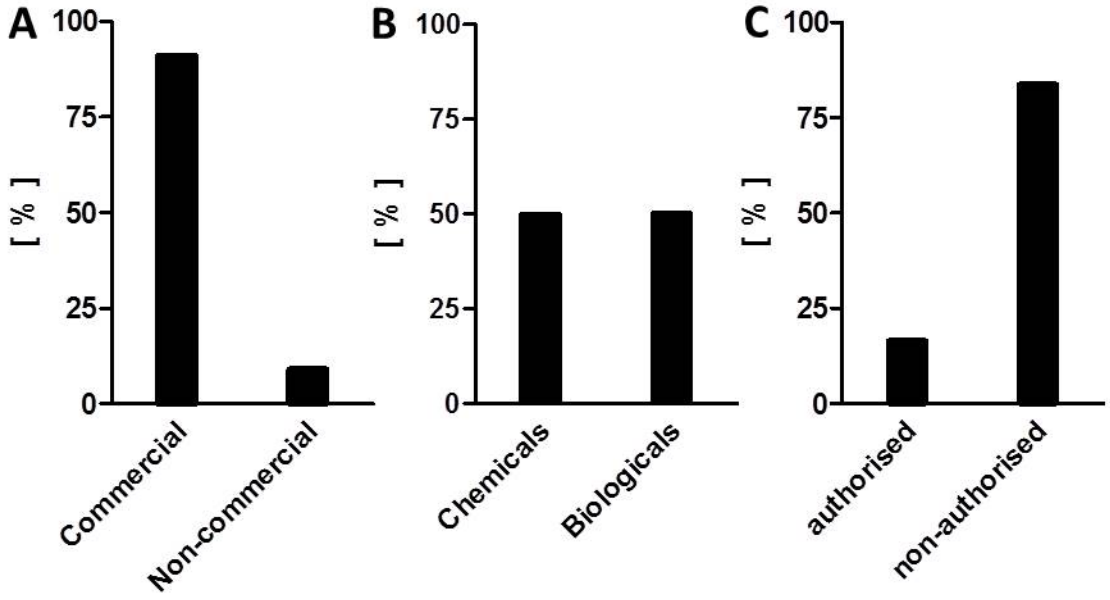

Fig. 9: Distribution of VHP by (A) Sponsor, (B) nature of IMP and (C) status of IMP
(source: VHP-Coordinator, PEI, results of VHP, status 20.1.2015)

3.5 Discussion - Strengths and Weaknesses of VHP

It is obviously that there are advantages and disadvantages when implementing a voluntary procedure in a highly regulated field like clinical research for improvement of harmonisation between 28 member states and numerous different stakeholders. Some of the companies that tried to use the VHP shared their experience and overall they considered the VHP as positive with good collaboration between CTFG and the sponsor leading to timely approvals of CTAs by the involved NCAs. The extensive cooperation between Member States generated by VHP results in enhanced harmonisation of the review procedure for CTAs of multinational clinical trials [9]. The main argument for the decision to undergo a VHP as a procedure taking place before the national approval process is the option to obtain a consolidated list of questions and a common scientific opinion with the chance to get approval for a uniform trial design in all participating Member States.

3.5.1 Pro VHP

Various stakeholders see VHP from different perspective; thus, the benefit is judged differentially.

Most NCAs support the VHP for multinational trials as a cost-effective process, which can be used with the currently applicable legislation without time-consuming changes in EU legislation. From the perspective of the NCAs and the CTFG the VHP is very useful to avoid divergent decisions and offers the features requested by a majority of stakeholders [16]: a one-stop shop for CTAs to obtain a positive decision for multinational clinical trials unified by the NCAs concerned, besides assessment of the electronically submitted single CTA dossier in English in appropriate timelines. As of the strong cooperation of the Member States the VHP accessed the best expertise in the Member States, without any obligation to participate. The joint assessment provided the possibility for less experienced NCAs to resort to more experienced NCAs to accept study specifics. A time saving SR-VHP can be offered and the number of substantial amendments is significantly reduced, which, in addition, lead to reduced workload on both sides NCAs and Sponsor.

The majority of Sponsors used the VHP so far are convinced of a clear benefit for the approval of multinational clinical trials.

The Sponsors major advantages on **scientific level**, as already mentioned, are the consolidated scientific assessment of the CTA, the binding VHP decision for all P-NCAs as well as the potential for less conflicting advice. It provides a simultaneous multi-member state review of the CTA resulting in a homogenous data package and subsequently de-risking of clinical development.

On **operational level** comparatively the VHP is a simple procedure for the applicant. There is only one single point of contact, the VHP-Coordinator, who is open for discussions even for planning. Only one set of core documents are required for application, all in one language (english). Translation and country specific documents can be prepared in parallel to the scientific assessment in the VHP before the national phase, thus, a faster submission of core CTA is possible, as national documents are only required in phase 3 of the VHP. Only one single harmonized list of questions, which has been discussed by all concerned member states, lead to significant reduction in number of questions and substantial amendments, especially

with the induction of the REF-NCA. Any divergent opinions were resolved during the VHP. Hence, there is only one round of Sponsor-NCA-interaction.

Timelines given in the VHP guidance are strictly adhered, which allows predictability of actions as well as optimizing resources and availability of experts. The operating experience has shown that non-participating NCAs may also consider the shorter timeline after the positive VHP opinion. Overall, additional benefit is gained by greater flexibility in internal resource management since VHP leads to reduction in applicant's workload and administrative burden, despite or perhaps as an additional step was introduced before the national assessment.

Strategically, the sponsor benefits by a streamlined CTA/SA approval process for common scientific review represented by VHP. NCAs consider VHP as a priority, and VHP provided a platform of broad expertise for networking with NCAs. Amendments during the execution of the clinical trial can also be submitted via the VHP process guarantees the maintenance of harmonized documentation. VHP represents a kind of pre-assessment of the CTA which allows identifying and possibly dropping difficult countries before the national phase. Additionally, post-VHP the Sponsor can add new member states to join the VHP-decision. In particular where many member states are involved reduced timelines to CTA in all P-NCAs are obviously.

