Single CTA - an Option for Drug Development in Europe

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

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Bonn 2010

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LIST OF ABBREVIATIONS

ACRO	Association of Clinical Research Organisations
AFSSAPS	Agence Francaise de Securite Sanitaire des Produits de Santé (France)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Germany)
BPI	Bundesverband der Pharmazeutischen Industrie (Germany)
CA	Competent Authority
CCMP	Central Committee on Research Involving Human Subjects (The Netherlands)
CHMP	Committee for Medicinal Products for Human Use
COREC	Central Office of Research Committees (UK)
CRO	Contract Research Organisation
CP	Centralised Procedure
CPP	Competent Regional Ethics Committee (France)
CTA	Clinical Trial Authorisation
CTD	Common Technical Document
CTFG	Clinical Trials Facilitation Group
DCP	Decentralised Procedure
DG SANCO	Directorate General for Health and Consumer Policy
EBMT	European Group for Blood and Marrow Transplantation
EC	Ethics Committee
ECCO	European Cancer Organisation
ECPC	European Cancer Patient Coalition
EEA	European Economic Area
EFGCP	European Forum for Good Clinical Practice
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
EUCROF	European CRO Federation
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FEAM	Federation of the European Academies of Medicine
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GNA	Grounds for Non-Acceptance
HMA	EU Heads of Medicines Agencies
IB	Investigators' Brochure
ICREL	Impact on Clinical Research of European Legislation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRAS	Integrated Research Application System (UK)
KKS	Koordinierungszentrum für Klinische Studien (Germany)
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
METC	Medical Research Ethics Committees (The Netherlands)
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MRP	Mutual Recognition Procedure

LIST OF ABBREVIATIONS (cont.)

MS	Member State(s)
NCA	National Competent Authority
NRES	National Research Ethics Service (UK)
PEI	Paul-Ehrlich-Institute (Germany)
P-NCA	Participating National Competent Authority
PWPRC	Permanent Working Party of Research Ethics Committees (Germany)
QP	Qualified Person
RFI	Request for Further Information
RMS	Reference Member State
SME	Small and Medium sized Enterprises
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Event
VHP	Voluntary Harmonisation Procedure
VHP-C	VHP-Coordinator

1. Introduction

The entry into force of the "Clinical Trials Directive" 2001/20/EC on April 4th 2001 represents an important milestone for the conduct of clinical research in the EU. As the rules and the regulatory framework for performing clinical trials varied significantly between the different MS (MS), Directive 2001/20/EC aimed at a simplification and harmonisation of the administrative procedures concerning clinical trials [1]. It should help to assure high-quality clinical research and to maintain the competitiveness of the European pharmaceutical industry.

One of the main goals of the Clinical Trials Directive (in the following cited as "the Directive") is to protect the health and safety of the participants in clinical trials. Trials must be scientifically sound and guided by ethical principles. Therefore the Directive states in Article 3(2a) that a clinical trial may be initiated only "*if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored*." [1]. For that reason it is requested in Article 6 that an Ethics Committee (EC) shall give its opinion before a clinical trial starts. In addition, in Article 9 of the Directive it is described that the sponsor is required to submit a valid request for authorisation of the clinical trial to the national competent authority (NCA) of the MS in which the trial will be conducted. This request to the competent authority is called the Clinical Trial Authorisation (CTA) application. The details of the process for the application and authorisation of a clinical trial on a medicinal product for human use are described in the recently updated Detailed Guidance 2010/C82/01 *"Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (CT-1)"* which had been implemented according to Article 9(8) of the Directive [2].

The MS had been requested to adopt the requirements of the Directive until May 2004, but finally the implementation of the Directive into national legislation of all 27 MS was completed in 2006. The authorisation of clinical trials by the national competent authorities and the favourable opinion of a single Ethics Committee within given maximum timeframes led to a remarkable harmonisation of clinical research in the EU. Also, in the opinion of most stakeholders, the safety, the ethical soundness and the reliability of clinical trials were improved.

However, apparently not all goals of the Directive in terms of harmonisation of procedures and reduction of administrative burden in preparing and performing clinical trials were reached. The details of the implementation of the Directive into national legislation vary from country to country as the Directive sets only the legislative and regulatory frame which in some cases is applied very differently by the competent authorities of the MS concerned [3]. This can lead to multiple problems and issues especially with regard to multinational clinical trials. In this context it is important to consider that approx. 25% of EU clinical trials are performed in more than one EU Member State which equals approx. 60% of all CTAs in the EU. Approx. 60-80% of all clinical trials performed in the EU are used for marketing authorisation applications later on. In this light it becomes clear that a harmonisation of the regulatory framework is crucial for the high-quality and cost-effective conduct of multinational clinical trials in the EU. Nevertheless, the national requirements and the assessment of CTAs by the NCAs are not identical for all MS participating at the same multinational trial which counteracts on the idea of harmonisation and facilitation of European and worldwide clinical research.

In addition, the administrative burden and the costs especially for the conduct of multinational trials have increased significantly since the entry into force of the Directive [4]. The main reason for this is that almost identical procedures have to be performed in multiple countries as the CTA has to be submitted to the NCA and to the EC and reviewed in detail in every participating country.

As a consequence, the high administrative burden resulting from the application for authorisation of a clinical trial and other differences in the implementation of the Directive in the MS lead to obvious disadvantages for clinical research in the EU. On the one hand, the costs and the need for resources for clinical trials are increasing. On the other hand and even more important, inconsistencies between the assessment of CTAs in different MS lead to delays for the start of clinical trials. As a result, it takes more time until patients get access to investigational drugs and until new treatment options are approved which has a negative impact on the attractiveness of clinical research in Europe.

During the last years intensive discussions have been ongoing how the described issues could be overcome and the administrative burden in multinational trials could be reduced. To assess the current situation the public consultation paper ENTR/F/2/SF D(2009) 32674 *"Assessment of the functioning of the Clinical Trials Directive 2001/20/EC"* was published by the European Commission in October 2009 and it raises and analyses, amongst others, the issues

described above [5]. All stakeholders in clinical research were asked to comment on the issues described in the public consultation paper in order to further improve the regulatory framework for clinical trials. In addition, the Heads of Medicines Agencies (HMA) have initiated the Clinical Trials Facilitation Group (CTFG) which works on the harmonisation of the requirements for the application and the assessment of clinical trials. Nevertheless there is no structured and joint effort in order to align the approval procedures in the different MS. As a first step the ICREL (Impact on Clinical Research of European Legislation) project was initiated which aimed at measuring quantitatively the impact of clinical trials legislation on commercial and non-commercial sponsors, ethics committees and competent authorities [4]. In addition, important initiatives have been set up like the "Road Map Initiative for Clinical Research in Europe" which was founded in 2008 [6]. This initiative brings together different stakeholders and organisations in the field of academic clinical research, regulators, pharmaceutical industry, ethics committees and patient organisations. It has the aim to work towards suggestions for new legislation with the goal of facilitating the performance of clinical research for the benefit of patients and to increase the competitiveness of clinical research on a European level.

One of the main goals of all initiatives and discussions is to reach more harmonisation for the CTA process. This could be achieved by the introduction of one single CTA dossier that would be identical for all MS participating in a clinical trial and by the implementation of a single CTA review process. In the opinion of many stakeholders, this approach would simplify the submission and approval process for a clinical trial, avoid multiple reviews in several countries and reduce the costs and the administrative burden.

Similar to the process of the application for a marketing authorisation there are several options how this approach could be implemented. The single CTA could be submitted to the NCAs of every participating country or to one central body that would have to be defined. The assessment of the application dossier could be conducted either by every NCA, in a mutual recognition procedure (MRP) or decentralised procedure (DCP) with a reference member state or in a centralised assessment procedure. A centralised procedure would lead to an authorisation of a clinical trial that is valid throughout the Community. A first step to a harmonisation in terms of the assessment of CTAs has been done by the CTFG which introduced a voluntary harmonisation procedure (VHP) which combines the disseminated review of a CTA with a joint assessment [7]. It is obvious that any of the briefly described options would require an adaptation of the regulatory framework that would affect all stakeholders in clinical research.

In this master thesis, the options for streamlining the process of submission, review and approval of CTAs in Europe are discussed. Based on the current regulatory framework for the CTA process, the general requirements and the status quo in different countries is described. With regard to the issues and options highlighted in the Public Consultation Paper of the Commission, the position of all relevant stakeholders (academia, pharmaceutical industry, cooperative groups, CROs, NCAs, ECs, EMA and patient organisations) towards the functioning of the Directive and their suggestions for an improvement of the CTA process are elaborated. Finally, proposals are made how the CTA process could look like in the future and the possible implications of the discussed changes are described.

2. Current regulatory framework for the application and authorisation of clinical trials

According to Section (2) of the Clinical Trials Directive 2001/20/EC, "*the accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration"* [1].

For that reason it is laid down in Article 1(1) that it is the scope of the Directive to define "*specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products as defined in Article 1 of Directive 65/65/EEC, in particular relating to the implementation of good clinical practice*" [1]. Before the entry into force of the Directive there were considerable differences between the practices regarding the preparation, authorisation and conduct of clinical trials among the MS resulting in difficulties in conducting clinical trials effectively in the EU. Therefore, as described in Section (10) the Directive aims at simplifying and harmonising the "*administrative provisions governing such trials by establishing a clear, transparent procedure and creating conditions conducive to effective coordination of such clinical trials in the Community by the authorities concerned"* [1].

It is stated in Article 9 (1) and Article 9(2) of the Directive that "*the sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and (...) the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance.* (...) *the sponsor shall be required to submit a valid request for*

authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial". [1]

The guideline "*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/CT2)"* [8] covers general aspects on how to prepare the application to an EC as well as the interaction and procedures during the conduct and the termination of a study. The process of the application to ECs and the resulting issues are not within the scope of this thesis and will not be further elaborated.

Regarding the application to NCAs it is stated in Article 9(8) of the Directive that the Commission shall draw up und publish in consultation with the MS "*detailed guidance on the format and contents of the request referred to in paragraph 2* (i.e. the above mentioned request for authorisation to the CA) *as well as the documentation to be submitted to support that request (...)"* [1]. Recently, the Detailed guidance ENTR/F2/BL D (2003, revision 2, 2005) was updated with the Guideline 2010/C 82/01 "*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)*" [2]. It describes in detail the requirements for a request for authorisation of a clinical trial. Before the publication of the updated guideline in March 2010 all stakeholders in clinical research were invited to comment on the proposed changes in a public consultation process.

2.1. Submission and approval of a clinical trial authorisation application

For all clinical trials the request is submitted to the NCA of every MS concerned. In accordance with Article 9(4) of the Directive and Article 15 of the Detailed guidance 2010/C82/01, the assessment of the CTA by the NCA shall be done as rapidly as possible and may not exceed 60 calendar days [1, 2]. A clinical trial is approved by the NCA if by day 60 no grounds for non-acceptance (GNA) have been raised (implicit authorisation). It is important to mention that the MS have the possibility to define a shorter period than 60 days and that the NCAs can notify the sponsor of a trial before the end of the 60-day period that there are no GNA. Exceptions regarding the described timelines are described in Article 9(4-6) of the Directive and in Article 17 of the Guideline 2010/C 82/01 and apply for medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. For these medicinal products an extension of a maximum of 30 days shall be permitted and this 90-day period

may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with the regulations of the MS concerned. In the case of xenogenic cell therapy there is no time limit with regard to the authorisation period. All MS are encouraged to accept the English language in their communication with applicants and for documentation (Article 25) but the MS are not obliged to do so. Documents that are provided to the subjects should be written in local language.

According to the revised version of the guideline the following documents must be submitted to the NCA of the MS concerned (Table 3, Section 2.9. of the Detailed Guidance [2]):

- Cover letter with the contents set out in Section 2.3
- Clinical trial authorisation application form
- Protocol with the contents set out in Section 2.5
- IB, or document replacing the IB, as set out in Section 2.6
- IMPD/simplified IMPD, as set out in Sections 2.7 and 2.7.3
- NIMP dossier as set out in Section 2.8
- The additional pieces of documentation as set out in Section 2.9

As described in Section 2.10. the NCAs can request additional documentation for the content of the CTA. According to Article 6(2) of the Directive, documents that are only assessed by the EC should not be submitted to the NCA at the same time. However, the MS can decide individually that the NCA is responsible for the assessment of

- the provisions for indemnity or compensation,
- insurance or indemnity to cover the liability of the investigator/sponsor,
- compensation and rewards of investigators and clinical trial participants, or
- the agreement between the sponsor and the clinical trial sites.

In this case the MS are obliged to notify the Commission, the other MS and the EMA.

It is obvious that the additional national requirements have the consequence that the content of a CTA for a multinational trial is not identical throughout the community which leads to a lack of harmonisation between the MS.

In the prior version of the Detailed guidance (ENTR/F2/BL D(2003), revision 2, October 2005) the additional country-specific information required by the MS was summarised in

Attachment 1. In the revision of the Detailed Guidance issued in March 2010 (2010/C82/01) Attachment 1 was deleted [2]. Although the revised guideline aims at introducing the same application dossier content in all Member States this omission of Attachment 1 was criticised by stakeholders like commercial sponsors, the EFPIA and the *"Road Map Initiative for Clinical Research in Europe"* during the public consultation process. As many MS still have specific requirements and the harmonisation has not been achieved yet, in the opinion of these stakeholders it would be helpful to publish the list of the national requirements again.

