“The New Regulation 536/2014 on Clinical Trials on Medicinal Products for Human Use – Opportunities and Challenges for European Clinical Research”

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1 List of Abbreviations

ATMP	Advanced therapy medicinal product
CA	Competent authority
CAP	Coordinated assessment procedure
cMS	Concerned Member State
CS	Commercial sponsor
CT	Clinical trial
CTA	Clinical trial application
CTAG	Clinical Trials Coordination and Advisory Group
CTD	Clinical Trials Directive
CTFG	Clinical Trials Facilitation Group
DCP	Decentralised procedure
e.g.	Exempli gratia
EC	Ethics committee
EMA	European Medicines Agency
EU	European Union
FP7	Seventh Framework Programme
FTE	Full time equivalent
GCP	Good clinical practice
GLP	Good laboratory practice
HMA	Heads of Agency
i.e.	Id est
IAR	Impact Assessment Report
ICREL	Impact on Clinical Research of European Legislation
IMP	Investigational medicinal product
MS	Member State
NCA	National competent authority
NCS	Non-commercial sponsor
NIT	Non-interventional trial
No.	Number
rMS	Reporting Member State
RMS	Reference Member State
SA	Substantial amendment
SUSAR	Suspected unexpected serious adverse reaction
WHO	World Health Organization
xEVMPD	Extended EudraVigilance Medicinal Product Dictionary

2 Introduction

"*In a clinical trial the rights, safety, dignity and well-being of subjects should be protected and the data generated should be reliable and robust. The interest of the subjects should always take priority over all other interests*" (1).With this first Recital the Regulation (EC) 536/2014 starts.

To meet these requirements clinical trials "*should be subject to prior authorisation*" (Recital no. 2 (1)).

Clinical trials conducted in the Member States of the European Union before 2004 were ruled by national law. In the course of further harmonisation within the Union, the Directive 2001/20/EC was released on April 4, 2001 and came into force on May 1, 2004. Since then clinical trials are authorised on the same legal basis in theory. As this was a Directive, only the principles had to be implemented in national legislation and thus, in practice, the same legal basis was not been implemented identically into national legislation. The slight differences in each national legislation caused e.g. administrative burdens for the sponsors when preparing an application dossier for authorising especially a multi-national clinical trial (which are 24% of all clinical trials in the EU (2)). The issue with multi-national clinical trials is the fact that "these *24% of clinical trials involve approximately 67% of all subjects enrolled in a clinical trial*" (2).

Within the FP7 framework, the European Commission launched a study called "*Impact on Clinical Research of European Legislation*" (3) to represent the impact of the Directive in the EU in 2009 (see Chapter 3.1). Subsequently, two public consultations were arranged by the Commission to find out about the issues mentioned by the stakeholders (see Chapter 3.2).

With these findings the Commission compiled an "*Impact assessment report on the revision of the "Clinical Trials Directive" 2001/20/EC*" (2) (see Chapter 3.3) as the basis for the "*Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC*" (4) in 2012.

After the amendments of the proposal by the Parliament and the Council in 2013, a negotiation was conducted by the Commission, the Parliament and the Council on the 22nd December 2013. This negotiation stage is called 'TRIAGE.

The result of the TRIAGE negotiations was considered to be the final text which passed the Parliament on April 4, 2014 and the Council of Europe on May 16, 2014. The final text was published in the Official Journal of the European Union with the name "*REGULATION (EC) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*" (1) on May 27, 2014.

This master thesis describes the development of "*the Clinical Trials Directive [as] the most heavily criticised piece of EU-legislation in the area of pharmaceuticals*" (Explanatory Memorandum (5)) to the Regulation (EC) 536/2014.
The main focuses are the assessment procedure of the application dossier and the technical requirements according to the Regulation (see Chapter 4).
This thesis does not deepen the aspects of the Ethics Committees, the protection of subjects and the conduct of a clinical trial.
The aim of this thesis is to illustrate the importance of regulating clinical trials on the European scale. "*Without clinical trials, there would be no new medicines, no further development of existing medicines, and no evidence-based improvement of treatments with medicines*" (Explanatory Memorandum (5)).

3 Need for Change

3.1 Impact on Clinical Research of European Legislation(ICREL)

In this subsection 3.1 the conclusions of the ICREL study are summarised (3).