3.5.2 Contra VHP

In terms of weaknesses one have to keep in mind that any CTA and approval by NCAs still have to follow the rules of the Clinical Trials Directive and its related guidances. Furthermore, VHP is still a voluntary program for both NCAs and Sponsors, and the fundamental problems related to the different national interpretation of the Clinical Trials Directive are not addressed through this voluntary approach. Thus, a positive point for the use of VHP is to know within two days, which Member States have refused to participate, so that the standard national procedures in the non-participating countries may be initiated quickly. But a major challenge is then to perform VHP and national CTA in parallel. If VHP calls for changes to core documents, it is difficult to keep the non-participating countries consistent and vice versa. Therefore, one clear disadvantage of the VHP is seen in the fact that some Member States are already opting out.

Regarding the scientific assessment some concerns came up if some opinion leaders may dominate the discussion, which could lead to potential conflicting device, depending on the opinion leader.

What can be seen as benefit on one hand is a disadvantage on the other. The procedure only allows a 10-day period for the sponsor for obtaining clarification and responding to the list of questions raised by the NCAs. This short timeline may be difficult to meet if requests from the NCAs involve submission of documents needed from different sources (e.g. contract manufacturing organizations). These issues should be kept in mind by the sponsor when deciding which pathway to select for their CTA (Quelle4). The timelines are not negotiable, but descriptions of the planned changes and commitments are acceptable at this stage, for implementation during the national phase.

To accommodate the short turnaround times and prevent potential resource problems resources must be planned tightly to address NCA queries. Additionally, some stakeholders stated that in a VHP resources are not used more efficiently because formal national applications and approval are still necessary after the parallel VHP assessments. This might lead to an additional prolongation of the timelines for the assessment. On the other hand, amendments have to be rolled out over all P-NCAs, no local amendments are possible.

In phase 3 of VHP, the formal national CTA takes place. Since VHP does not address the problem regarding different national requirements the sponsors will be granted a short period of 20 days for national CTAs. If submitted within 20 days the 10 days approval time is guaranteed; however, if submitted later extended approval time may be still taken into consideration by the NCAs. Approvals at national phase usually take longer than ten days in some Member States and unpredictable timelines at national phase still make planning study start-up activities difficult. In some countries VHP takes longer than the national route (UK, the Netherlands, Belgium).

A major and often inquired issue is that Ethics Committee (EC) review is outside the scope of the VHP. In some member states a rejection from EC could lead to an administrative rejection by the NCA. In other cases EC approval is required before the NCA may issue the national regulatory approval. Anyway, EC approval is

required before conducting the clinical trial with possible delay of the initiation of the clinical trial.

3.5.3 VHP (+) Pilot

Ethics Committee review is outside the scope of the VHP, and therefore, the current problems relating to harmonisation of procedures and decisions between NCA and ECs still remain. To gain experience with stronger cooperation between NCAs and ECs version 3.1 of the VHP guidance introduced a pilot involvement of ECs [12]. For the four Member States Spain, Portugal, Hungary and Germany (see also Annex 3) applicants are invited to contact the VHP-C for details if they are interested to involve ECs in a VHP. The joint assessment currently focuses on the clinical trial protocol and investigator's brochure. The submission of the specific documents for ECs occurs during the national phase of the VHP. ECs participate in the discussion of the assessment step I during phase 2 of the VHP and contribute to the consolidated list of GNAs as well as the discussion of responses. During phase 3 the separate formal submission to ECs take place to obtain ECs opinion. There is a gentle agreement that GNAs should not be raised again in the national procedure. Nonetheless, there is no or only slide reduction in national review by ECs as not all documents for ECs, like suitability of sites and investigators, informed consent and insurance, were assessed in VHP (+). [5; 22; 23]

3.5.4 Discussion

The VHP has not been able to address all of the fundamental problems resulted from the divergent interpretation of the Clinical Trials Directive. As lay down in chapter 1.3, main issues of the Clinical Trials Directive are the divergent application in the member states and the increased administrative burden for clinical trials in view of regulatory requirements which do not take into account practical needs, nearby the fact that the Clinical Trials Regulation does not sufficiently consider the increasingly global scale of clinical trials [24]. As a result within the current system of clinical trial approval processes this causes different document submission requirements, different submission formats, different focus on Ethics versus Regulatory and last but not least different review times across all member states. To keep the attractiveness of the European Union for clinical research, further harmonisation seems to be essential because of the increasing trend for multinational clinical studies, the already

described wide variation in administrative requirements in the Member States, increased administrative burden and costs for conducting clinical trials as well as substantial delays for launching a clinical trial due to the variety of procedures

When discussing the impact of the VHP on the described issues with the Clinical Trials Directive one has to keep in mind that the submission, assessment and regulatory follow-up for the same clinical trial are conducted in different member states is completely separated from one another; accompanied by the fact that these processes does not provide for any kind of cooperation or exchange of information across Member States. Moreover, within each Member State the information is submitted separately to the two assessment bodies NCA an EC. Even though the outcome of the assessment may not differ, the feedback from the NCAs varies as regards requests for additional information, national changes to the clinical trial protocol or GNAs. [24]

This provided the place to start for the VHP with the concept of improvement through harmonizing and streamlining existing processes wherever possible without the time consuming need for new legislation to be introduced. Furthermore does the VHP based on strong cooperation of the participating national competent authorities and intensive coordination by the VHP-C (for all VHPs) as central contact point for the applicant and NCAs during and regarding the procedure. To improve harmonization of the administrative process and to simplify the regulatory requirements for clinical research in the European Union the VHP provide a ‘one-stop-shop’ procedure. Electronic submission of a single core dossier in one language to a single repository reduces markedly the bureaucratic burden. The parallel submission through the VHP-C to all participating member states enables joint assessment of clinical trials and exchanges between NCAs of the Member States concerned. This allows for coordinated scientific discussion and decision on the same clinical trial and improves the scientific review outcome by NCAs. The sponsor benefits from reduced workload as there is only one single list of questions to be answered. Moreover, a joint assessment in reliable timelines avoid substantial delays for initiating the clinical trial which occur if the clinical trial protocol has to be adapted to conflicting assessments from different member states. Nevertheless, VHP does not replace the separate national submission procedures. To consider article 9 of the Clinical Trials Directive, in the final phase the proposed trial goes for formal assessment by each P-NCA, but

this step will then probably take no more than 10 days [25]. The fact that the VHP is voluntary, and Member States may decide not to participate, was often criticised. And of cause, this may diminish benefit and success of VHP by subsequently incomplete harmonization.