In addition to the described inconsistencies in terms of the CTA process there are several other issues resulting from the different implementation of the Directive in the MS. These are for example the interpretation of what could be considered as a substantial amendment, the multiple reporting of SUSARs and the scope of the Directive which covers only interventional studies with investigational medicinal products but not any non-interventional studies.

2.2. Submission and approval of substantial amendments

Provisions for notifications and assessments of amendments after the commencement of a clinical trial are outlined in Article 10 of the Directive [1]. *"After the commencement of the clinical trial, the sponsor may make amendments to the protocol. If those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall notify the competent authorities of the Member State (...) and shall inform the ethics committee (...) in accordance with Articles 6 and 9."*

In the Detailed Guidance 2010/C82/01, Section 3 "*Notification of amendments and related measures*" it is laid down that "*amendments to the trial are regarded as 'substantial' where they are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants, or the scientific value of the trial.*" It is up to the sponsor to assess whether an amendment is to be regarded as 'substantial' [2].

In case of substantial amendments, the sponsor needs to notify the CAs and the ECs as appropriate. Furthermore, the Directive requires ECs to provide an opinion to the sponsor or applicant within a maximum of 35 days. If the opinion of the EC is favourable and the CA of the MS has raised no grounds for non-acceptance the sponsor shall conduct the clinical trial following the amended protocol. The Directive sets no timelines for the assessment of

substantial amendments by the CA. However, in Article 137 of the Detailed Guidance it is stated that *"the national competent authority is invited to respond within 35 calendar days of receipt of the valid notification of an amendment. Validation of the submission is included in this period*". Compared with the prior version of the Detailed Guidance (ENTR/F2/BL D(2003), revision 2, October 2005) the revised Guideline gives detailed examples for typical substantial and non-substantial amendments (section 3.4.).

According to section 3.7. of the Detailed Guidance 2010/C82/01 the notification of a substantial amendment should include the following:

- a signed cover letter
- the Amendment Notification Form
- a description of the amendment
- supporting information including, where applicable:
    - summaries of data,
    - an updated overall risk/benefit assessment,
    - possible consequences for subjects already included in the trial,
    - possible consequences for the evaluation of the results;
- if a substantial amendment involves changes to entries on the clinical trial application form, a revised copy of the XML file incorporating amended data.

It is important to mention that the sponsor does not have to notify non-substantial amendments to the NCA or ECs. However, non-substantial amendments should be recorded and contained in the documentation of the trial.

Similar to the process for a CTA application, substantial amendments have to be submitted in every MS participating in a multinational clinical trial and are reviewed separately in every MS concerned. Therefore, the preparation, submission and authorisation of substantial amendments contributes significantly to the high administrative burden in the context of clinical trials. This means that a revision of the CTA process should not be conducted without an update of the process for substantial amendments.

2.3. EudraCT database

Directive 2001/20/EC states that information on the content, commencement and termination of a clinical trial and where the clinical trial takes place should be available to all MS and that all MS should have access to the same information. Therefore, the European database EudraCT bringing together this information was set up. It provides an overview of all clinical trials in the Community and facilitates the communication between MS, the Agency and the Commission on clinical trials. The legal basis for the EudraCT database is provided in Article 11 and in Article 17 of Directive 2001/20/EC [1]. The Detailed Guidance ENTR/CT 5 incorporates information on the data to be included in the database, on the procedures for data entry and control, and on the methods for electronic communication of the data. One important feature of EudraCT is that the database is only accessible to the CAs of the MS, the EMA and the Commission. This means that sponsors are not allowed to access the database or to make any entries.

The EudraCT process contains the following steps:

- Sponsors use the web-based tool to obtain their unique EudraCT number prior to applying for permission to conduct a trial. The number provides the unique identifier of each trial in the regulatory systems in Europe and in the database.
- Sponsors then create and save data sets (in .xml format on their local computer system) and print the completed clinical trial application form. The signed application form, the electronic data file and other supporting documents are submitted to the NCAs for authorisation to conduct the clinical trial.
- The NCAs in the MS enter the data set from the .xml-file into the secure EudraCT database. They complete information on their authorisation of the trial, the EC opinion, amendments, the end of the trial and on inspections.

2.4. Examples for national requirements in the CTA process in selected Member States

Despite the gains achieved through the implementation of the clinical trial legislation, some aspects of the Directive with respect to the harmonisation of administrative processes were not fulfilled. To get an impression of the extent of national differences a short description of the submission and review process for a clinical trial for the European countries France, Germany, UK, Italy and The Netherlands will be given [9].

2.4.1. France

For an application for the authorisation of a clinical trial in France the *"Code de santé publique"* applies as well as different other regulations according to the scope of the research. Through the "*Loi 2004-806 du 09 août 2004, relative à la politique de santé publique"* the Directive 2001/20/EC was implemented.

Clinical trial sponsors have to submit their protocols both to the competent regional ethics committee (CPP), and to the competent authority AFSSAPS. The submissions can be done either in parallel or sequentially. There are interactions between the CA and the EC in order to exchange information during the approval process. The CA sends a copy of all their questions to the CPP. The CPP has 35 days from the reception of the protocol to give a written advice. If no advice is issued the submission is considered as refused. The competent authority acknowledges the receipt of the protocol and informs the sponsor of the date after which in the absence of any remark the trial can start (implicit approval). When the CA asks the sponsor for additional information the questions are transmitted to the CPP. There is no central EC in France.

2.4.2. Germany

Clinical trials involving drugs are covered by the German Drug Law (Arzneimittelgesetz, AMG). The implementation of the Directive into national legislation was performed with the 12th Amendment on the AMG on August 6th 2004. Further details are provided in the corresponding GCP-Ordinance ("GCP-Verordnung"). The sponsor submits a CTA request to the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) or the Paul-Ehrlich-Institut (PEI), containing the elements required by the GCP-Ordinance. The BfArM is responsible for CTAs for chemically defined medicinal products, whereas the PEI works on CTAs for vaccines and medicinal products developed by means of biotechnological processes like e.g. antibodies. PEI and BfArM have published a comprehensive guidance document for the CTA process as well as for the documentation to be submitted (*3. Bekanntmachung zur klinischen Prüfung von Arzneimitteln am Menschen" of 10th August 2006*) [10]. Generally, the timelines for review of a CTA are 30 days for the BfArM (implicit approval if no grounds for non-acceptance are raised) and 60 days for the PEI (explicit approval).

There is no central EC in Germany but the EC of the Coordinating Investigator is defined as the "Lead EC" for the assessment process in multi-centre trials. This Lead EC coordinates the review of the site aspects with the local ECs of all Principal Investigators involved.

Interactions between the NCA and the Lead EC during the approval process are possible, but usually do not happen in an established way. NCA and Lead EC inform each other about the outcome of the review. The applications can be done either sequentially (in either order) or parallel. In Germany some additional documents like a declaration about data protection and a statement justifying the gender distribution in the trial have to be submitted to the NCA.

2.4.3. UK

For an application for the authorisation of a clinical trial in UK *"The Medicines for Human Use (Clinical Trials) Regulations 2004"* (clinical trials of investigational medicinal products including Phase 1 trials and gene therapy research) applies.

The sponsor submits his application to the Medicines and Healthcare Products Regulatory Authority (MHRA), which is the competent authority for the whole UK. The assessment for phase II-IV studies is performed within 30 days. It has been agreed that applications for phase I healthy volunteer studies will be assessed and processed within an average of 14 days or less. There is a single organisation to which to apply for ethical review, the National Research Ethics Service (NRES), which in April 2007 replaced the Central Office for Research Ethics Committees (COREC). The ethical review time for a clinical trial is 60 days, whereby the local site suitability is assessed by the local Trust's R&D Committee in NHS studies and communicated to the lead EC in multi-centre trials.

There is no routine interaction between the NCA and the ECs during the approval process. However, the ethics committee and the MHRA may share relevant information during the approval process under the terms of a Memorandum of Understanding (MoU) agreed in October 2006. The MoU is published on the NRES website. The MHRA Clinical Trials Unit has access to the Research Ethics Database. The applications may be made either sequentially (in either order) or in parallel. The United Kingdom is one of the few MS whose NCAs ask only for the core study documents.

2.4.4. Italy

For an application for authorisation of a clinical trial in Italy the applicable legislation is the Ministerial Decree of November 2007 *"Transposition of Directive 2005/28/EC relating to principles and guidelines for good clinical practice for medicines in experimental phase for human use, and requirements for the authorization to produce and to import these medicines"*

and the Legislative Decree no.211 of June 2003 *"Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use"*.

In Italy, the respective hospital administration is considered the "competent authority" providing study approval and therefore, in most cases, the sponsor must apply to the local CA in order to obtain an authorisation to conduct a clinical trial. The CA can authorise the trial within 60 days. If the CA has not informed the sponsor of any grounds for non-acceptance within 60 days, the trial is considered as authorised. Only for clinical trials with gene therapy, somatic cells therapy and for first-in-man use trials the authorisation is granted by a central CA (Agenzia Italiana del Farmaco AIFA and Istituto Superiore di Sanità, respectively). In order to start a clinical trial, a sponsor must enter the data into a web-based database of the "Osservatorio Nazionale per la Sperimentazione Clinica". At the end of the electronic procedure, it is possible to print the data to receive the CTA form in Italian language which is submitted to the CA and EC.

In Italy there is no central EC and there is no interaction between NCA and ECs during the approval process. The CTA can be submitted parallel or sequentially.

2.4.5. The Netherlands

In The Netherlands research involving human subjects has been legally regulated since 1999 via the "*Medical Research Involving Human Subjects Act"* (WMO). A revised version of the WMO, which gives effect to the Directive 2001/20/EC, came into force on 1 March 2006. The NCA in The Netherlands is the Central Committee on Research Involving Human Subjects (CCMO). There are 30 accredited Medical Research Ethics Committees (METCs). In cases of medical research within particular areas like gene therapy, xenotransplantation, heroin addiction etc., the CCMO acts as the responsible (central) EC. The identical set of documentation needs to be submitted to the EC and the CA whilst the CA will only perform a marginal review of the application.

Only one single decision of one accredited METC is required for research projects in the Netherlands including multi-centric studies. This differentiates the Dutch systems from the other countries described above. It is important to mention that the Stoiber-Group recommended that central approach in its expert opinion on the Directive.

The Dutch CA has a maximum of 14 days after the receipt of the complete file to issue a possible 'motivated objection'. The CA will do this through mail. If the CA has no objection the applicant receives an email report. The CA informs the accredited METC about the outcome of their review within 14 days. The application to the EC and the NCA can be done either sequentially or in parallel.

2.4.6. Timelines and requirements for CTAs in twelve selected EU countries

The main differences in national legislation consist in the number and role of CAs, the number and role of ECs, the process leading to the single ethical opinion and the interaction between CAs and ECs. There remain differences between MS in the IMPD requirements and a lack of transparency concerning the Member State requirements. Insurance for academic research is covered by the public health system in some countries, and in others the union of pharmaceutical companies has contracted a national insurance package covering all industry-sponsored trials. In some countries the EC decides on the need for insurance. There are differences in the interpretation of the definition of the investigational medicinal product (IMP) with major consequences for SUSAR reporting and labeling. There are also differences between MS with regard to the timelines for the assessment, including validation periods and clock-stops added to the 60 days given in the Directive.

The information given in the following tables were derived from different NCAs websites (see Annex 1), a survey conducted with colleagues working in different European countries and documents provided in the *"EFGCP Report on The Procedure for the Ethical Review of Protocols for Clinical Research Projects in the European Union"* which was updated in April 2010 [9]. They give an overview of the timelines for the review of CAs and ECs in twelve selected EU countries:

	Belgium	Czech Republic	Denmark	Finland	France	Germany
HA Review						
Original submission	Max 15 days for phase I Max 28 days for phases II to IV	10 days validation + 60 days 10+90 days for biotech IMP	60 days	60 days	60 days	30 days BfArM 60 days PEI
Amendment	Max 15 days for phase I Max 28 days for phases II to IV	30 days	30 days	35 days	35 days	20 days BfArM 35 days PEI
EC Review						
Original submission	Max 15 days for phase I Max 28 days for phases II to IV	60 days	60 days	Submission 15 days before EC meeting, timelines based on Directive	60 days (35 days without GNA)	30 days single centre study 60 days multicentre study
Amendment	Max 15 days for phase I Max 28 days for phases II to IV	35 days	30 days	Submission 15 days before EC meeting, timelines based on Directive	30 days	20 days
Submission						
Parallel	yes	yes	yes	yes	yes	yes
Sequential	yes	yes	yes	yes	yes (first EC then CA)	yes

	Ireland	Italy	Netherlands	Spain	Sweden	UK
HA Review						
Original submission	60 days (30 days without GNA)	60 days	14 days	60 days (+10 days validation period)	60 days (LoQ after d30, AtoQ before d40)	60 days (30 days without GNA)
Amendment	35 days	35 days	14 days	45 days	35 days	35 days
EC Review						
Original submission	60 days	60 days	60 days	60 days	60 days, mostly within 30 days	60 days
Amendment	35 days	35 days	30 days	35 days	30 days	35 days
Submission						
Parallel	yes	yes	yes	yes , preferable sequential	yes	yes
Sequential	yes	yes	yes	yes	yes	yes

As mentioned before, in attachment 1 of the Detailed Guidance (ENTR/F2/BL D(2003), revision 2, October 2005) the country-specific information required by the MS was summarised. Attachment 1 was deleted in the revised Detailed Guidance from March 2010 (2010/C82/01).