3.1.1 Introduction

In 2006 the Directive 2001/20/EC had finally been implemented in all EU Member States. Its effects on clinical trials with medicinal products needed to be investigated in the European Union. Therefore, a call for an independent academic research project was released by the European Commission's Research Directorate within the FP7 framework. A consortium led by the European Forum for Good Clinical Practice (EFGCP) and consisting of several academic institutions was awarded the project to examine the impact of the CTD on the interested groups, i.e. the applicants (non- & commercial sponsors) and the authorising institutes (Competent Authorities & Ethics Committees). (6)
The main objectives inter alia were (3):

- The achievement of the directive with respect to clinical trials and improvability of the concerned Directive
- The influence of the new directive on the clinical research practice of the different sponsor-types
- The impact of the CTD concerning the budget, capabilities and the success for all aggrieved parties
- The outcome of the implementation of the CTD in the Member States

In summary "*[t]he ICREL study was a longitudinal, retrospective, observational and comparative study (survey) carried out in four stakeholder groups (...) to assess the impact of the CTD on the number, size and nature of clinical trials, on workload, required resources, costs and performance.*" (3)
All available research from other research groups were compiled and presented. A questionnaire was created for each stakeholder group and sent to all European competent authorities, most ethics committees, all large and mid-sized as well as a large number of small pharma companies and to all academic institutions linked with the consortium partners. The sampling period for this questionnaire was from June1 to September 30, 2008. The rate of responses was variably. Nearly every competent authority replied (25 of 28) whereas the participation of the Ethics Committees was extremely moderate (64 questionnaires filled in of 708 questionnaire sent). While 66% of the top 15 companies

responded the overall response rate was 8, 98% for commercial sponsors (CS) and 38% from non-commercial sponsors (NCS)). (3)
Generic companies were not considered, because already the preparation of the project revealed that most of the trials conducted by generic companies are bioequivalence studies and they were mainly conducted in non-EU countries.
The outcomes of the ICREL study were used for diverse subsequent documents, e.g. the public consultation in 2009 (7) and the impact assessment report (2) both concerning the Clinical Trials Directive 2001/20/EC.
In the following the results of the questionnaires are described concerning the weaknesses and the strengths as well as recommendations for a reform of the CTD. (3).

3.1.2 Strengths and Weaknesses of the CTD

The strengths of the Clinical Trials Directive were the improved protection of the patients and taking on responsibility for the clinical trials by the sponsors, the competent authorities and the Ethics Committees. This led to a reduction of the investigators' responsibility.
These strengths were weakening by four general major issues and by a lack of clear defined terms.
The major weaknesses were:

- The Directive was transposed differently into the national legislation of the EU Member States and caused that "*the harmonisation target was partly missed for clinical trials on medicinal products*" (3)
- The scope of the Directive was limited to clinical trials on human subjects with medicinal products. Based on the previous existing national legislation some MS had widen the scope by "*covering other types of clinical research*" (3) as they implemented the CTD into their national legislation. This led to "*totally divergent systems*" (3) in the EU Member States.
- The CTD did not differentiate in the requirements and rules between clinical trials with investigational medicinal products mostly performed by commercial sponsors and clinical trials with authorised medicinal products mostly performed by non-commercial sponsors. Having similar requirements irrespective of the type of the trial led to a difficulty for academic research. "*[Multinational] non-commercial trials are difficult to organise in an efficient way because a sponsor based at an academic institution in one EU Member State has not the institutional coverage to take over legal responsibility for clinical trial activities performed at an academic institution in another Member State.*" (3)

- The requirements of the CTD increased the administrative burden of all stakeholders, which led to "*a need for increased resoureces with the related costs generation, delays in study preparation (...) and the danger of reduced protection of trial participants*" (3) because the EC did not have enough capacities in terms of administrative tasks.

Further the CTD was weaken by a lack of definitions like the terms 'Sponsor', 'substantial amendment' and 'investigational medicinal product'.
The national implementation was disharmonised which resulted from different strategies developed by the Member States, inter alia the involvement of the Ethics Committees, who had to deliver a single opinion per Member State. "*Differences in the interaction between ethics committees and competent authorities in process, composition, training, fees, number and activity of ethics committees, in their independence, and in the cultural context of ethic review result in major discrepancies between countries in protocol and patient information requirements, review timeframes, costs and acceptability for a single protocol in a multinational study.* " (3)

3.1.3 Summary of the results

In the following the outcome of the four stakeholder groups (competent authority, Ethics Committee, commercial sponsors and non-commercial sponsors) are summarised.

1. Competent authorities

One of the most discussed issues of the Directive 2001/20/EC was its harmonisation within the MS. (3)
Unfortunately, there was a discrepancy in the opinion of the participating competent authorities. By some CAs the harmonisation was described to be the strongest point and some other CAs concluded that harmonisation was not sufficiently achieved.
The quality of the clinical trials conduct was also mentioned as an improvement. Only four authorities concluded that the Directive had strengthened the safety of subjects.
The Directive brought a tremendous change in terms of bureaucracy. The authorities were experienced a substantial increase of workload and pronounced this point as a weakness of the CTD. This workload induced an increase in the number of employees (FTEs – Full time equivalents). The table below represents the (average) FTEs required for the administration of Clinical Trials Applications in the competent authorities of the Member States during 2000 and 2007.