VHP addresses not only the submission process but also the assessment process of a clinical trial application. Regarding regulatory follow-up of the clinical trial the number of substantial amendments, which may executed via VHP-SA, is markedly reduced. However, the VHP does not consider other regulatory follow-up requirements of the clinical trial, such as submission of SUSARs, the end-of-trial notification or the annual safety report. And again, one of the major issues of the Clinical Trials Directive that the VHP does not solve regarding both initial and follow-up requirements remains the fact that besides applying to the NCA in each Member State to obtain approval of a clinical trial, Sponsors also have to apply to the respective Ethics Committees.

The VHP offers greatest advantages where many Member States are involved, divergent opinions are anticipated and national documentation not immediately available to achieve harmonised and quick approvals of clinical trials in one procedure. But there is scope for improvement, both in the procedure and with adherence to it. For future activities, resources of this voluntary approach are not sufficient for the broad application. But it provides the unique opportunity to make use of the experience of the voluntary procedure for the development of a structured cooperation mechanism with legally-binding and enforceable timelines for the cooperation of the Member States in order to explore options for the already adopted new approval procedure.

4 Future Regulatory Framework

The adoption of the Clinical Trials Directive in April 2001 defined the "Good Clinical Practice "(GCP) as a binding principle for all clinical trials with human medicinal products in Europe with the objection to simplify and harmonize the regulatory framework for clinical trials within the European Union. In December 2008, the European Commission announced that the impact of the Clinical Trials Directive on

practice should be reviewed. This announcement had been followed by extensive consultation processes on which basis the European Commission focused the Revision of the Clinical Trial Directive as follows [7; 11]:

- creation of a modernized framework for submission, evaluation and accompanying monitoring for CTAs and the conduct of these studies,
- risk-adapted regulatory adjustment of regulatory requirements for the study type and the characteristics of the investigational medicinal products, and
- compliance with the global dimension of clinical drug development with the purpose of ensures GCP compliance worldwide.

The explanation for the need of a new regulatory framework stated that the Clinical Trials Directive has led to a reduction of clinical research in the European Union. An essential argument is that in the years 2007 to 2011 the number of clinical trials has declined by 25% (see Fig 10). [15]

However, this reduction cannot only be attributed to the Clinical Trials Directive, which came into force no later than 2004. The period 2005-2006 was not mentioned as well as the fact that the number of clinical trials has declined in the United States, too. This is, however, attributed to reduction of investment due to severe global economic crises [32]. The need for a further harmonized procedure was seen, in particular, by the fact that 67% of all patients were captured by multi-national clinical trials; although these were only 24% of all studies within the EU. Anyway, the fact remains that the vast majority of clinical trials has not been created multinational (see Fig. 11) [28].

Based on these arguments, on 17 July 2012 the European Commission published the proposal of a European Clinical Trials Regulation (EU-CTR). It tried to address some of the issues of the Clinical Trials Directive including reducing unnecessary administrative burden, without compromising

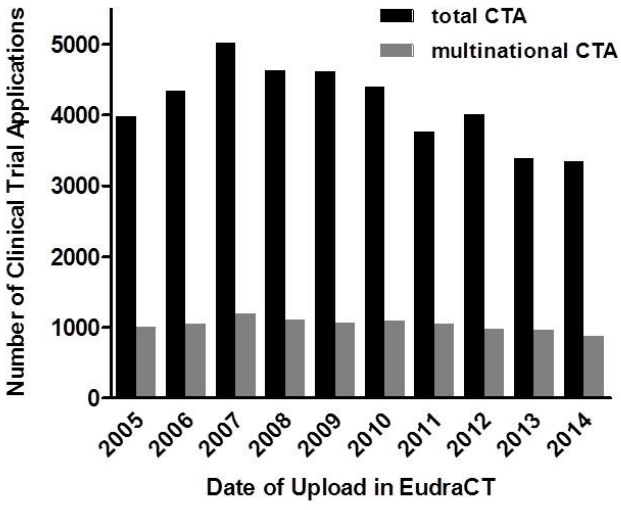

Fig. 10: Number of Clinical Trial in Europe, all CT per year including multinational CT (source [31])

quality, and improving the attractiveness of the European Union for clinical research. The EU-CTR, (EU) 536/2014, was approved in April 2014 and published in the Official Journal on 27th May 2014. The earliest the Clinical Trials Regulation will apply is no sooner than 28th May 2016, and at least six month after the submission portal through which all applications are going to be made is declared fully functional [26; 30]. The EU-CTR is directly applicable in all Member States and differs from a Directive by the fact that no transformation in national law is required. The matter of interpretation for the Member States should therefore be abolished for improving a harmonized assessment within the European Union [28]. When applicable, the EU-CTR will repeal the Clinical Trials Directive. Currently, it is expected that the future regulatory framework will apply by mid-2016.