As there is still country-specific information required, for this master thesis the national CTA requirements (for submission to HA) provided in Attachment 1 of the Detailed Guidance (ENTR/F2/BL D(2003), revision 2, October 2005) were checked for 12 countries and supplemented with additional information which represents the current national practice for the submission of CTAs. A table indicating the results of the investigation which was conducted through internet research and through a survey among different DRA departments can be found in Annex 2.

3. Initiatives and options to reach harmonisation of the CTA process in the EU

As mentioned before, the entry into force of the Directive led to important improvements in terms of harmonisation of clinical research in the Community. However, to address the unintended negative consequences of the Directive, several important initiatives and discussions were launched during the last years:

- The European Commission requested the EMA to organise a conference involving all stakeholders on the state of the implementation of the legislation related to clinical trials. The objective of the conference was the provision of an overview of the experience to date with the Directives 2001/20/EC and 2005/28/EC, to describe their impact, to specify issues and to offer recommendations for the future. The "Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future" was held on October 3rd 2007 and brought up important discussions among the different stakeholders [11].

- Following the implementation of Directive, the HMA established the CTFG to coordinate the implementation of the Directive across the MS and further improve harmonisation of regulatory requirements with regard to clinical trials in the EU.

- Organisations like the European Federation of European Industries and Associations (EFPIA) have worked out several concrete proposals to streamline and facilitate the CTA like the EFPIA paper "*Clinical Trials in Europe: A Proposal for a Community Clinical Trial Authorisation System*". [12]

- The ICREL study (*Impact on research of European Legislation*) was a longitudinal, retrospective, observational and comparative study carried out in four stakeholder groups (commercial sponsors, non-commercial sponsors, ECs and CAs to assess the quantitative impact of the Directive on the number, size and nature of clinical trials, on workload, required resources, costs and performance [4]. It was performed in 2008.

- The "Road Map Initiative for Clinical Research in Europe" has been launched by a high number of stakeholders in clinical research like commercial and non-commercial sponsors, the *European Forum for Good Clinical Practice* (EFGCP) and ICREL. The initiative seems to be a very promising joint effort to reach a better harmonisation with regard to expectations for a future regulatory frame work for clinical trials. In workshops in 2009 and 2010 the concept of a single CTA was intensively discussed and important proposals and contributions have been developed by this initiative [6].

- The Commission announced in December 2008 that an assessment of the need for revision of the Directive would be made. The public consultation paper *"Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC" ENTR/F/SF D(2009) 32674* critically described achievements and shortcomings of the Directive [5]. In addition, the public consultation paper raises different options for an improvement of the CTA process. The public consultation was conducted from 9 October 2009 to 8 January 2010 and all stakeholders in clinical research were asked to elaborate on their position with regard to the current situation and identified issues. The summary of responses to the public consultation was published in March 2010 [13]. In April 2010 DG SANCO announced that it will continue to gather additional data in 2010 to decide about the next steps and that new legislative proposals will not be adopted until October 2011.

The different options to reach a more efficient and harmonised CTA process are briefly presented in the following. For all described procedures applies that the submission of a single dossier to a central database (e.g. EudraCT) would be beneficial.

- The **Voluntary Harmonisation Procedure** (VHP) was launched by the CTFG in early 2009 and enables joint assessments of clinical trials and exchanges between NCAs of MS concerned. It is described in detail in the *"Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications*" and was revised in March 2010 [7]. The VHP is based on the concept of a voluntary parallel submission of a CTA core dossier to all participating MS followed by an individual application for approval to the individual NCAs (see flowchart chapter 5.2.2.). After the first year of experience with the VHP it can be stated that 26 applications with an average assessment time of 51 days (plus 12 day for the national approvals) have been made. The key features of the VHP are an electronic submission, reliable timelines, a harmonised scientific discussion and reduced workload for sponsors as there is only one single list of questions to be answered.
- A process similar to the **decentralised procedure (DCP)** or the **mutual recognition procedure (MRP)** for the application of a marketing authorisation (MAA) could be set up for the single submission and review of CTAs [14]. The submission of the CTA dossier would be made to a central body or to a NCA. The MS concerned have to

come to an agreement within the authorisation process for a clinical trial. Similar to the process for MAAs the CTA assessment would be made by one of the MS concerned (Reference Member State, RMS). The other MS could be consulted and could assist in the assessment by providing additional expertise. The authorisation of a trial would be applicable for all MS concerned and the decision would be issued by the NCAs or by the Community.

- The **central procedure** with central assessment of the CTA would correspond to the centralised procedure (CP) which is performed for MAAs [14]. One single CTA would be submitted electronically to one central database (e.g. EudraCT). The assessment and review of the CTA would be performed by a central body. A central authorisation would be issued which would be valid for all EEA countries. A central submission and review of CTAs will be described in detail in chapter 5.2.1.

4. Positions of different stakeholders in clinical research towards the CTA process

The positions of commercial sponsors, NCAs and CTFG, EMA, ECs, non-commercial sponsors, CROs and patient organisations towards the CTA process are presented in the following. The views and opinions of the stakeholders are derived from the responses to the Commission's public consultation paper [13, 15] and from personal interviews conducted with representatives of the different groups.

4.1. Commercial sponsors

As the majority of clinical trials are sponsored by the pharmaceutical industry, commercial sponsors play a major role in the context of the submission, the authorisation and the conduct of clinical trials. Commercial sponsors state that the administrative burden and the costs for clinical trials have increased significantly since the entry into force of the Directive [15]. According to ICREL, staff needs in pharmaceutical companies for submitting the requests for authorisation of a clinical trial have doubled [4]. The reason for this is that for multinational trials largely identical procedures with differences in the details of national processes have to be carried out in multiple countries and conflicting requests for protocol modifications have to

be handled which needs additional internal resources. Of course, large pharmaceutical companies have set up dedicated departments for the preparation and submission of CTAs but for small companies it is sometimes not possible to fulfil the complex requirements. According to the experience of the industry, in many cases the different implementation of the Directive in different MS leads to divergent comments and requests on the same clinical trial. As a consequence, in some cases trials can not be conducted in certain MS or the start of the trial is delayed which deprives the patients from the access to innovative treatment options.

Nevertheless, it is important to mention that the pharmaceutical industry acknowledges that the introduction of the Directive led to positive and fundamental changes of clinical research in Europe like the implicit approval mechanism for CAs, the parallel assessment by CAs and ECs and – in most countries – a single EC opinion in a given MS. Commercial sponsors also welcome that the protection of patients has been improved in some areas. However, although the application process for a clinical trial is laid down in the Directive the goal of harmonisation between the MS has not been reached. It is the aim of the European pharmaceutical companies to maintain and to improve the competitiveness of clinical research in Europe. To reach this goal, it is crucial to achieve a harmonised environment for clinical trials across the EU and pharmaceutical industry welcomes the proposed revision of the Directive.

In this context, one important field amongst others is the harmonisation of CTA requirements. National peculiarities lead to a significant additional workload for the companies in the conduct of multinational clinical trials. In the opinion of the pharmaceutical companies there seems to be no reason why the documentation for a CTA should differ between the MS. Therefore, industry requests to introduce a single CTA dossier including the IMPD that is acceptable for all MS in the EU.

This approach is also supported by the European pharmaceutical industry association (EFPIA) which brings together 32 European national pharmaceutical industry associations and 40 major companies. EFPIA says that a centralised submission and review of CTAs should complement the present regulatory framework and not replace it. This means that the single CTA should be optional and should be operated in parallel with the existing CTA approval system. This would allow sponsors to switch from one approval system to another depending on the stage of development, the category of the product or the therapeutic area.

With regard to the different options for streamlining the authorization process for clinical trials the position of the major European pharmaceutical companies is as follows:

EFPIA believes that no voluntary concept like the Voluntary Harmonisation Procedure (VHP) which allows for regular exchanges between the assessors of the different NCAs will be able to solve the existing problems. One reason for that standpoint is 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. In addition, as the participation in the VHP is completely voluntary, some MS have already opted out and the fundamental problems related to the different interpretation of the Directive are not addressed through this voluntary approach.

From the experiences with applications for marketing authorisations (MAA) EFPIA points out that a mutual recognition procedure (MRP) would probably not work properly for CTA applications because of the long time until approval and because of the fact that real mutual recognition of the original assessment is achieved rarely. EFPIA also does not believe that a decentralised procedure (DCP) could lead to significant improvements. Although it seems to be more efficacious than a MRP it requires a very high degree of harmonisation between the MS concerned which currently does not exist. Therefore, the implementation of a MRP or DCP would not be feasible until the legislative framework is revised and becomes more detailed. The fact that in different countries the scope of responsibility of NCAs and ECs are different is regarded as an obstacle for the MRP/DCP as well.

Pharmaceutical industry strongly supports the central submission of an electronic single CTA dossier leading to a centrally issued clinical trial authorisation which is valid throughout all countries in the EEA. The existing EudraCT system should be used for the new procedure. The assessment would be performed by one existing body, preferably the EMA which is already managing the EudraCT database, coordinating inspections and issuing guidelines related to clinical trials.

The German "Verband Forschender Arzneimittelhersteller" for example states that it should be the goal to introduce as an additional option a centralised application and authorisation procedure run by the EMA with effect to all MS. Of course, in the case of national trials the advantages of the centralised procedure are less obvious. Thus, the proposed changes could be realised by a new wording in Article 9(2) of the Directive: *"Before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial; in case of a multinational trial the sponsor may as an alternative submit a request for single approval to the EMA."*. Another main advantage of a central authorisation of a clinical

trial would be that new countries or investigators could be added to an approved trial after the favourable opinion of the EC was issued without consultation of NCAs of other MS.

In addition, through a central CTA process a link would be established between the marketing authorisation of medicinal products and the authorisation process for clinical trials and other development issues like CHMP scientific advice. The approach of a single CTA would lead to a standardised and harmonised procedure in all MS avoiding multiple assessments of CTA dossiers. The Community review of the single CTA application would still be performed in parallel with the review of the Ethics Committee. The proposed centralised procedure would not be limited to certain subsets of clinical trials or particular therapeutic areas.

It is obvious that the proposed solution of submitting a single CTA dossier and the central authorisation of clinical trials would require a change in legislation binding in all MS of the EU. Therefore the changes should result in an adoption of the contents of the Directive in the form of a regulation which lays down the CTA process in more detail and would guarantee the highest degree of harmonisation between the MS.

In addition to the suggestions described above, the German "Bundesverband der Pharmazeutischen Industrie" (BPI) representing mid-size and smaller companies points out that it also supports the single CTA approach. For the BPI it is crucial that the sponsor can choose between the different CTA procedures and that the costs for the authorisation of clinical trials will not increase. According to the BPI rapporteurs from all MS should be represented at the legal body assessing the CTA dossiers. The BPI did not mention the EMA in this context.

4.2. National competent authorities and the CTFG

The national competent authorities emphasize strongly that the Directive has brought considerable improvements in terms of patient safety and reliability of data due to a reliable, thorough review of the application dossier in all Member States [15]. This represents an added value from the implementation of the Directive. It is acknowledged that clinical research has become more costly but the Heads of Medicines Agencies' CTFG points out that this is due to the fact that any introduction of regulations in previously weakly regulated fields lead to a significant increase of staff and costs anyway. The German BfArM confirms that complete harmonisation between the MS was not reached by the Directive but at the same time one has to consider the different diagnostic, medical and therapeutic standards in the MS which might be the reason for diverging evaluations of CTAs. The CTFG adds that the national

assessments of CTAs in each MS concerned contribute to reach the highest-possible standard of the assessment and that the speed of the CTA assessment has to stand back for the thorough evaluation of safety and efficacy. According to the French AFSSAPS it is important to keep in mind that 75% of all trials conducted in the EU are national trials and that a full harmonisation is only needed for the 25% multi-national clinical trials. In contrast to the experiences of commercial sponsors, the NCAs state that ultimately divergent decisions of different NCAs on the same trial are very rare (<0.1%) and the problem of divergent assessments seems to be overstated as for most of the divergences the sponsors seem to find suitable compromises [15].

Concerning the different options for streamlining the CTA process the opinion of NCAs like BfArM, AFSSAPS, the MHRA and the CTFG is as follows [13, 15]:

The majority of NCAs support the VHP as the most cost-effective procedure for multinational trials which can be applied within the current regulatory framework without any changes in the EU legislation. In the opinion of the NCAs and the CTFG, the VHP helps to avoid divergent decisions and provides many features that are requested by the sponsors: a one-stop shop for CTAs, electronic submission of one single CTA dossier in English, simultaneous assessment of the CTA in appropriate time lines and a unified final position by the NCAs concerned. AFSSAPS points out that the extended implementation of the VHP might lead to a decentralised system which is coordinated by the CTFG and with a process corresponding to the HMA's Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh). The MHRA also favours the VHP as the process of choice for applications for multinational trials. In this context, the MHRA proposes a formalisation in law of the current VHP process, similar to the structure underlying the CMDh. As one of the main advantages the VHP would build on the best expertise available in the MS without obliging them to participate. However, the participation in the assessment process should not be limited to the countries participating in a certain trial in order to avoid reassessments if a trial is expanded to further countries afterwards.