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	1.25	1.61	2.02	2.12	2.43	2.28	2.81	3.30
Sample size EU	10	9	9	17	12	14	16	21

Table 1: Mean number of FTEs per institution required for administrative tasks in the EU (3)

The workload of handling SUSAR reports and the different comprehension of the definition of a substantial amendment were stated also as a weakness.
Three competent authorities mentioned also the "*[increased] difficulties for academic research*" (3) as an issue.
The feedback from the authorities concerning recommendations for changes to the CTD was poor. Some of them proposed a more precise definition of SUSAR reporting and simplifying procedures for NCS. (3)

1. Ethics Committees

The Ethics Committees considered the harmonisation and the protection/safety of the subjects as an improvement. The biggest burden of the CTD was the enormous increase of administrative tasks. This was caused, for example, by the achievement of a single opinion within a Member State (see Figure 1).

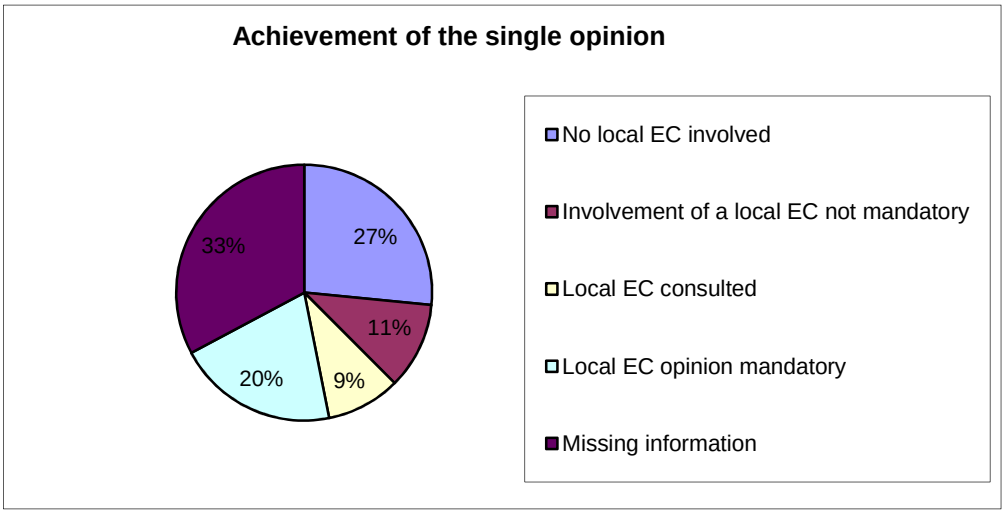

Figure 1: Achievement of the single opinion (3)

Also the need for ECs to manage the reporting of SUSARs was a burden. But proposals of the ECs for a change in the CTD were rare. An unlimited access to the EudraVigilance or any other database regarding adverse events was suggested by a few ECs. (3)

2. Commercial sponsors

The responses of the commercial sponsors were divergent. Some points were stated both as strengths and as weaknesses of the CTD at the same time.
Most of the sponsors described the harmonised, fixed timelines for the authorisation procedure as the strength of the CTD. But at the same time some commercial sponsors complained about the non-compliance of some CAs and ECs to the given timelines.
The harmonisation of procedures and the CTA dossier requirements within the European Union was appreciated by some sponsors and stated as strength of the CTD. But other CS criticised these aspects to be the weaknesses of the CTD.
The increased workload in administration issues and dossier requirements crystallised as a burden.
One of the suggestions for improvement was to create the possibility to submit one single application in different Member States and get therefore the procedures simplified and harmonised.
Some commercial sponsors even proposed a regulation instead of a directive. (3)

3. Non-Commercial sponsors

A multitude of the non-commercial sponsors replied to the question “Where are the strengths and weaknesses of the CTD?”.
Some of the NCS recognised positively that the CTD led to a partial harmonisation. Also the increased safety of the subjects and a better quality of research were mentioned as strengths.
A strong negative feedback was given by other non-commercial sponsors regarding the insufficient harmonisation and the severe load of administration, high costs and increased time. An increase of personnel was inter alia a reason for the high costs (see Figure 2).