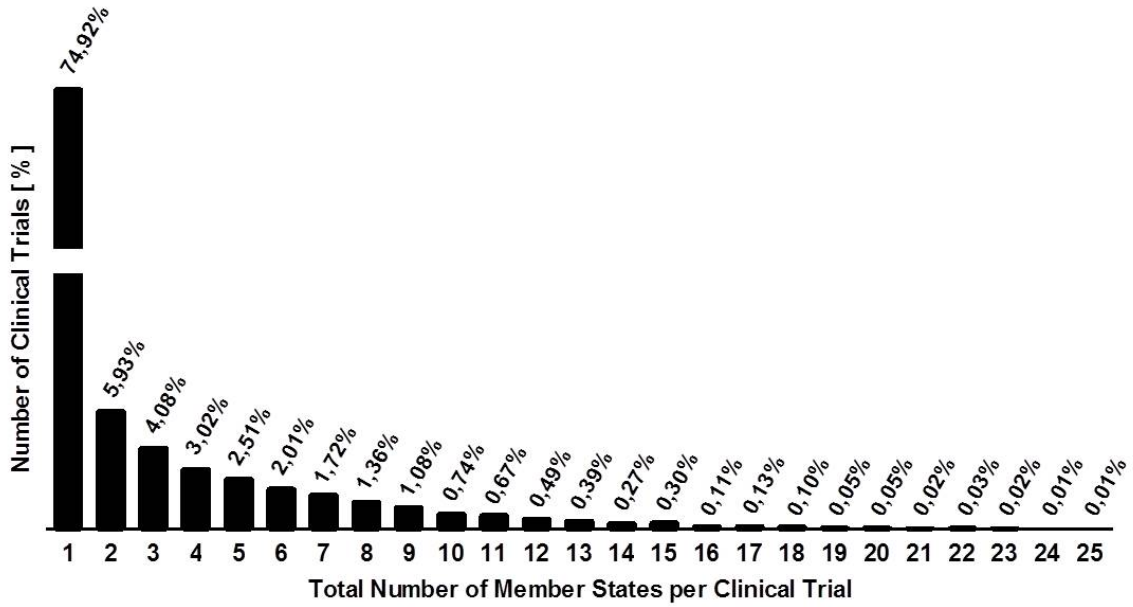

Fig. 11: Distribution of Clinical Trials within the European Union (source [31], status 17.10.2013)

The scope of the EU-CTR is identical to the Clinical Trials Directive, so far, that it relates to all operations regarding clinical trials carried out in the European Union. However, several key definitions have been clarified, for example clinical study, clinical trial, non-interventional study or substantial modification, or introduced, as start of clinical trial, for instance. On the operational site the Clinical Trials Regulation determines new processes regarding authorisation procedure, notification requirements, safety reporting and reporting of clinical trial results.

Basically, the EU-CTR regulates the cooperation of the Member States in the assessment of an application for authorization of a clinical trial, except the areas that related exclusively to national or ethical aspects. This basic approach should be achieved by introduction of a single application dossier, two split procedures in general and national aspects for the evaluation of the application. A major innovation for the entire approval process is the establishment of a web-based centralized EU-portal. Precondition for the harmonized approval process is a common format of the CTA dossier which has to be submitted via this centralized EU-portal. Additionally, future communication channels with regard to the approval process of clinical trials should run solely through this portal. Direct contact between the authorities and applicants is no longer intended. The EU-portal will be set up by the EMA, and no further than six month after an independent audit has confirmed the functionality of the EU-portal and the associated database the EU-CTR will enter into force. [6]

4.1 The Procedure of the Clinical Trials Regulation

In order to get a CTA approved the Sponsor will submit a single application dossier via the EU-portal to all Concerned Member States (MSc) where the study will be conducted at the same time. The harmonized format of the application dossier will consist of two parts according to Annex I of the EU-CTR (see Tab. 4). Parts I and II may be submitted together or, alternatively, only part I and up to 2 years after final evaluation of Part I either Part II. The reviews run in parallel in the same time periods, which means a huge time savings. Since Part I is associated with all the MSc it seems to have little to gain by delaying the submission of Part II, unless there are complex questions regarding the protocol, or some details of the national Part II are not available [29]. The regulation tried to provide a clear distinction between the aspects in which the cooperation of all Member States is required (Part I of the approval process) and the areas in which the Member States conduct the assessment at a national level (Part II of the approval process). [6]

Within the CTA the sponsor has to propose one of the MSc as Reporting Member State (rMS) who will coordinate the approval process. If the proposed Member State may refuse to act as rMS but if there is no agreement among the Member States concerned, the proposed reporting Member State shall be the reporting Member

State and provided the confirmation to the sponsor via the EU-portal within 6 days. In view of workload and responsibility of the rMS, the EU-CTR intends to prepare recommendations on criteria for the rMS selection by a “Clinical Trials Coordination and Advisory Group” (CTGA) with the objective of the prevention that workload is concentrated on a small number of Member States [6; 30]. Such as the application dossier consists of two parts the new evaluation procedure will be a two-part assessment and distinguishes between scientific and national aspects.

Submission Content of “Part I” - Common Scientific Documents for all MS
• Introduction
• Covering Letter
• Application Form
• Clinical Trial Protocol
• Investigator’s Brochure
• IMP Dossier / Simplified IMPD / SmPC (if applicable)
• Manufacturing and/or import authorisation and/or Qualified Person Declaration
• Good Manufacturing Practice compliance certificate
• Auxiliary Medicinal Product Dossier
• IMP / Auxiliary Labels
• Copy of summary of any scientific advice
• Paediatric investigational plan (if applicable)
• Proof of fee payment
• Statement of compliance with EU Data Protection hier oder Part II?
Submission Content of “Part II” - National Documents
• Recruitment Arrangements
• Patient Information Sheet / Informed Consent Form
• Information on Investigators and Sites
• Proof of Insurance
• Financial Arrangements

Table 4: **Content of the CTA submission** (source [6])

The initial **validation** of Part I of the the submitted dossier takes place by the rMS (<10d) taking into account comments of all MSc. Any validation issues must be resolved by the sponsor within 10 days with concomitant review of the response only by the rMS. At this point it is essential to estabish generally accepted rules in order to achieve unified validation and avoid disagreement between concerned Member States. There is no validation of part II scheduled. If authority or applicant does not comply with the timelines there is a tacit approval or an automatically withdrawn of the application regulated. [6]

For **scientific assessment of Part I** the evaluation period of 45 days will be divided in the initial assessment at which end after 26 days the rMS provides a draft of the assessment report. Within a further 12 days, the so-called Coordinated Review Phase between rMS and MSc begins. At its end is the Consolidation Phase of 7 days where finalization of the assessment report by the rMS and concomitant submission to sponsor and MSc takes place. Annotations of the MSc should be taken into account and their considerations have to be documented. The part I assessment report shall contain a conclusion whether the conduct of the trial is acceptable, acceptable subject to specific conditions or not acceptable. A conclusion by the rMS that the trial is not acceptable shall be deemed to be the conclusion of all MSc [29].

Considering issues raised by MSc, only rMS may request additional information. In this case, the applicant has the obligation to file the documents within a maximum of 12 days. The review period for the rMS then is extended up to 31 days [27]. Just as for the validation of the application, the lack of sponsor’s response within the given timeframe will be considered as withdrawal of the application in all MSc. Consistent requirements on the assessment report are not provided so far, as well as any demand of the MSc at this point of the procedure. But common consensus should be reached to ensure high harmonisation level and standardized widespread quality of the assessment reports.