The legal implementation of a decentralised procedure or mutual recognition procedure for the assessment of CTAs would offer mainly the same features as the VHP but in a new regulatory framework. In addition, the preparation and introduction of a new legal framework would lead to considerable costs and need for additional resources. However, some countries like Denmark (Danish Ministry of Health and Prevention) support the idea of a community procedure for multinational trials which should build on the experience of the DCP and the

VHP. The authorisation decision should be applicable to clinical trials in all MS concerned and issued by the individual NCAs.

In the opinion of the NCAs and the CTFG it is important that a national option for the CTA process is maintained as 75% of all clinical trials are still performed in only one MS. For that reason, for the majority of trials a centralised CTA process would lead to additional delays and complexity.

As a general standpoint of NCAs and the CTFG a centralisation of the authorisation process of clinical trials is considered non-beneficial for many reasons. A new centralised procedure would require new structures and staff at the EMA as well at the NCAs which would result in an increase in costs. A central submission or a centralised assessment of CTAs could be optional, mandatory for all trials or mandatory for trials in a certain stage of development or for certain classes of compounds. It would not be realistic to include all clinical trials in Europe in a centralised procedure because of the immense need for resources. In the opinion of the CTFG it would not be comprehensible to restrict a centralised procedure for example to products which require a centrally authorised marketing authorisation. A central assessment which relies on the review in the MS would require the establishment of an expert committee comprising MS and an arbitration process would be needed. According to the MHRA this would lead to extended approval times compared to the current situation. In addition, the fees for the central authorisation of a clinical trial are expected to be higher than the costs in the concerned MS.

As a new CTA procedure would need to be laid down in a regulation, the CTFG points out that a regulation would require huge efforts in terms of legal and procedural changes for only a limited number of trials. The BfArM adds that a legally binding regulation would not automatically deliver more harmonisation as it does not relieve the Commission of its obligation to clarify the current wording of the Directive. For that reason the first step would have to be to avoid or limit national peculiarities which are currently admitted in Article 3 of the Directive.

Besides the described advantages and disadvantages CTFG concludes that none of the proposed processes (VHP, MRP/DCP, centralised procedure) would be suitable to solve one of the fundamental problems which is the lack of harmonisation between the NCA and EC procedures. In this context, the BfArM supports the concept of a joint submission to the NCAs and the ECs through a joint application form which is submitted electronically.

Taken together, the NCAs disagree to the proposal of a centralised submission and assessment of CTAs. They would like to contribute to a reduction of the regulatory burden without a major new legislative initiative as the existing legal framework offers sufficient possibilities for an efficient cooperation of the MS within the VHP [15].

4.3. European Medicines Agency

The European Medicines Agency (EMA) represents an important stakeholder in clinical research. Many of its activities which are closely related to the conduct and the outcome of clinical trials are defined in the Directive or in its implementing texts. Currently, EMA and NCAs have different tasks and responsibilities during the lifecycle of a medicinal product. It is important to mention that until now the EMA is not actively involved in the assessment of CTAs.

With regard to the CTA authorisation process EMA strongly supports the introduction of a single point of application and assessment for all clinical trials [15]. This would result in an authorisation that is centrally issued and valid throughout the Community. The sponsor should have the possibility to choose the central or the national assessment depending on the stage of development and the properties of the medicinal product. This proposal towards a single CTA is consistent with the opinion of the commercial sponsors.

As the majority of information in the application dossiers to NCAs and ECs is identical the EMA adds that a single application dossier should be used for the application to both institutions. EMA criticises that currently the IMPD is updated with each CTA for each member state. Therefore, to avoid multiple and divergent assessments the main proposal of the EMA is to create a single European IMPD for each new compound at the time of its first contact with the regulatory system. An European IMPD would also be opened for already marketed medicinal products once any new trial with the compound starts. The holder of the IMPD would be the company/sponsor developing the new compound or the marketing authorisation holder, respectively. In addition, after the granting of a marketing authorisation there would be a simplified IMPD which could be used by non-commercial sponsors or generic companies. With regard to the process for CTAs, an application linked to the new central European IMPD would be made only once via a central point to NCAs and ECs and therefore facilitating the procedure.

The EMA further states that the current regulatory framework does not meet the practical requirements in some points. In this context, the EMA proposes to revise the legal framework to simplify the initiation and the conduct of clinical trials, especially important for academic sponsors [15].

4.4. Ethics Committees

The importance of the ECs has been strengthened by the implementation of the Directive in 2004 which led to more professional structures and processes regarding the ethical review of clinical trials. However, in the perception of some ECs the Directive did not lead to a better protection of the patients [15]. It is the task of the ECs to assure that the rights, the safety and the well-being of subjects involved in clinical trials are protected. However, ECs state that there are significant differences between the cultural traditions, laws, therapeutic standards and health care systems in the countries of the European Union and therefore it is not possible to apply common and harmonized regulations for the ethical assessment of clinical trials throughout all MS. Equally, it would not be possible to develop standardised documents such as the subject information sheet or the informed consent form. National peculiarities must be considered and respected in the ethical review of a clinical trial. For example, the "Permanent Working Party of Research Ethics Committees in Germany" (PWPREC) states that the German history makes the conduct of clinical trials in patients not capable of giving their consent very difficult and even placebo controlled trials could lead to ethical objections. The ECs agree that an improved communication and networking between ECs in Europe could be beneficial but they doubt that a closer cooperation regarding the assessment of CTAs could work. The reasons for this attitude are the different national cultural habits, the legal requirements, the diverging medical practice in the countries and language barriers especially of the lay members in ECs.

It seems that most of the ECs reject the concept of a "one-stop-shop" for the submission of one single CTA dossier to ECs and NCA. One of the reasons for this is that certain documents have to be submitted to ECs and/or NCAs according to national legal and regulatory requirements. Although the majority of documents are based on the requirements of the Directive, there are many national peculiarities that have to be respected. In addition, there are differences between the countries concerning documents to be submitted to ECs and NCAs. ECs are afraid that a new review procedure would require more staff and would increase the costs for the assessment. ECs also doubt that the confidentiality of an electronically submitted

CTA dossier could be adequately assured. The PWPERC even raises the point that a single CTA dossier could lead to fundamental legal conflicts. They are afraid that such a concept would restrict the freedom of academic research that is guaranteed by the constitution. In contrast to this opinion, the UK has made very positive experiences with a common submission and the Central Portuguese Ethics Committee for Clinical Research, responsible for the ethical review on a national level, states that it would agree to the proposal of a one-stop shop for submission of the dossier. However, in this case it has to be guaranteed that all the needs for an adequate assessment of all aspects related with the ethics of clinical trials research are preserved.

Many ECs acknowledge that there is an overlap in the current scope of assessment between NCA and EC. However, such overlap is not considered as a disadvantage because assessors of NCAs and ECs have different views on the application dossier which leads to a better protection of the patient. According to the opinion of the PWPREC only physicians with current practical experience are able to assess all aspects of a clinical trial protocol, but such professional coverage is not necessarily guaranteed in medicines agencies. Therefore, a clearer legal definition of the scope of responsibilities is not considered to be necessary. If needed that should be done by national legislation on the basis of the specific national requirements.

Taken together, for ECs it is very important that all ethical aspects in the assessment of a clinical trial should clearly stay under the responsibilities of the MS. A one-stop shop for the submission of dossiers is rejected by most ECs keeping in mind the different national requirements and experiences. Therefore, the system should stay as it currently is and the ECs do not see the necessity for a revision of the Directive concerning the modalities for the ethical review of the application dossier. Room for improvement is seen in the education and training of staff at CROs and sponsors which could result in fewer requests for modifications and shorter timelines until the start of the study [15].

However, it becomes clear that there is currently no close communication and collaboration between the ECs in the EU. In addition, it seems that there is no strongwish for a closer collaboration of ECs on a pan-European level. As a consequence there is no aligned opinion of the European ECs on the functioning of the Directive and on the proposals for a revision of the CTA process.

4.5. Non-commercial sponsors

36% of all clinical trials in the EU are sponsored by non-commercial sponsors and 20% of all CTAs are derived from investigator initiated trials [5]. Often these trials have the goal to improve the use of already authorised drugs but they also play a role in the development of new medicinal products. As can also be seen in ICREL, the non-commercial sponsors (academia) represent a very heterogeneous group, ranging from large organisations and research networks to universities and small research groups. It is obvious that the availability of resources varies significantly within the group of academic sponsors and therefore the issue of costs and administrative processes plays a major role for the activities of these stakeholders in clinical research.

All associations of non-commercial sponsors confirm that the costs and the administrative burden for the conduct of clinical trials have increased dramatically [15]. The "Federation of the European Academies of Medicine" (FEAM) states that the Directive has not solved the problems it was designed to do but the EU has become a less attractive location for research. According to FEAM and the "European Organisation for Research and Treatment of Cancer" (EORTC) the Directive did not result in an improved protection of the patient and in the ethical soundness of clinical trials. Groups like the "European Group for Blood and Marrow Transplantation" (EBMT) see a reduction in the number of new trials. Whereas ICREL was designed to measure the quantitative impact of the Directive there is unfortunately no project ongoing that evaluates the qualitative aspects. In contrast to the opinion of FEAM and EORTC, the German "Koordinierungszentrum für Klinische Studien" (KKS) points out that the Directive led to an increased patient protection for example through internal audits and increased monitoring.

The multiple and divergent assessment of CTA applications is considered to be a major issue which results in increased administrative costs and delays in the start of trials [15]. Also the sponsors' need for qualified staff for the preparation and submission of CTA applications has increased dramatically. The EORTC states that more resources are needed to conduct fewer trials without an improvement in quality. Resulting from that, academia recognises a shift in the type of conducted trials. Due to the increased costs academia is forced to establish various partnerships with the industry which could be a threat for the independence of research.

In terms of possible options for streamlining the authorisation process for clinical trials there are slightly different opinions among different non-commercial sponsors. In general, the VHP initiative is supported but academia would prefer a mutual recognition procedure for the

authorisation of multi-national clinical trials. One clear disadvantage of the VHP is seen in the fact that some Member States are already opting out. Academia strongly agrees that one single CTA dossier in English (one-stop shop) which is submitted to both ECs and NCAs and which is accepted in all Member States would be beneficial as a first step towards harmonisation of CTAs. Also the scope of responsibilities of ECs and NCAs should be clarified to achieve a reduction in the number of conflicting assessments. The ethical review should be done in parallel with the regulatory review of NCAs. FEAM hopes that in the long-term the ethical review process could evolve to a system of central ECs which could take the lead in a pan-European review of multi-national trials and which would be supported by national ethical review of local issues.

All non-commercial sponsors support a change in the authorisation process of clinical trials which ensures a stronger cooperation of the MS. Whereas groups like the EORTC prefer the continuation of the VHP model or the development of a MRP with a reference opinion of one or two MS, other groups from academia like for example the EBMT support the option of a centralised procedure with one point of contact for multinational trials. In this case the sponsor should have the possibility to choose between the current procedure and the new centralised procedure. According to the EBMT the main advantage of an authorisation applicable throughout the Community is that no new authorization would have to be requested in case the clinical trial is expanded to further MS.

FEAM adds that independent of the type of the new model the responsible bodies must appoint rapporteurs according to the appropriate expertise rather than seeking to achieve geographical balance. For trials that are conducted only in one MS it would make sense to continue to submit the CTA to the national CA.

There is no agreement between the different associations of non-commercial sponsors how the legislative changes for a reform of the Directive should be conducted. Many groups believe that a revision of the guidance documents can contribute to a reduction in the administrative burden as an interim step in the short-term. However, the guidance documents are not legally binding and this would not solve the problems resulting from the Directive itself. Therefore, other groups are of the opinion that a full revision of the Directive would be the best solution. There is no consensus if these changes should be governed by a Regulation. FEAM believes that the newly acquired responsibility of DG Sanco for pharmaceutical policy will facilitate these discussions.

4.6. Contract Research Organisations

Many tasks in the conduct and preparation of clinical trials are often outsourced by sponsors to contract research organisations (CROs). There are two major associations of CROs: The "European CRO Federation" (EUCROF) which represents 202 CROs from seven European countries and the "Association of Clinical Research Organisations" (ACRO) which represents the world's leading CROs with more than 23.000 employees in the EEA. The feedback of EUCROF and ACRO to the Public Consultation paper on the functioning of the Directive will be taken as representative for the position of CROs.