The **Part II national assessment** will be conducted separately by each individual MSc involving one application. Each MSc prepares an assessment report on Part II and passed it to the sponsor through the EU-portal. Similarly, for questions for additional information and the answers provided by the sponsor the EU-portal must be used. The same timelines than for Part I evaluation apply and must be covered otherwise automatic rejection of the CTA in that country will result. [6]

Despite a common format is defined for the clinical trial application, amount and type of data for Part II will remain governed by national laws. The precise information which must be provided to satisfy Part II requirements is not explicitly defined, and here is no separate validation step scheduled for Part II. In order to achieve a high level of harmonization, close cooperation between the Member States is essential regarding the implementation of the EU-CTR. Additionally, Part II covers aspects usually considered by Ethics Committees but their review may also contain aspects of Part I. It is left to each Member State to organize the participation of the ECs and the concomitant parallel assessment within the timeframe that apply to the authorization procedure, despite the fact that communication via the EU-portal is an unusual situation for ECs [27; 29]. Therefore, a constructive coordination and cooperation between the competent authorities and ethics committees is a major challenge for the successful implementation of the Clinical Trials Regulation.

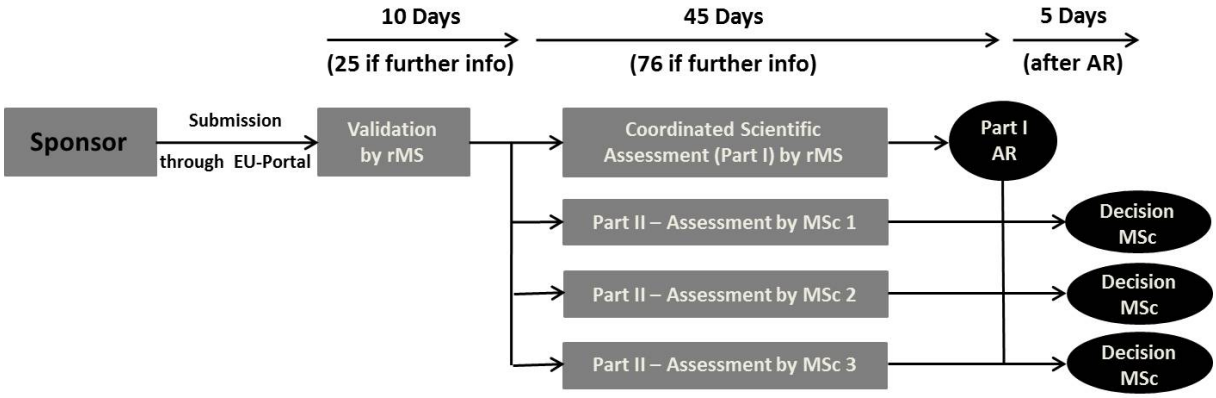

Fig. 12: Summary of initial authorization procedure under Clinical Trials Regulation (rMS = reporting Membes State, MSc = Member State concerned, AR = Assessment Report; modified according to [29])

The single **decision** by each Member State, covering both Part I and Part II, is given via the EU-portal within 5 days of the Part I reporting date or on the last day of the Part II assessment, whichever is later. The Member States will notify the applicant whether the trial is authorised, authorised with conditions or not authorised. If there is no decision by one MSc within these timeframes, the decision given by the rMS in the final assessment report is adopted by the respective MSc [29].

Additionally, if the final rMS assessment report concludes for approval with conditions this decision is transmitted to all MSc. Although the MSc will need to provide a

detailed justification in case of disagreement, the possibilities to opt out leave room for national interpretation. Likewise, a conclusion that a CTA is not acceptable by the rMS is deemed to be the conclusion of all MSc with no option to refuse this decision A MSc has only three alternatives to disagree with rMS conclusion of Part I assessment report [6]:

1) infringement of its national law as referred to in Art. 90 (i.e. with regards to restricted use of specific types of human or animal cells or medicinal products deriving from these cells or on abortifacients or narcotics by national laws or UN Convention)
2) considerations as regards subject safety and data reliability and robustness
3) considerations that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the MSc.

4.2 Discussion - Potential Benefit - Potential Issues

Several advantages and simplifications are expected by the new EU-CTR. The most important of these are a harmonized application dossier that covers regulatory and EC approval. For study specific documents of Part I all MSc will cooperate in the assessment of scientific, therapeutic and safety aspects. Whereas regarding country and site specific documents of Part II the assessment will be made by each MSc individually and would apply to items such as clinical trial agreements, informed consent, recruitment of subjects, etc.

Efficiency may be enhanced through a single portal for the electronic submission of the clinical trial applications, no matter how many countries will be involved - an effort which was already successfully conducted by the VHP - followed by a single decision per MSc through the EU portal. New Member States could be added with Part I remaining valid as already approved, unless there is a disagreement on the basis of circumstances permitted by the EU-CTR, such as safety or data reliability. By harmonizing the requirements, using a single application dossier and one central point for submission, the submission itself have been simplified from what might have been a total of 28 submissions. This is expected to streamline the processes, despite the fact of greater predictability and reduction of overall review times for multi-national clinical trial.

However, beside the expected advantages some potential issues should be addressed before the benefits of the EU-CTR could be develop to its full extent.

4.2.1 Coordination of the assessment

As mentioned before the current situation is that submission, assessment and regulatory follow-up for the same clinical trial are conducted completely separately in the Member States concerned. It does not provide for any kind of cooperation or exchange of information. The extent of assessment differs in each Member State, depending on national traditions and expertise. This creates even voluntary cooperation between Member States more difficult. In this context, it must be recognized that there are many different and partly contradictory requests for additional information, grounds for non-acceptance or national changes to a protocol [24]. Due to the active coordination and the strong scientific cooperation during the assessment phase in the VHP this situation is significantly improved. Beside assessment of the electronically submitted single CTA dossier in English in appropriate timelines, which was already provided by the VHP and is now an important part of the EU-CTR, the joint assessment has yet to be adapted. In this regard, the success of the EU-CTR is clearly dependent on the engagement and commitment of the Member States. As of the strong cooperation of the Member States the VHP accessed the best expertise in the Member States, without any obligation to participate. Within the VHP process the VHP-Coordinator (VHP-C) as a CFTG representative and administrative coordinator is in charge of coordinating all VHP for CTAs. For the successful implementation of the EU-CTR this could serve as paradigm to address the possible problem that a coordinating body [34], which actively takes part in the coordination of the cooperation of the NCAs concerned, is not foreseen in the EU-CTR; aside from clear recommendations concerning the criteria for rMS selection and a fair distribution of workload between the Member States which are not provided till now. One can determine that the EU-CTR not really reduces the workload in total, but there will be a shift towards the NCAs. Whereas, nowadays the Sponsor is responsible to ensure harmonisation of the core documents of the CTA before starting a clinical trial, in the future it is in the responsibility of the Member States to organise harmonised scientific discussions resulting in harmonised CTA in every MSc.

As in the VHP, the EU-CTR requires a proposal for rMS from the sponsor. This determination is binding as long as not all concerned NCAs accept a different Member State as rMS. One main argument against this practice is that the right of determination of the rMS by the sponsor bears the risk that proposal of critical reporting Member States will be deliberately avoided [32]. Furthermore, as in the VHP, the Sponsor has the opportunity of subsequent addition of a concerned Member State according to Article 14 of the EU-CTR if the sponsor wishes to extend an authorised clinical trial to another Member State. The initially nominated rMS shall remain the rMS for the subsequent procedure [6]. According to the guidance of the VHP, the initial REF-NCA will remain the same in the SR-VHP as well but the number of member states nominated in the SR-VHP should be less than in the initial VHP of the clinical trial. Because this limitation does not apply to the EU-CTR, the sponsor has an option to force an rMS. Experiences from the VHP show today, Sponsors proposal for REF-NCA consists in most cases of only two countries. Furthermore, today 23 Member States participating in VHP, but only a few of them were ever proposed by Sponsors as REF-NCA at all. Besides, a clear scope of the joint assessment is definitely required. Thus, Member State cannot 'escape' a coordination of the assessment by claiming that a given issue is of an intrinsically national or ethical nature. This would ensure, unlike the VHP because of its voluntary nature, that all Member States have to participate in the joint assessment of a clinical trial application, and that this is not left to a case-by-case decision of the Member State concerned. As the observations from the VHP reveal, faire distribution of workload and especially of REF-NCA ship does not autonomous run like clockwork, but needs to be actively and professionally promoted. In regard to work-sharing and discussion between MSc during the scientific assessment phase as well as best expertise and practices in and between Member States binding regulations have to be created in order to achieve clear and fair distribution of responsibilities and workload.

Nomination as rMS will result in a workload for the NCA also. The dimension will be directly dependent on the number of participating Member States and the number of CTAs and follow-up procedures like substantial modifications, IB- or IMPD-updates concerning different CTAs with several rMS; the coordination between NCAs and ECs in every MSc will lead to additional workload as well. The new legislation

explicitly provided that the ECs are involved in parallel to the authorization procedure by NCAs. The objective is to provide one single decision per Member State. For this purpose it can be expected that updates of national legislation will occur in a timely manner to prepare the implementation of the EU-CTR in the different Member States. To address this issue and to gain first experience with stronger cooperation between NCAs and ECs the VHP(+) was introduced in version 3.1 of the VHP guidance (see chapter 3.5.3).

Further, not only the assessment of a CTA but also the decision should be carried out in a jointly manner by the participating Member States. An outvoting by the rMS should be absolutely avoided in particular in light of the tight specifications for the refusal by a Member State. The VHP has successfully been shown that a common agreement between all MSc even with short timelines is possible under consideration of the opinion of all MSc and national perspectives.

4.2.2 Timelines

Another controversial and heavily discussed issue are the timelines of the CTA process described in the EU-CTR. Reliable timelines for Sponsor and Member States are a key feature of the VHP. Experiences from the VHP process demonstrate that on average a mean of 53 days are sufficient for a joint assessment of a clinical trial (with a maximum in 75 days) [35]. According to the EU-CTR, approval may be possible after 60 days; however, it could take up to 106 days and even longer when more time is allowed for Advanced Therapies Medicinal Products and biological medicinal products (a maximum timeline of 156 days), and in addition 52-83 days for the inclusion of a new Member State in the clinical trial. The European Federation of Pharmaceutical Industries and Associations (EFPIA) stated that if these timelines are applied on a routine basis, the European Union could have some of the longest timelines worldwide and called on Member States to consider the impact of timelines on the overall attractiveness to conduct clinical research in this region [36]. EFPIA appeals on Member States to establish the processes within timelines which keep the overall attractiveness of conducting clinical trials in the European Union [36].

In contrast, there are raising concerns regarding the flexibility in timings for responding to the request for additional information. The applicant has the obligation to file the documents within a maximum of 12 days, which might not be a difficult task

in particular for international sponsors as well as in the academic field. Additionally, this time window is coupled with a tacit withdrawal. But that, in turn, means an additional workload for the Member States concerned if the sponsor starts a resubmission of the CTA. In this regard, also in the VHP process the desire for a clock stop has frequently been mentioned by the applicants - limited in time, as is already the case in Germany [32].

All timelines given in the EU-CTR are maximum timelines and may be shortened by the corresponding rMS. But one has to keep in mind the workload of the rMS particularly with regard to the above mentioned possible focusing on a small number of countries likely to act as rMS for the majority of applications. Referring to this, the tacit approval can be discussed critically. From the Sponsors point of view tacit approval is inseparable from timelines but it does not contribute to a thorough scientific examination of the application at all.

Additionally, the Ethics Committee review will be required to be performed within the same timetable. EC approvals have to be gained nationally. Thus, it is in the responsibility of the Member States to ensure efficient collaboration between NCAs and ECs within the timelines that apply to the authorization procedure. One single decision per member state seems highly promising but the adoption of this approach is not likely to be the ideal method for promoting fast and flexible decisions, because the VHP have already shown that the national authorization periods are longest in those Member States where NCAs and ECs have decide jointly [35].