The CROs recognise that the Directive provided benefits in certain areas of clinical research. However, there is room for improvement in aspects related to different interpretation and implementation in national legislation resulting in insufficient harmonisation between the MS [15]. It seems to be very difficult to measure the impact of the Directive on qualitative aspects of clinical trials, e.g. improved protection of subjects. With regards to multiple and divergent assessment of clinical trials, CROs acknowledge that ultimately divergent decisions on CTAs are quite rare. However, the questions raised by the NCAs are often very different which makes clear that the regulatory framework is interpreted differently. EUCROF estimates that in 20% of multinational trials national protocol amendments are requested as a response to concerns raised by only one or a few NCAs. One of the reasons for that might be that especially in small countries NCAs often do not have sufficiently qualified staff for the assessment of CTAs in certain therapeutic areas. In addition, the CTA review process is negatively influenced by the fact that the scope of responsibilities between NCAs and ECs is not sufficiently clear. According to ACRO this is especially the case in the review of first in human trials and trials with healthy volunteers. Of course, the duplicated assessment and the divergent results of the assessment between different countries have significant impact on the timelines until the start of a trial.

With regard to the different options for streamlining the CTA process the CROs have the following positions: The current approach of the VHP is limited due to several reasons. It is only available for selected study types and should be extended to all studies. In addition, it does not address the problem that different national requirements regarding the requested documentation still remain. For some countries the review time of the VHP (max. 60 days for core review plus 20 days for national approval) can be longer than the time for the national review. Unfortunately, it is not possible to add additional MS without a new review procedure after the study has been approved.

The CROs highly appreciate the proposals for a MRP/DCP approach with a RMS or a centralised procedure which is managed by the EMA. A MRP/DCP approach could be acceptable if all the issues described for the VHP were addressed and the timelines were competitive in comparison to national procedures. It would be important to define the role of a RMS and, the sponsor's possibility to influence the choice of the RMS. In addition, the process for the "arbitrage" would need to be described in detail.

However, the majority of CROs prefer the option of a procedure similar to that of the centralised procedure for MAAs if more than one MS is involved. Some CROs would like to maintain in parallel the option of the established national assessment procedure for monocentric studies and small multicenter studies. The central submission and assessment of a single CTA in English (electronic CTA, linked to the EudraCT system) would have the advantage that the authorisation would be valid throughout the Community and that no additional authorisations would be necessary to expand a clinical trial to other MS. There would be a single set of required documentation across all MS. The Community approval system would be managed and coordinated centrally, preferentially by the EMA because of the already existing structures. The system should not be limited to certain therapeutic areas or stages of development. The ethical review should be done parallel. The CROs emphasize that ethical issues should remain within the ambit of the MS. However, a single EC in each MS could further reduce the complexity of the current situation. As a consequence of the centralised procedure, the conduct of multinational clinical trials in the EU should become more attractive for applicants as less administrative work would be required. Of course, legislation would have to be adapted. ACRO and EUCROF strongly support the replacement of the Directive by a regulation after its contents have been adequately revised to avoid in future a nationally divergent implementation of a Directive's principles [15].

4.7. Patient organisations

Patients participating in clinical trials deliver an important contribution to the development of new treatment options. On the other hand, by participating in clinical trials patients get access to investigational medicinal products which could potentially result in improved benefits and outcomes. For that reason, the patient and the patient organisations representing patients' voice in different indications are very important stakeholders in the field of clinical research. Helsinki Declaration and Clinical Trials Directive define the protection of human rights and the dignity of a human being as the basis for the conduct of clinical trials. Therefore, the

question whether the implementation of the Directive reached the goal of harmonising clinical research in the EU affects patients as well as the other stakeholders.

Patient organisations welcome that the Directive introduced Good Clinical Practice principles and some harmonisation of processes in clinical research in Europe. But, in the view of the patients, the Directive had many detrimental effects [15]. It slowed down the start of trials and therefore the access to new treatment options without a significant improvement in the safety of the patients and in the competitiveness of clinical research in Europe. The different interpretation of the regulatory framework and the lack of harmonisation between the MS lead to increased costs and additional administrative workload during the preparation and the conduct of clinical trials. The most unfavourable effects can be seen for trials not aiming at registration of a compound and for academic clinical research. In some cases, due to the high administrative burden, new or already existing therapies which are not very attractive from a commercial point of view are not scientifically evaluated any more. In the opinion of patient organisations like the European Cancer Patient Coalition (ECPC) and the European Cancer Organisation (ECCO), the Directive does not address the specific concerns of non-commercial clinical trials. This leads to the fact that the number of new clinical trials has declined during the past years whereas the costs have increased and the time to initiation has become longer. Therefore, patient organisations strongly support a revision of the Directive and especially of the process of clinical trial authorisation [15].

The patient organisations recommend harmonising the procedures for set up and conduct of clinical trials in the EU. They would like to avoid differences in CTA dossiers between Member States leading to an increased administrative burden and divergent assessments. This means that a central European EC and a central body representing the national competent authorities should approve a trial for all MS. This single trial authorisation should be implemented irrespective of the number of Member States concerned. This could be achieved through the development of a central procedure or through a MRP. The VHP would also be an option but for example the ECPC believes that the VHP might struggle with the large number of assessments of all European multinational trials and lose out against the currently existing shorter timelines in some MS.

It is proposed that a single initial investigational new drug (IND) dossier should be established for a non-marketed drug before the first clinical trial with a new compound can start. Subsequent trial protocols are submitted as amendments to the IND which would be a very efficient and time-saving approach.

In summary, according to the patient organisations the described regulatory changes like a single European evaluation and authorisation process for multinational clinical trials could lead to a significant improvement in patient focused research.

5. How could a single CTA process look like?

As described before, there is a lack of harmonisation with regard to the submission and review process of CTAs within the EU. Besides other inconsistencies like for safety reporting, GMP requirements as well as definition and approval of substantial amendments, there are also significant differences between Member States in the requirements for the CTA dossier. These differences have a negative impact especially on the conduct of multinational clinical trials. Therefore, it should be the goal to reduce the administrative burden for the application and authorisation of multinational clinical trials. Several options for a more efficient CTA process without multiple assessments of the same trial are presented in the following.

5.1. Single CTA application

An important first step is an agreement on the same application dossier in all EU Member States for national and multinational clinical trials, submitted to a central secretariat at the EMA. The single CTA submission is valid throughout the whole EU/EEA. This means that the CTA is a standardised dossier (including the IMPD) and that the MS are not allowed to request any additional national documentation. The CTA dossier is submitted in an electronic format based on the e-CTD to the EudraCT database. The validation of the CTA dossier is conducted according to a pre-defined unique list of contents at a central secretariat within a validation period of 5 days. The dossier is centrally filed in the EudraCT system and is accessible for NCAs but not for applicants. The submission to a central secretariat at EMA applies for the submission of substantial amendments as well.

The change of the existing national submission system to a single central CTA submission could be implemented through a regulation which applies for both national and multinational clinical trials.

Implications on the EudraCT database:

For the single CTA application the EudraCT system needs to be adapted to the new process. The central submission system IRAS in UK can serve as basis for the update.

Independent of the nature of the revised CTA review process the responsibilities for the entries into the EudraCT database have to be defined. The preferred approach would be that the applicant submits the application form and the CTA dossier directly to the database. The EudraCT system is updated automatically with the information contained in the application form and the dossier is automatically filed in the database which is only accessible for the

NCAs and the EMA. In the application form new fields for the recipient of the CTA application have to be generated. If the box for central review is ticked only the central secretariat at the EMA receives the CTA application. For national CTAs or for the DCP/MRP the corresponding NCA(s) is/are informed about the CTA application through the EudraCT system as well. After review of the CTA the outcome of the procedure is entered through the central secretariat in case of a centralised procedure or through the NCA in case of a national or a DCP/MRP-like procedure. After receipt of a national EC opinion the NCA enters the content of the opinion into the database.

5.2. Single CTA review

5.2.1. Centralised Procedure with EEA wide approval

Parties involved:

- EMA
- Central secretariat for submission and validation of single CTA application and substantial amendments
- Assessment team, rapporteur (members of the NCAs)

Process for CTAs and substantial amendments:

The management and coordination of the CTA process in a centralised procedure (CP) is conducted centrally at the EMA. This means that the EMA is responsible for the tracking of ongoing central CTA review procedures and for keeping the timelines. The validation of the submitted single CTA dossier is done at a secretariat at the EMA. Through the EudraCT database the NCA is notified about a central clinical trial authorisation.

Similar to the process of the Community Marketing Authorisation there is a team of multinational assessors from across all MS with an assessment coordinator. Thus, it would be guaranteed that the best expertise available is the main criterion for the appointment of the assessors. The assessment team is not allowed to request country specific documents after receipt of the validated CTA. Questions raised during the review process are addressed to the sponsor in English language and requests and concerns from ECs are followed up by the assessment team.

Like in the CP for a Marketing Authorisation the role of a rapporteur is established. The MS that has the function as a rapporteur is “responsible” for the product, act as rapporteur for all

further CTA assessments and in case of a request for a MA in the future it should stay rapporteur for the MA process. In this context, it has to be clarified if it is possible for the MS to act as rapporteur for a MA due to capacity reasons.

As a result of the central review of the CTA one central authorisation for the trial is issued by the EMA which is valid throughout the Community. No additional follow-up authorisation by the NCAs is needed. Therefore, a clinical trial can start in a country when the Community authorisation was issued and when the favourable EC opinion for the MS concerned was granted. The inclusion of new study sites in the same or in additional countries is possible after the favourable EC opinion without involving the assessment team at the EMA. The information on the EC opinion is entered in the EudraCT database by the NCA concerned.

According to the described procedure for the CTA, substantial amendments are electronically submitted for central review to the EMA as well. They have to be submitted in a standardised format and are validated at the central secretariat. The approval of substantial amendments is issued by the EMA and valid throughout the whole Community. A consistent procedure defining which type of changes to the protocol have to be submitted as a substantial amendment is needed. For this purpose, the updated Detailed Guidance which gives explanations and examples for substantial and non-substantial amendments can be used [2].

Timelines for review of CTAs and substantial amendments:

The time for the central review is limited to a maximum of 60 days (including a validation period of 5 days) but the same exceptions apply as outlined in the Clinical Trial Directive Article 9(4-6). In Article 9(4) it is stated that "*The competent authority can nevertheless notify the sponsor before the end of this period that it has no grounds for non-acceptance.*". There is only one possibility to issue grounds of non-acceptance by the review committee and one possibility for the sponsor to amend the content of the CTA accordingly.

For the review of substantial amendments the same assessment process within a maximum timeframe of 30 days applies as for the initial CTA. A validation period of 5 days is included in the response period of 30 days.

Required level of legislation:

A regulation or an amendment of Article 9(2) of Directive 2001/20/EC is needed to implement a centralised procedure for the single review of a CTA.

One possibility to implement the process of a centralised CTA submission and approval procedure is a revision of the Clinical Trials Directive 2001/20/EC, Articles 9(2-4) which could read as follows:

"2. Before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial or for community authorisation to the EMA.

3. If the competent authority of the Member State or the EMA notifies the sponsor of grounds for non-acceptance, the sponsor may, on one occasion only, amend the content of the request referred to in paragraph 2 in order to take due account of the grounds given. (...)

4. Consideration of a valid request for authorisation by the competent authority or the EMA as stated in paragraph 2 shall be carried out as rapidly as possible and may not exceed 60 days. (...) The competent authority or the EMA can nevertheless notify the sponsor before the end of this period that it has no grounds for non-acceptance."

Another approach for the implementation is the adoption of the revised contents of the Directive into a regulation. In contrast to a directive, which is only binding in terms of the result and not in terms of the applied methods, a regulation removes national transposition measures and its requirements are binding for all MS. For example, the submission process of a CTA could be described in more detail and different national interpretations would be avoided.

With regard to a possible transformation into a regulation it is important to apply the subsidiarity principle to allow the MS to refuse because of ethical reasons in the protocol or regarding the investigational product. An example for a similar approach can be found in the Regulation (EC) 1349/2007 on Advanced Therapies in the Introduction (7) *"The regulation of advanced therapy medicinal products at Community level should not interfere with decisions made by Member States on whether to allow the use of any specific type of human cells, such as embryonic stem cells, or animal cells. It should also not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products containing, consisting of or derived from these cells."* and in Article 28(3) *"(...) This Directive and all Regulations referred to therein shall not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these cells, on grounds not dealt with in the aforementioned Community legislation. (...)."* [16]

5.2.2. Voluntary Harmonisation Procedure

Parties involved:

- NCAs of MS concerned
- VHP-Coordinator
- CTFG

Process and review timelines of CTAs and substantial amendments:

The VHP is a scientific assessment under a harmonised procedure and it consists of three phases: Phase 1 is the request for the VHP and the submission of the documentation which is addressed to the VHP-Coordinator. In phase 2 the CTA is reviewed by the participating NCAs of the MS concerned. This step is followed by phase 3 (national step) which is the formal application of the CTA to each NCA as described in the Directive.

One of the participating NCA takes the lead for the scientific review of the CTA. The documents are submitted electronically via e-mail/eudralink (VHP-CTFG@VHP-CTFG.eu) in a defined electronic structure. It is important to know that no approval for a clinical trial is granted during the VHP. After the conduct of the VHP (timeline for review 60 days) the CTA has to be submitted for approval to the NCA in each participating country and each NCA should issue the approval within a specified timeframe of additional 10 days. Within the VHP no additional MS can be added after the review has been completed.