4.2.3 IT-Infrastructure

Submission of a single application dossier electronically via a central EU-Portal is seen as one of the great advantages of the EU-CTR. According to the EU-CTR the EMA is responsible for the development and maintaining of the required IT-infrastructure (EU-Portal and EU-Database) at Union level. The EU-Portal and Database represents a single entry point for the submission of data and information relating to clinical trials. It will represent both the single interface for CTA dossier submission and associated processes and the single data repository for associated documents. Just to name a few features, the EU-portal has to cover the following [37]:

- enable communication between sponsors and competent authorities
- enable citizens to have access to the information about IMPs
- enable sponsors to refer to previous submissions through a medicinal product number for IMPs without marketing authorisation and a EU active substance code for IMPs with marketing authorisation
- public access with exception of personal data, commercially confidential data, communication in relation to assessment preparation
- user interface available in all European languages
- supersede existing regional and national databases
- consider EudraCT and link with EudraVigilance databases

After development of the EU-portal the full functionality will be checked by an independent audit. Once this process has been completed successfully, the European Commission will publish a notice in the Official Journal. The EU-CTR will come into force six months after this publication; so that any delay in the development of the EU-portal and database will cause delayed application of the EU-CTR. The EU-database and EU-portal are key components of the EU-CTR to ensure the highest level of harmonisation in the process. Their full functionality will ensure that the new application processes is workable and efficient. But most of the details are still unclear till today. Precondition for high level of harmonization is a high level of harmonized scientific discussion. But how the communication platform is organized - in-between Member States and within one Member States for communication between NCA and ECs, for instance - is not yet known, too. The EMA has started to work with Member States and a range of stakeholders with the intent to confirm full functionality by December 2015. This is therefore a key implementation step for the application of the EU-CTR.

C Conclusion and Outlook

All clinical trials performed in the European Union are required to be conducted in accordance with the Clinical Trials Directive 2001/20/EC until the new Clinical Trial Regulation EU No 536/2014 will become applicable, which will be no earlier than 28 May 2016 (EMA). The EU regulation on clinical trials (EU-CTR), Regulation (EU) 536/2014, certainly represents a significant step towards harmonisation for the conduct of clinical trials in the European Union. Since the Clinical Trials Directive became active in 2004, the quality and safety of clinical trials in Europe has been improved. But this increased quality is offset by high administrative requirements. Thus, converting the legal form of the regulatory framework from a Directive to a Regulation provides a more detailed, binding manner to address the procedure for submission of applications for authorisation with the instant success of a standardised application dossier submitted to a single central filing portal as basis for a coordinated review which leads to a single decision within set timeframe. This allows the Sponsors to plan and conduct their multinational clinical trials on the basis of one identical regulatory framework rather than on divergent national transpositions. However, even if the legal form is a Regulation diverging implementing practices are not excluded in their entirety. Requirements could still be interpreted differently in the practical application, unless a clear defined cooperation mechanism for the joint assessment of a multinational clinical trial application by all concerned Member States is in place. Hence, this leaves room for national interpretation but also for multinational interaction. Thus, good collaboration between Sponsors and EU bodies is necessary for the successful harmonised implementation of the new system. Member States are faced with the enormous challenge to determine responsibilities and organization of authorities and ethics committees at national level that national standards does not conflicting with the procedures of the EU-CTR. This means fundamental decisions on cooperation between authorities and ethics committees, which must be established by law, but also that commercial and academic Sponsors have to organize their processes in a way that they meet the requirements of the EU-CTR with respect to the content, design and timelines.

For the establishment of a process that has to address both submission and assessment, several years of experience with the VHP should be evaluated carefully. VHP has approached closer to the implementation phase of the EU-CTR. It provided an excellent platform for kind of testing approaches of the EU-CTR in practice and for successful implementation of valuable experiences for the current necessary process of establishing the new legislation. For example, the concept of REF-NCA nomination in the current version of the VHP guideline illustrated a preparatory step for the implementation of the EU Clinical Trials Regulation. The VHP is flexible enough to implement such key changes to evaluate their impact on overall assessment of CTA. For this scope to use, VHP will be offered until the EU-CTR comes into force. Of cause, the VHP has in this case the advantage of being voluntary and not legally binding. In this regard the system is flexible and all who attended were equally committed and motivated to push the cause forward. With the experience gained from the VHP and the clearly defined legal basis of the EU-CTR, it is now important to establish a procedure that is subjected to both defined regulations and uniform interpretation by all Member States in the European Union. Legislation and guidance on the process for authorising clinical trials will not solve all issues, IT-challenges for the single portal and for the procedural steps of CTA approvals would need to be carefully thought through, and that the future framework should be sufficiently flexible to allow for case-by-case decisions

The revised legislation is a great step towards more streamlined processes surrounding clinical trials in Europe, as well as towards a responsible transparency surrounding clinical trials. The opportunity to use many years of experience with the VHP should not be missed given that the success of this legislation will depend on how it is applied in practice. Thus, there is still work to be done, like clear distribution of responsibilities and best practices between Member States, Sponsors ready to assist fair distribution of the work of multi-national clinical trial applications, and implementation of new concepts of NCAs to support the development of new medicines both as regulators and as providers of advice. Collaboration of the relevant stakeholders will be essential to ensure they have the opportunity to provide input if we want to achieve a system that will support the innovation we need to improve patient outcomes.

D Summary

Implementation of the Clinical Trials Directive 2001/20/EC into national law of all European Member States has clearly improved the level of harmonization of the conduct of clinical trial applications and approval process. But apparently not all the objectives of the Directive with regard to the harmonization of procedures and reducing administrative burdens in the preparation and performing of clinical trials have been achieved. Differences in interpretation of the processes harmonised by the CTD, resulted in even higher complexity levels – especially in the performance of multi-national clinical trials.

To address some of the key issues raising by different stakeholders in 2009 the Clinical Trial Facilitation Group has introduce the Voluntary Harmonisation Procedure (VHP). Within the current legal framework the VHP provide the opportunity and the basic conditions for a coordinated or shared scientific assessment of multinational clinical trials with the aim to set up best practices between Member States. This leads to improved interactions between the National Competent Authorities and to harmonised processes and practices to avoid divergent decisions.

Thus, the VHP has successfully provided a process through which some of the concerns of the Clinical Trials Directive have been addressed without introducing a new legislation. However, it has not addressed many other issues linked to the interpretation of the Clinical Trials Directive, particularly those where clinical trial application approval is linked to Ethics Committee review. Therefore, there is still a requirement to enhance the regulatory environment to make the European region a more attractive place to conduct clinical trials. To achieve this objective and to offer a modern regulatory framework the new Clinical Trail Regulation EU No 536/2014 has been developed. Similar to the VHP, the Regulation will introduce a streamlined, electronically submission procedure for all clinical trial applications, both single and multinational trials.

This Master Thesis brings into focus the development and usefulness of the VHP - first originally introduced to address raising concerns with the Clinical Trials Directive and to present flexible solutions; and second extremely valuable to provide experiences for planning and implementation of the clinical trial application procedure of the new European Clinical Trial Regulation.

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Annex

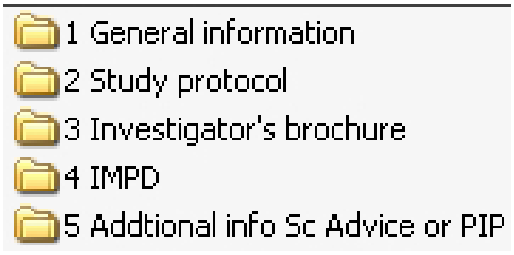
1 Content of a “Request for VHP”

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 IV, 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 (winzp or 7zip)

The eudralink should have the maximum expiry date (90 days) and no password of the eudralink is preferred.

(source [5])

2 Member States participate in VHP by 1.1.2015

Participation	Rejected Participation
Austria	Croatia
Belgium	Cyprus
Bulgaria	Lichtenstein
Czech Republic	Luxembourg
Denmark	Slovakia
Estonia	Slovenia
Finland	
France	
Germany BfArM	
Germany PEI	
Greece	
Hungary	
Iceland	
Ireland	
Italy	
Latvia	
Lithuania	
Malta	
Netherlands (only products in the responsibility of CCMO: ATMPs, unauthorized vaccines, oligonucleotides, RNA interference, GMO and some early phase research with medicinal products in minors and incapacitated subjects*).	
Norway	
Poland	
Portugal	
Romania	
Spain	
Sweden	
United Kingdom	

*Please contact CCMO directly for more information; For products not mentioned in the list, national applications in parallel to the VHP could be submitted.

(source [40], status 1.1.2015)

3 Ethics Committees with potential participation in VHP

Ethik-Kommissionen bei den Ärztekammern
***(Ethics committees at Medical Associations responsible for the coordinating investigator in Germany*)**

- Ethik-Kommission bei der Landesärztekammer Baden-Württemberg
- Ethik-Kommission der Bayerischen Landesärztekammer
- Ethik-Kommission bei der Landesärztekammer Rheinland-Pfalz
- Ethik-Kommission der Ärztekammer des Saarlandes
- Ethik-Kommission der Landesärztekammer Thüringen
- Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster
- Ethik-Kommission bei der Landesärztekammer Hessen

Ethik-Kommissionen bei den Universitäten
***(Ethics committees at University Hospitals responsible for the coordinating investigator in Germany*)**

- Ethik-Kommission an der Medizinischen Fakultät der RWTH Aachen
- Ethikkommission der Medizinischen Fakultät der Ruhr-Universität Bochum
- Ethik-Kommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn
- Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen
- Ethik-Kommission der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf
- Ethik-Kommission der Medizinischen Fakultät Friedrich-Alexander-Universität Erlangen Nürnberg
- Ethik-Kommission des Fachbereichs Medizin der Johann Wolfgang Goethe-Universität Frankfurt
- Ethik-Kommission der Medizinischen Fakultät der Georg-August-Universität, Göttingen
- Ethik-Kommission der Medizinischen Fakultät der Martin Luther Universität Halle-Wittenberg
- Ethik-Kommission der Medizinischen Hochschule Hannover
- Ethik-Kommission der Medizinischen Fakultät der Christian-Albrechts Universität zu Kiel
- Ethik-Kommission der Medizinischen Fakultät der Universität zu Köln
- Ethik-Kommission der Otto-von-Guericke-Universität an der Medizinischen Fakultät, Magdeburg
- Ethik-Kommission der Medizinischen Fakultät der Ludwig Maximilian Universität, München
- Ethik-Kommission der Fakultät für Medizin der Technischen Universität München
- Ethik-Kommission an der Medizinischen Fakultät der Eberhard-Karls-Universität und am Universitätsklinikum Tübingen
- Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster
- Ethik-Kommission der Medizinischen Fakultät der Universität Würzburg

Ethik-Kommissionen bei den Landesbehörden
***(Ethics committees at Competent Authorities of the States responsible for the coordinating investigator in Germany*)**

- Ethik-Kommission des Landes Berlin
- Ethik-Kommission des Landes Sachsen-Anhalt

(source [41]; status 1.2. 2015)

4 Flow-Chart

4.1 Flow Chart VHP and SR-VHP

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 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 (VHP-C) 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 VHP-C 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 revised CTA to VHP-C by the applicant	
Around Day 56	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 is 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 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-C	
Day 78	Information of the applicant via VHP-C 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[1] After P-NCA's decision	Procedure and decision according to national laws 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.

4.2 Flow Chart VHP with ATMP

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 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 55	If no GNA: information (VHP-C) of the applicant on acceptance	End of VHP and start of phase 3 →National step
Day 55	In case of GNA : transfer of GNA by VHP-C 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-C by the applicant	
Around Day 82	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 90	If a revised CTA is 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 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-C	
Day 108	Information of the applicant via VHP-C 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[2] After P-NCA's decision	Procedure and decision according to national laws Information of the VHP-C by the applicant on the outcome of the national CTAs (with respect to the VHP decisions)	

[2] 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.

4.3 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-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 21	Requests for limited additional explanations or clarifications by VHP-C 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 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	
	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-C	
Day 53	Information of the applicant via VHP-C 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 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[3] After P-NCA's decision	Procedure and decision on SA according to national laws 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

[3] 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.

(source [5])

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Kerpen, 22. Mai 2015 _____

Mareille Warnken-Uhlich