The revision of the VHP-Guideline led to the following important changes:

- All clinical trials (commercial and non-commercial sponsors) that are conducted in at least three MS can be assessed within the VHP.
- Substantial amendments for CTAs which underwent the VHP can be submitted via the VHP as well.
- For each VHP, one of the participating NCAs (Rapporteur MS, selected by the CTFG) takes the lead in the scientific consolidation of the letter with grounds for non-acceptance.
- The duration of phase 1 (request for VHP) was reduced by approx. 2 weeks

The flowchart describes the different phases and steps within the 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, Compliant 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	
Phase 2	**VHP CTA assessment step I**	
Day 1	Start of VHP	
Day 30	If no GNA or RFI: information (VHP-C) of the applicant on acceptance	End of VHP and start of phase 3 → National step
Day 30	In case of GNA and/or RFI: transfer of GNA/RFI by VHC-C to the applicant and the P-NCAs (Response has to be submitted within 10 days)	
	Day 40 – Day 50 VHP assessment step II	
Day 40	Deadline for electronic submission of additional documentation and revised CTA to VHP-C by the applicant	
Day 50	If the revised CTA is considered approvable: information (by the VHP-C) of the applicant on acceptance	End of VHP and start of Phase 3 → National step
Day 60	If a revised CTA 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 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	
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 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 decision might result.

Required level of legislation:

The VHP is already implemented. It is described in detail in the *"Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications*" and was revised in March 2010 [7]. The VHP is a voluntary procedure.

5.2.3. Decentralised Procedure

Parties involved:

- NCAs of MS concerned
- Central secretariat for submission and validation of single CTA application and substantial amendments

Process for CTAs and substantial amendments:

The further development of the VHP could lead to a decentralised procedure (DCP) for the single review of a CTA within Europe. This would mean that the single CTA approval is only effective in the MS involved in the CTA review. Similar to the CP, a single CTA is submitted to the central database and the central secretariat performs the validation. The dossier is electronically filed in the EudraCT database. The MS concerned are informed about the submission of the CTA application through the EudraCT system. The further process for a DCP could be set up correspondingly to the DCP for the application for a MA which is described in Directive 2001/83/EC Article 28 (1) [14]. One NCA acts as RMS and takes the lead for the scientific assessment. The DCP would also apply for the approval of substantial amendments.

One of the open questions within the DCP is if a mutual recognition process is required if an additional MS is added after the initial multinational authorisation of a clinical trial.

Timelines for review of CTAs and substantial amendments:

The same timelines for review as previously described for the CP should apply (60 days for the review of the CTA application and 30 days for substantial amendments).

Required level of legislation:

Prerequisite for the implementation of a DCP is a harmonisation of the legal requirements for CTA applications. Therefore, the best way for the implementation of a DCP is in the form of a regulation which is directly binding in all MS without any necessary transposition into national legislation. This avoids differing national documentation requirements due to the different local interpretation of the Directive.

5.2.4. Mutual Recognition Procedure

Parties involved:

- NCAs of MS concerned
- Central secretariat for submission and validation of single CTA application and substantial amendments

Process for CTAs and substantial amendments:

A single CTA is submitted to the EudraCT database and the central secretariat performs the validation. The dossier is electronically filed in the database. A CTA process similar to the Mutual Recognition Procedure (MRP) to obtain a MA can be applied in the following case: When a clinical trial starts in one MS only the concerned NCA reviews the CTA application and the substantial amendments which means that the established national review process applies. If the clinical trial is expanded to a multinational trial because of the addition of one or several further MS a MR approval should be obtained based on the RMS assessment. (Directive 2001/83/EC Article 28 (2)) [14]. The applicant updates the application form and submits the request to include additional MS to the EudraCT database. The NCAs of the additional MS are informed about the request of the applicant through the EudraCT system. The approved CTA dossier is accessible for the MS through the central database. Based on the assessment from the RMS the additional MS issue the national approval of the clinical trial. Substantial amendments are approved by the RMS as well and the NCAs of the MS will adopt the approved substantial amendments.

Timelines for review of CTAs and substantial amendments:

For the approval of the CTA and of the following amendments the national timelines of the RMS apply. After the applicant's request to include additional MS the RMS provides the assessment to the MS concerned within 15 days. The MS concerned inform the RMS within additional 10 days about their decision.

Required level of legislation:

A true mutual recognition step without additional national requests is necessary for the functioning of this approach. Therefore, before the implementation of such an approach an

EU-wide harmonisation of documentation requirements for gathering a clinical trial authorisation is needed. Similar to the situation for the DCP, the MRP should be implemented in form of a regulation to avoid multiple national requirements and differing interpretation of the regulatory framework in the MS.

6. Discussion

The Clinical Trials Directive 2001/20/EC, the Directive 2005/28/EC and the Detailed Guidance 2010/C82/01 represent the legal and regulatory framework for the application, review and authorisation of clinical trials in the EU [1,2,17]. Without any doubt the implementation of the Directive has led to improvements in terms of safety and ethical soundness of clinical trials. Nevertheless, there are also many weaknesses arising from the fact that the Directive was transposed differently into national legislation resulting in a lack of harmonisation between the MS. As a consequence, the administrative burden and the costs for the conduct of clinical trials have increased during the last years. In the opinion of many stakeholders, this leads to a decreased attractiveness and competitiveness of clinical research in Europe.

One of the main administrative processes is the preparation of the CTA application which involves considerable resources both at the sponsors and the NCAs. Due to national peculiarities with regard to the required documentation sponsors and CROs have established dedicated departments and specialised staff to fulfil the numerous requirements in terms of CTAs for multinational trials. As a consequence, the costs to carry out largely identical parallel processes for every country participating in a clinical trial are very high without increasing the quality of the assessment or the protection of the patients. This represents a problem especially for SMEs, universities and other non-commercial sponsors who do not have sufficient resources or staff. According to ICREL a decrease in the number of trials sponsored by academia could be noticed. For that reason it should be a goal that funding schemes for academic sponsors are adequately adapted to the increase of administration costs for clinical trials [4].

It is difficult to answer the question how often NCAs come to different decisions on the same CTA. Regulators argue that this is the case for less than 0,1% of all clinical trials whereas sponsors argue that it is not rare that a trial can not be conducted in a certain MS. However, diverging assessments of NCAs lead to differing sets of questions, differing grounds for non-acceptance and the implementation of multiple amendments which results in delays for the start of the trial. Mainly sponsors, CROs and patient organisations criticise that fact which deprives patients from early access to investigational compounds and prolongs the time until the granting of a marketing authorisation [15]. In contrast to this opinion the NCAs, the CTFG and the ECs state that multiple assessments are due to the diverging therapeutic standards in different countries and that the multiple assessments contribute to reach the

highest-possible standard for the evaluation of the CTA. In this context, NCAs and ECs clearly declare that the speed of the assessment has to stand back behind a thorough evaluation of safety and efficacy. In addition, in the opinion of ECs it is not possible to develop standardised documents, e.g. for the ICF and that national peculiarities always have to be respected [15].

To the described issue adds, that a clinical trial has to be submitted either sequentially or in parallel to the NCA and to the EC. In many countries the scope of responsibilities of NCAs and ECs is not sufficiently clear and it comes to overlaps in the assessment of the same clinical trial. In addition, for the application at the ECs other national documentation and requirements are necessary than for the application at the NCAs. In the opinion of sponsors and patient organisations these requirements cause additional costs and delays for the start of the trials which would not be necessary. The long time until the first patient can enter the trial seems to be a big disadvantage in terms of the competitiveness of clinical research in Europe, especially in comparison with the US where approval times for a CTA are much shorter. Therefore, all stakeholders with the exception of the ECs themselves agree that the roles and responsibilities of CAs and ECs should be harmonised and defined more clearly across all MS [15]. It should be the goal to define on a European level the scope of responsibilities of ECs and NCA within the review of CTA applications. The EC review should be done parallel to the review at the HA. The definition of responsibilities should be laid down in an updated legislation, preferably in a regulation. The regulation should apply for both the national CTA submission and a new centralised CTA process.

In this master thesis, the different positions of the stakeholders towards achievements and shortcomings of the Clinical Trials Directive with regard to CTAs are described in detail. Currently, there are many ongoing discussions and initiatives with the aim to simplify and harmonise the CTA process in the EU. The public consultation paper on the functioning of the Directive makes important proposals how the CTA procedures could be streamlined [5]. The goal is to strengthen the cooperation of MS and to introduce a more centralised CTA approach. The different options comprise the Voluntary Harmonisation Procedure, a Mutual Recognition or Decentralised Procedure or a Central Procedure. In addition, the option of a centralised submission of the CTA is described and discussed.

The **central electronic submission** of one single CTA in English which is linked to the EudraCT system is one of the main requests from many stakeholders with the exception of NCAs and ECs. The preferable point of submission would be the EMA. The reasons for the

choice of the EMA are that it is as an existing body and that for an implementation of the electronic submission no additional administrative structures would have to be established at each NCA. In the case of a central submission of one single CTA application the MS would not be allowed to request additional national documentation which would result in a significant increase in harmonisation and in an immense reduction of administrative processes. The central submission should apply for national CTAs as well. It is one of the measures that could be reached in the medium term. For the long term one might think about the question whether the central submission could be expanded to a one-stop shop for the submission to both NCA and EC. In this context, the British IRAS system (established in the UK in 2008) could serve as an example. IRAS is a platform that allows the simultaneous submission to MHRA and NRES in one application form. Study related data is shared between IRAS and the EudraCT database and all the information about a clinical trial can be entered through IRAS in one place. One of the most important prerequisites for the European implementation of a one-stop shop for the submission to NCA and EC is a legally binding definition of the scope of responsibilities of these two bodies which is valid in all MS. ECs in most countries reject this approach whereas sponsors, patients and the EMA would welcome such a concept [15] and positive experiences have already been made in the UK.

The implementation of the central electronic CTA submission would have several consequences on the existing **EudraCT system**. The applicant should submit the application form and the CTA dossier directly to the database which is updated automatically with the information from the application form. Thus, the current practice that NCAs in all MS concerned enter similar data for the same clinical trial is avoided and significant resources at the NCAs are saved. NCAs should still be responsible for the entry of CTA approvals and EC opinions. This approach means that the access to EudraCT is still a closed system reserved to NCAs and EMA and that sponsors do not get direct access to the database. This prerequisite is considered as very important in terms of data protection and reliability of the EudraCT system.

The VHP which was initiated by the CTFG is a first step towards a central submission and a harmonisation of the assessment of the CTA dossier [7]. The VHP could evolve to a true DCP in the mid-term. All CAs and the CTFG strongly support the VHP because it offers many features like a one-stop shop for CTAs, the electronic submission of the CTA dossier in English, a single list of question to be answered and a unified opinion at the end of the procedure. However, it has to be stated that the VHP does not address the fundamental issue of the diverging national CTA requirements. In the VHP only a core CTA is reviewed and

other documents are outside the scope of VHP. A national authorisation from the NCA is still necessary after the VHP which prolongs the timelines until approval. The participation at the VHP is completely voluntary and not all NCAs are taking part. It is important to know that the VHP includes no attempt for an alignment of the EC system and the responsibilities of CA and EC are not clarified. As long as the EC review is not included in a single review process it will still be difficult to differentiate the duties of CA and EC. One of the open questions is how national requirements and requested changes from ECs should be handled in the VHP. Surprisingly, the VHP was not incorporated into the new guidance 2010/C82/01 and it will be very interesting how the VHP will evolve in the future.

Another option for the CTA review process would be the **MRP or the DCP** like it is used for the application for a marketing authorisation. The authorisation of the trial would be effective in all MS concerned. In terms of the efficient use of resources a RMS performing the assessment should be defined because the parallel review through each NCA would require the same amount of resources as the national procedure. With regard to the DCP it should be clarified whether the RMS was to continue to act in this role when the product would be subject of a marketing authorisation. An issue in this context is that probably not all NCAs have the capacity and the expertise to take over the role of a RMS. In addition, the question has to be raised how the procedure would look like in case one or several MS concerned do not agree to the authorisation of the CTA. It would have to be decided whether in such cases the trial can only be conducted in the MS that had agreed, whether it is conducted in all MS or whether it is rejected completely. An arbitrage process and the impact that such a process has on the overall timelines would have to be defined. The timelines should be competitive with the existing timelines for national review and they should not be prolonged through the arbitrage process. It also would have to be clarified whether the approval is issued on a national level by each NCA or whether the approval is issued by the Community. It is obvious that a MRP or a DCP would require a very high level of harmonisation between the MS which is currently not the case. This is needed to avoid different criteria for the assessment in the MS. It also would have to be clarified how the expansion to additional sites and MS is going to be handled if they join the clinical trial after the initial approval process. The MRP/DCP does not seem to be a very flexible approach regarding that issue.

Many stakeholders (commercial sponsors, CROs, patient organisations, the EMA and a part of the non-commercial sponsors) strongly support the concept of a central submission in combination with a **central CTA review** (centralised procedure) [15]. The EMA was identified as the central body that should be responsible for the central review of CTAs and

substantial amendments. One standard CTA dossier (including the IMPD) with defined format and content would be needed and also clear language requirements would have to be defined. As only 25% of all clinical trials are conducted in several countries it seems to make sense that the central review would complement the existing regulatory framework as an additional option.

The **centralised procedure** has several **advantages**. The central CTA submission and review would lead to a reduced workload at the NCAs and a significant decrease in the administrative burden. As a result of the avoidance of divergent HA decisions no substantial amendments due to differing opinions would be needed any more. As a result clinical trials could start earlier and patients get faster access to new drugs. Especially SMEs and non-commercial sponsors would welcome the fact that fewer resources and fewer efforts are needed for the preparation of the CTA for multinational clinical trials. At the moment, only the core IMPD is identical for all EU MS but there are a lot of local requirements in the different MS which have to be fulfilled by the sponsor and which in many cases do not contribute to the safety and the protection of patients. These national requirements are sometimes not transparent (for most NCAs no or only partial information in English is available on the homepage) and for the sponsor of a clinical trial, especially for academic sponsors and SMEs, this lack represents an extra burden for the CTA submission. In the case of multinational clinical trials this cumulative effect of workload can even lead to a movement of research activities into other countries with a more "favourable" regulatory environment. At the moment, the timelines for CTA review vary from country to country. Defined standard timelines for the centralised procedure would make the planning for sponsors easier. The same would be true for the process of application and approval of substantial amendments which should be revised according to the CTA process. In the new process a distinct timeline of 30 days should be defined for the review of substantial amendments and the amendment should be submitted to the central body as well. One of the main features of a central CTA review is that the decision about the approval of clinical trials and substantial amendments would be valid throughout the whole Community. The authorisation of a trial would be issued by the EMA. The advantage of a Community-wide authorisation would be that the MS do not have to confirm the decision locally and that additional MS can be added (given that the EC has issued a favourable opinion) after the trial has been approved. An advantage of establishing the single CTA approval process at the EMA would be that the gap between the authorisation process for clinical trials during the development and the marketing authorisation procedure for CP products would be closed. In addition, the EMA is already involved in the management of the

EudraCT and EudraVigilance databases and hosts meetings of the CTFG. EMA strongly supports that the single CTA approval process will be located at the Agency. One of the open questions is whether the centralised procedure were to really lead to reduced fees. Preferably the fees for an application of a clinical trial should be the same across all countries and they should be as low as possible.

But of course there are also some **critical aspects of a centralised procedure** which have to be discussed. Currently, it is relatively easy for sponsors to get in contact with the NCA during the review process and established relationships between sponsors and NCAs are beneficial for an efficient communication. This option would probably diminish with a CP. Therefore, a single CTA review process should run in addition and should not replace the existing national system. With this approach the sponsors would have the choice which process should be applied and the national review system could for example still be used for national clinical trials. The processes for the single CTA review and the national system should run under the same regulatory and legal requirements. Of course, the CP would require additional staff and new structures at the EMA which would result in significant costs. As the NCAs could act – similar to the process of the receipt of a marketing authorisation – as rapporteur or co-rapporteur the question must be asked whether the NCAs have sufficient capacities to fulfil this task. It also would have to be clarified how the coordination within the NCAs would be organised as they would have to deal with both national and central CTA procedures which would require a reorganisation of their structure. In terms of internationally acting companies the workload for CTAs would be significantly reduced which might lead to a reduction of jobs in the dedicated departments. Mainly SMEs and non-commercial sponsors are afraid that the introduction of a CP could lead to increased fees. A fee reductions for SMEs and academic sponsors should be discussed. To facilitate research for non-commercial sponsors and SMEs it would be desirable that an office at the EMA would support them with regard to the formal requirements on CTA submission and procedures.

The responsibility for the **Ethical opinion** is lying in the national competence of each MS and at this stage it will remain there. For the moment it would be desirable to include the submission of the CTA to the EC into a “one-stop shop” process like the IRAS in UK in order to create a common database and to reduce the administrative burden for multiple submissions. As a mid-term goal a single central ethical review process should be introduced in the MS, similar to the process already successfully implemented in The Netherlands. This proposed changes are currently not supported by the ECs themselves.

In this context it should also be discussed whether a **single European Ethics opinion** could be part of the idea of a single review process for clinical trials. Without any doubt this approach would take a long time because of the immense number of ECs in the EU, the differences in national traditions, therapeutic standards and healthcare systems and the different centralised or decentralised processes to get a favourable opinion in the MS concerned. There would also be different ways to implement the single Ethics opinion into the process. This could be a stand alone system for the central EC review or an integrated process with EC and HA assessors issuing together one real single CTA approval. Of course, it also has to be considered that a check has to be performed if a local study site is feasible for study participation. The local ECs then would have to give feedback to the coordinating EC or lead EC about their assessment.

With regard to the described issues it seems probable that the ethical aspects remain within the ambit of the individual MS. Thus, it is assumed that the national single EC opinion per MS remains as such under national law. But despite this, the implementation of a single CTA submission to ECs could represent a big step towards a facilitation of the CTA process.

Not only the CTA process is affected by diverging interpretation and inconsistencies of the Clinical Trials Directive. One of these aspects is the existing uncertainty about the classification of **substantial amendments**. In the MS there are different requirements to classify an amendment as substantial because of the different interpretation of the guideline and a differing comprehension of risk. There also exists a feeling of lack of comfort by the sponsor in not notifying CA and EC about changes classified as non-substantial and vice versa some CAs and ECs are feeling uncomfortable about not being notified about changes. In the case of classifying an amendment as non-substantial sponsors fear to be challenged later for this decision of not having informed EC and CA about the change. In addition, sponsors have to deal with divergent decisions on an amendment in the different MS.

A first step to improvement is the recently published revision of the Detailed Guidance 2010/C82/01 on the request to the CAs for authorisation of a clinical trial, the notification of substantial amendments and the declaration of the end of the trial (CT-1) [2]. Within the revised guidance there are examples for substantial and non-substantial amendments and clarifications on the sponsor's responsibilities with regard to the classification of an amendment and obligations on the submission of amendments. Clarification was made that "*Neither national competent authority of the Member States concerned, nor its Ethic Committee can oblige the sponsor to submit non-substantial amendments.*" (Article 107) [2].

One can take this as an interim solution until a new regulatory community framework will be implemented. It is important that for any change of the current CTA system (single CTA application, single CTA review within a CP, MRP or DCP) the process for the submission and approval of substantial amendments is considered and revised as well. The central submission and approval of amendments based on standardised contents and harmonised requirements would help to save resources of sponsors, investigators, CAs and ECs. It is also important that EC and HA do respect the classification on substantial or non-substantial of the sponsor. This classification has to be based on harmonised requirements described in an EU guidance.

An important question is which **regulatory framework** is suitable for the implementation of the proposed changes with regard to the inconsistencies of the Directive and to the CTA process. A short term and interim solution is the revision of the existing guidelines. Within the updated guidelines a clarification of processes, like SUSAR reporting requirements, has to be addressed. As a first step towards a more harmonised approach within the MS regarding the content, submission and review of CTAs is the revised version of 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)"* which was published on March 30th 2010 by the Commission [2]. The new Guidance now for example requests more information on the content of the covering letter and gives the possibility to cross-refer to IB, SmPC and IMPDs of previous authorised CTs. The fact that attachment 1 which indicated the country specific requirements was deleted pretends a wrong conclusion on the degree of harmonisation. It might lead to additional workload for the applicants who now have to search on the NCA's websites for the corresponding information. One could have the impression that the aim of the revised guideline seems to prepare for a single submission of CTAs. However, one of the weaknesses is that the VHP is not mentioned and there is no hint that the CTA process could evolve into the direction of the centralised procedure.

Regardless which option – CP, DCP or MRP – for a more harmonised and centralised CTA process becomes effective in the near future it would be the best solution to implement the process through a **regulation**. In contrast to a directive a regulation is directly binding in the MS without transposition into national legislation which is a time consuming process. This would avoid differing national requirements due to a different local interpretation and implementation into national law. In a regulation the submission and assessment process for a CTA and following amendments could be addressed in a more detailed and binding manner.

Within a new clinical trial legislation the requirements for the CTA process should be the same for all kind of sponsors without any difference. If clinical trials conducted by non-commercial sponsors were excluded from the scope of the Directive/Regulation, as a consequence, the results of such trials could not be used for a MAA. It would be necessary to repeat such trials and this approach is questionable for ethical reasons. Furthermore it would be a step back in terms of quality and safety of the trial subjects if there were differences in terms of legal obligations for different kinds of sponsors.

In February 2010 the regulatory responsibility for pharmaceuticals and medical devices as well as for the EMA were transferred from DG Enterprises (Directorate General Industry and Entrepreneurship) to **DG SANCO** (Directorate General for Health and Consumer Policy). This transfer might reflect the shift of the Commission to patient centricity and a more public health oriented vision. But what does this transfer mean for the discussions and the expertise on the single CTA concept which are connected with DG Enterprises? One could ask in which way DG SANCO will continue to pay attention to the necessary investments for the development of new and innovative drugs and whether the single CTA discussion will be supported as intensively as before.

The public consultation on the functioning of the Directive was conducted by the Commission from 9 October 2009 to 8 January 2010. In March 2010 a summary of responses of the different stakeholders was published [13]. On the basis of these responses, DG SANCO has issued a "roadmap" in April 2010 which summarises the reported shortcomings of the Directive and gives an outlook over the next planned steps [18]. DG SANCO considers the implementation of a more harmonised authorisation of clinical trials which is based on a joint assessment by the MS and the clarification of certain aspects of the Directive in order to reduce divergences among the MS. In addition, the aim is to strengthen the international dialogue and cooperation. According to DG SANCO, these goals could be reached either by amending the Directive, by replacing it with a regulation, by revising the EU guidelines and/or by enhancing the voluntary cooperation between MS. It seems that the EMA will play an important role in the future process of submission, review and approval of CTAs for multinational clinical trials. DG SANCO will continue to collect additional data in expert meetings in 2010 and therefore no new legislative proposals which could lead to a significant change or harmonisation of the CTA process will be adopted until October 2011 [18].

7. Conclusion and Outlook

It is widely acknowledged that the implementation of the Clinical Trials Directive 2001/20/EC has resulted in significant improvements in many aspects of clinical research [6, 13, 15]. Principles like the authorisation of a clinical trial by the CA and the favourable opinion of a single EC within defined maximum timelines led to significant harmonisation of the clinical trial approval process. However, as a consequence of the divergent transposition of the Directive into national legislation in the MS substantial differences in the regulatory framework make planning and execution of multinational clinical studies still very difficult and lead to increased costs and a higher administrative burden [4]. As a result of the divergent national requirements and the differing interpretation of the Directive the process of submission, review and authorisation of clinical trials through the NCAs is not sufficiently harmonised among the MS. Therefore, the existing legal framework for CTA application submission and review should be updated in order to get harmonised EU-wide binding requirements for CTAs and their assessment without national peculiarities. For the existing national processes a parallel submission of the same CTA application to EC and NCA at a "one-stop shop" like it is already implemented in UK would be desirable.

A first step and interim solution for a better European harmonisation was the recently published revised version of the Guideline 2010/C82/01 on the request to the CAs for the authorisation of a clinical trial, the notification of substantial amendments and the declaration of the end of the trial (CT-1), however the concept of a single CTA review seems not to be supported within the Guideline [2].

As a medium-term step the central electronic submission of a single CTA should be implemented. The first move into that direction could be the electronic submission of the CTA in the VHP. The central submission would definitely improve the process currently in place because the administrative burden would be reduced. As a further step, the feasibility of a single submission of the CTA application to ECs should be discussed.

The central submission of a CTA would represent an important step towards a central CTA review as an additional option for the assessment of multinational clinical trials. As the main advantage of the central review, a central body like the EMA would be able to issue an authorisation for a clinical trial valid throughout the whole EEA. This would avoid multiple reviews and diverging assessments in different countries. The new review process should work as an alternative in parallel to the existing national CTA review system.

From a legal point of view, the centralised CTA review should be implemented as a long term measure through a regulation which would be binding to all MS and which would avoid a differing transposition into national legislation. If these changes are to be implemented successfully, there might even be the possibility that the idea of a single CTA review will be developed further and include a "single European Ethics opinion" in the future. Irrespective of the fact what kind of changes to the CTA process will be implemented in the near or long-term future the goal should be to start trials faster without a loss in quality and patient protection.

It has to be acknowledged that the Commission's approach to assess the functioning of the Directive in a public consultation led to important insights from all relevant stakeholders. It is now the responsibility of DG SANCO to drive the process of putting in place a need-adapted modern regulatory framework for clinical trials in Europe. DG SANCO announced that due to the complexity of this process no new legislative proposals will be adopted until October 2011 [18]. This means that despite the fact that many issues are identified and addressed the current CTA process will still remain unchanged over a certain period of time.

Taken altogether, all stakeholders in the area of clinical research have to envisage changes which will affect their daily business and the way clinical trials are planned, approved and conducted. How these changes are really going to look like is not clear at the moment. The introduction of a single CTA submission and review process could be one of the changes that would contribute to reduce the administrative burden for clinical trials and that would help to guarantee the attractiveness of clinical research in Europe. This important approach represents an ongoing process consisting of several steps which will be further discussed in the near future.

In conclusion, the conduct of clinical trials always has to focus on the protection and well-being of the patients. One must never forget that the most important fundament for ethical clinical research is to ensure the safety of the study subjects. A maximum level of harmonisation of the legal requirements between the European countries will allow patients faster access to new treatment options while safeguarding the protection of the study subjects and the quality of the investigational medicinal products.

8. Summary

The entry into force of the Clinical Trials Directive 2001/20/EC was an important step towards a better protection of trials subjects and a higher level of harmonisation of the requirements for clinical trials in Europe. However, the Directive did not reach all its goals and led to an increased administrative burden and higher costs for the conduct of clinical trials. The divergent implementation of the Directive into national legislation in the different Member States counteracts on the idea of harmonisation of European clinical research. This is especially true for the process of submission, review and authorisation of clinical trial applications for multinational clinical trials because almost identical procedures have to be carried out by sponsors, Ethics Committees and National Competent Authorities in every participating country. To overcome the shortcomings of the Directive and to streamline the CTA process several initiatives were launched by different stakeholders during the last years, e.g. the public consultation on the functioning of the Directive by the EU Commission, the Clinical Trials Facilitation Group by the Heads of Medicines Agencies, the ICREL project and the "Road Map Initiative for Clinical Research in Europe". In this master thesis, the views of all relevant stakeholders in clinical research towards the current and the possible future CTA process are elaborated.

As a first step towards a better cooperation between the MS the CTFG introduced the Voluntary Harmonisation Procedure which combines disseminated review of a CTA with a joint assessment of the MS. In addition, the updated Guideline 2010/C82/01 could lead to some improvements in terms of harmonisation of clinical research. However, many stakeholders including commercial and non-commercial sponsors, CROs, patient organisations and the EMA suggest the introduction of one single CTA dossier which is identical for all countries participating in a clinical trial and which is submitted electronically to one central body. As a next step, similar to the process of application for a marketing authorisation, the review of the CTA dossier could be conducted similarly to a mutual recognition procedure, a decentralised procedure or a centralised procedure. The central review of a single CTA application could be implemented as an additional option complementing the existing national review process. It would lead to an authorisation of a clinical trial that is valid throughout the Community and would avoid divergent national assessments and reduce the administrative burden. The submission of a single CTA dossier to a central body followed by a central procedure seems to be the most appropriate approach for a revision of the CTA process. It is obvious that a change of the regulatory framework will be necessary to implement any of these options. Many stakeholders support the adoption of the

legislative changes into a regulation which is directly binding for all MS without any transposition into national legislation. Independent of the introduction of a single CTA process the European legislation should be updated in order to harmonise in a binding manner the requirements for the national CTA submission and review. This could be achieved through the transposition of the Directive into a regulation as well.

The shortcomings of the Directive 2001/20/EC and the possible options for a harmonisation and simplification of the CTA process have been addressed by all stakeholders in clinical research. In this master thesis, the different views and proposals with special regard to the central submission and review of a single CTA dossier as an option for drug development in Europe are discussed in detail. It is the responsibility of the EU Commission and of all other stakeholders acting in clinical research to further drive this ongoing process in order to reduce the administrative burden for clinical trials and to maintain the competitiveness of clinical research in Europe in favour of the well-being of the patients.

References

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[15] Responses to the Public consultation paper "Assessment of the functioning of the 'Clinical Trials Directive' 2001/20/EC", March 2010
http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/developments/responses_2010-02_en.htm

[16] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF

[17] Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF

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http://ec.europa.eu/governance/impact/planned_ia/docs/47_sanco_clinical_trials_directive_en.pdf

Annex 1.

Websites of the NCAs of the twelve selected EU countries:

Country	**NCA website**
Belgium	http://www.fagg-afmps.be/en/ The website of the Federal Agency for Medicines and Health Products http://www.health.fgov.be/bioeth The website of the Belgian Advisory Committee for Bioethics
Czech Republic	http://www.sukl.cz The website of SÚKL, the competent authority (no English information available)
Denmark	http://www.dkma.dk The website of the Lægemiddelstyrelsen, competent authority
Finland	http://www.finlex.fi/en/laki/kaannokset/1999/en19990488 The website of the Medical Research Act http://www.nam.fi The website of the National Agency for Medicines (Lääkelaitos).
France	http://www.afssaps.sante.fr The website of the AFSSAPS
Germany	http://www.bfarm.de The website of the Federal Institute for Drugs and Medical Devices http://www.pei.de The website of the Paul-Ehrlich-Institut
Ireland	http://www.imb.ie The website of the Irish Medicines Board
Italy	http://www.agenziafarmaco.it/en/ The website of the Italian Medicine Agency (Agenzia Italiana del Farmaco)
Netherlands	http://www.cbg-meb.nl The website of College ter Beoordeling van Geneesmiddelen (CBG) http://ccmo-online.nl The website of the Central Committee on Research Involving Human Subjects (CCMO)
Spain	http://www.agemed.es The website of the Spanish Medicines Agency
Sweden	http://www.lakemedelsverket.se http://www.mpa.se The website of the Medical Products Agency (Lakemedelsverket)
UK	http://mhra.gov.uk The website of the Medicines and Healthcare Regulatory Agency (MHRA)

Annex 2.

CTA requirements for submission to HA in 12 selected EU countries according to current national practice

(Documentation items that are not covered in attachment 1 of the Detailed Guidance ENTR/F2/BL D(2003), revision 2, October 2005 or modified are highlighted in green)

Documentation		Belgium	Czech Republic	Denmark	Finland	France	Germany	Ireland	Italy	Netherlands	Spain	Sweden	UK
1	**General**												
1	Cover Page	yes	yes	yes	Table of contents	Table of contents	Table of contents	Table of contents	yes	no	no	Table of contents	no
1.1	Receipt of confirmation of EudraCT number	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
1.2	Covering Letter	yes	yes	yes	yes	yes, national template	yes	yes, national template	yes	no	yes, national template	yes, locally adapted incl ToC	yes
1.3	Application Form (pdf version)	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes, only used for overview reference	yes
1.3	Application Form (xml version)	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes, locally adapted	yes
1.4	List of Competent Authorities within the Community to which the application has been submitted and details of decisions	yes	no	no	no	yes	yes	yes	yes	yes	no	yes, preferably	no
1.4.1	List of participating countries	yes	yes	yes	yes	yes	yes	yes		no	yes	yes, preferably	yes
1.5	Copy of EC opinion in the MS concerned	no	no	no	yes, but not needed for submission	yes	no	no, notification of submission and details of decision	no	no	yes	no, only notification	Only if available
1.6	Copy/Summary of any Scientific Advice	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	yes

Documentation		Belgium	Czech Republic	Denmark	Finland	France	Germany	Ireland	Italy	Netherlands	Spain	Sweden	UK
1.7	Letter of authorisation enabling the applicant to act on behalf of the sponsor (if the applicant is not the sponsor)	no	yes	yes	no	yes	no	yes	yes	yes	yes	yes	yes
1.8	Will accept application to CA in English	yes	yes	yes	yes	yes, but ICF, subject information, protocol summary in French	yes	yes	no	yes		yes	yes
2	**Subject Related**												
2.1	Informed Consent Form	no	yes, in local language	yes, in local language	yes, in local language	no	no	yes, locally adapted	yes	yes, in local language	yes	yes, locally adapted	no
2.2	Subject information leaflet	no	yes, in local language	yes, in local language	yes, in local language	no	no	yes, locally adapted	yes	yes, in local language	yes	yes, locally adapted	no
2.3	Arrangements for recruitment of subjects	no	no	no	yes, in cover letter. If recruitment is advertised it has to be added to the application	no	no	no	yes, if applicable	yes	no	no	no
3	**Protocol Related**												
3.1	Protocol with all current amendments and post-text supplements	yes	yes	yes	yes, with version number and date	yes, with version number and date	yes, with version number and date	yes, with version number and date	yes	yes	yes, with version number and date	yes, with version number and date	yes
3.1.1	Protocol	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	Protocol signature page	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes, incl. Local PI signature	yes
	Protocol post-text supplement	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
	Protocol amendment	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

Documentation		Belgium	Czech Republic	Denmark	Finland	France	Germany	Ireland	Italy	Netherlands	Spain	Sweden	UK
	Protocol amendment signature page	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes, incl. local PI signature	yes, a working protocol incl. amendment is required
3.1.2	Case Report Form	no	yes	no	no	no	no	no	no	no	no	no	no
3.2	Summary of the protocol in national language	no	yes	no	no	yes	no	yes in English (not Irish)	yes	no	no	no	no
3.3	Peer review of trial when available, not compulsory	no	no	no	no	yes	no	no	yes, if available	no	no	no	no
3.4	Ethical assessment made by the principal/coordinating investigator	no	no	yes	no	no	no	no	yes, if not already included in the protocol	no	yes	no	no
4	**IMP Related**												
	IMP Table of Contents	yes	yes	yes	yes	yes	no	yes	yes	no	no	yes, locally adapted	no
	IMP glossary of terms and abbreviations	yes	yes	yes	yes	yes	no	yes, if available	yes	no	yes	yes	no
4.1	Investigator's Brochure	yes	yes	yes	yes, if product has no MA	yes	yes	yes	yes	yes	yes	yes	yes
4.2	Investigational Medicinal Product Dossier (IMPD	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
4.2.1.S	Drug substance	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
4.2.1.P	Medicinal product	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
4.2.2	Non-clinical pharmacology and toxicology data	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
4.2.3	Clinical trial and previous human experience data	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
4.2.3	Cover page	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes
4.2.3.1	Clinical pharmacology	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
4.2.3.2	Clinical pharmacokinetics	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
4.2.3.3	Human exposure	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

Documentation		Belgium	Czech Republic	Denmark	Finland	France	Germany	Ireland	Italy	Netherlands	Spain	Sweden	UK
4.2.3.4	Benefits and risk assessment	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
4.3	Simplified IMPD for known products	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes, if applicable	yes
4.4	Summary of Product Characteristics (SmPC) for products with MA in the community	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes, if applicable	yes
	If NIMP (escape or rescue medication)is used, add SmPC for products with MA in the community	yes	yes	no	no	yes	no	no	yes	no	yes	yes, if applicable	no
4.5	Outline of all active trials with the same IMP	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	no	yes
4.6	If IMP manufactured in EU and if no Marketing Authorisation in EU:												
4.6.1	Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	yes	yes	yes	yes (all manufacturers need to have a valid GMP certificate or a MA)	yes	yes	yes	yes	yes	yes	yes	yes
4.7	If IMP not manufactured in EU and if no MA in EU:												
4.7.1	Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality	yes	yes	yes	yes (all manufacturers need to have a valid GMP certificate or a MA	yes	yes	yes	yes	yes	yes	no, only in special cases; Manufacturing License, GMP Certifcate or EU inspection report preferred	yes
4.7.2	Certification of GMP status of active biological substance	yes	yes	yes	yes	no, national annex 2	yes	yes	yes	yes	yes	yes, if applicable	yes

Documentation		Belgium	Czech Republic	Denmark	Finland	France	Germany	Ireland	Italy	Netherlands	Spain	Sweden	UK
4.7.3	Copy of the importer's manufacturing authorisation	no	yes	no	yes	yes	yes	yes	yes	no	yes	no, reference to the application form	yes
4.8	Certificate of analysis for test product in exceptional cases (where impurities are not justified by the specification or when unexpected impurities are detected)	yes, on request	yes	yes, if applicable	yes, if applicable	yes	no	yes	yes	yes	yes	yes, if applicable	yes
4.9	Viral safety studies when applicable	yes	yes	yes, if applicable	yes, if applicable	no, national annex 2	yes	no	yes	yes	yes	yes, if applicable	yes
4.10	Applicable authorisations to cover trials or products with special characteristics e.g. GMOs, radiopharmaceuticals	yes	yes	yes, if applicable	yes, if applicable	yes	yes	yes	yes	yes	yes	yes, if applicable	yes
4.11	TSE Certificate when applicable	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
4.12	Examples of the label in the national language	yes	no	no	no	no	yes	no	yes	yes	no	yes	yes
5	**Facilities and Staff Related**												
5.1	Facilities for the trial	no	no	no	no	no	yes	no	yes	no	no	no	yes - not as a separate document, details in sect. G of annex 1 of application
5.2	CV of the coordinating investigator in the MS concerned	no	no	no	yes	no	no	yes	yes	yes	no	no	no
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principle investigator)	no	no	no	no, list of all investigators needed if not mentioned in the CTA form	no	no	yes	yes	yes	no	no	no
5.4	Information about supporting staff	no	no	no	no	no	no	no	no	no	no	no	no

Documentation		Belgium	Czech Republic	Denmark	Finland	France	Germany	Ireland	Italy	Netherlands	Spain	Sweden	UK
6	**Finance Related**												
6.1	Provision for indemnity or compensation in the event of Injury or death attributable to the clinical trial	no	no	no	no	no	no	no	yes	no	no	no	no
6.2	Any insurance or indemnity to cover the liability of the sponsor or the investigator	no	no	no	no	yes	no	no	yes	yes	no	no	no
6.3	Compensations to investigators	no	no	no	no	no	no	no	no	yes	no	no	no
6.4	Compensations to subjects	no	no	no	no	information not provided to Afssaps but to another body of the CA	no	no	yes (only for healthy volunteers studies)	yes	no	no	no
6.5	Agreement between sponsor and the trial site	no	no	no	no	no	no	no	yes	yes	no	no	no
6.6	Agreement between the investigators and the trial site	no	no	no	no	no	no	no	no	no	no	no	no
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	no	no	no	no	no	no	no	no	no	no	no	no

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

Nürnberg, den 26. Mai 2010

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Stefanie Muth