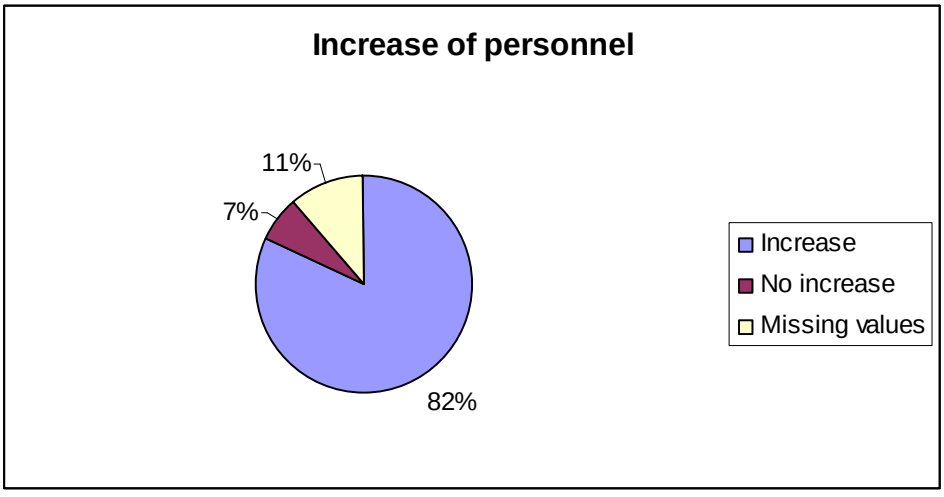

Figure 2: Perceived increase of personnel (3)

A risk-based approach concerning clinical trial authorisation and supervision was not considered in the directive. Also international Investigator-driven trials were not adapted to the CTD.
The non-commercial sponsors argued for a risk-based approach to reduce the burden for low-interventional studies, better harmonisation and more manageable requirements. (3)

3.1.4 Conclusions

For all stakeholders the increased administrative burden was a clear result of the CTD as clinical trial performance required more personnel (especially for competent authorities and non-commercial sponsors) and time and thus resulted in higher costs.
Some Member States showed an increase in clinical trials and some a decrease, especially in non-commercial trials. A "*[reason] for these trends could be the way the CTD was nationally implemented and/or other factors like the local research activity of some pharma companies*" (3). Since 2004 a strong increase of multi-national trials could be deteced particular in non-EU countries (a reason for the general decrease of clinical trials in the European Union). This could also be a reason for the strong increase of substantial amendment since 2005 in order to to adapt the different requirements of the countries.
"*[The] time interval between protocol finalisation and the first inclusion of patients has considerably increased, possibly due to complexity of the preparation of the application dossier upstream to submission (…) an/or to poor synchronisation between the submission to multiple competent authorites and ethics committees for multi-national studies.*" (3)
Also the timeline for the implementation of a substantial amendment "*increased by approximately 30%*". (3)
The increased workload for clinical trial assessment created the need for higher personnel resources in the competent authorities and resulted in higher fees.
The insurance companies used the implementation of the CTD to change their fee structure which led to much higher insurance costs without impacting the damage coverage of the trial participants, a problem, especially for the NCS. The whole process to conduct a clinical trial got more complex and induced a raise of activities and expenses. (3)

3.2 Public consultations

Two public consultations were conducted by the European Commission in order to review and "*to put forward (...) a legislative proposal to revise the Clinical Trials Directive 2001/20/EC*". (8) The advantages and the shortcomings were stressed, and suggestions for changes were specified. The results of the ICREL-study were also considered.
One concept paper for public consultation was submitted in 2009 named "*Assessment of the Functioning of the "Clinical Trials Directive" 2001/20/EC*" (7) and the other was submitted in 2011 the "*Revision of the 'Clinical Trials Directive' 2011/20/EC*" (8)
The results of these concept papers and the summaries of the public consultations were also used for compiling the "*Impact assessment report on the revision of the "Clinical Trials Directive" 2001/20/EC*" (2).
In the following both concept papers and the summaries of the consultations are consolidated.

3.2.1 Concept paper for public consultation in 2009

In this public consultation five key issues were highlighted and accompanied by eighteen more items. Furthermore different possible approaches were to consider. Each issue was desired to be reviewed by the interested parties. Statements to all items and approaches and suggestions for improvement should be provided.
In the following only the key issues are specified.

The first key issue mentioned concerned the "*multiple and divergent assessments of clinical trials*". (7)
About 25% of the clinical trials did not take place in only one MS. So the protocol of a particular clinical trial had to be submitted to both CA and EC in all concerned MS.
"*[Sponsors had] to respond to the various required changes, adapt their protocol in view of diverging assessments by the NCAs or [could not] pursue the envisaged clinical trial any further in one or more Member State.*" (7)
This led to rising administrative costs without any added value. The preparation of the applications for a multi-national trial needed to be adapted to the different requirements of the Member States. This administrative work increased the costs, which could "*reach prohibitive levels*" (7), especially for non-commercial sponsors.
Further these administrative works caused delays in starting a clinical trial as a result of additional information required by the different Member States or as a result of different reasons for non-acceptance (see Figure 3).

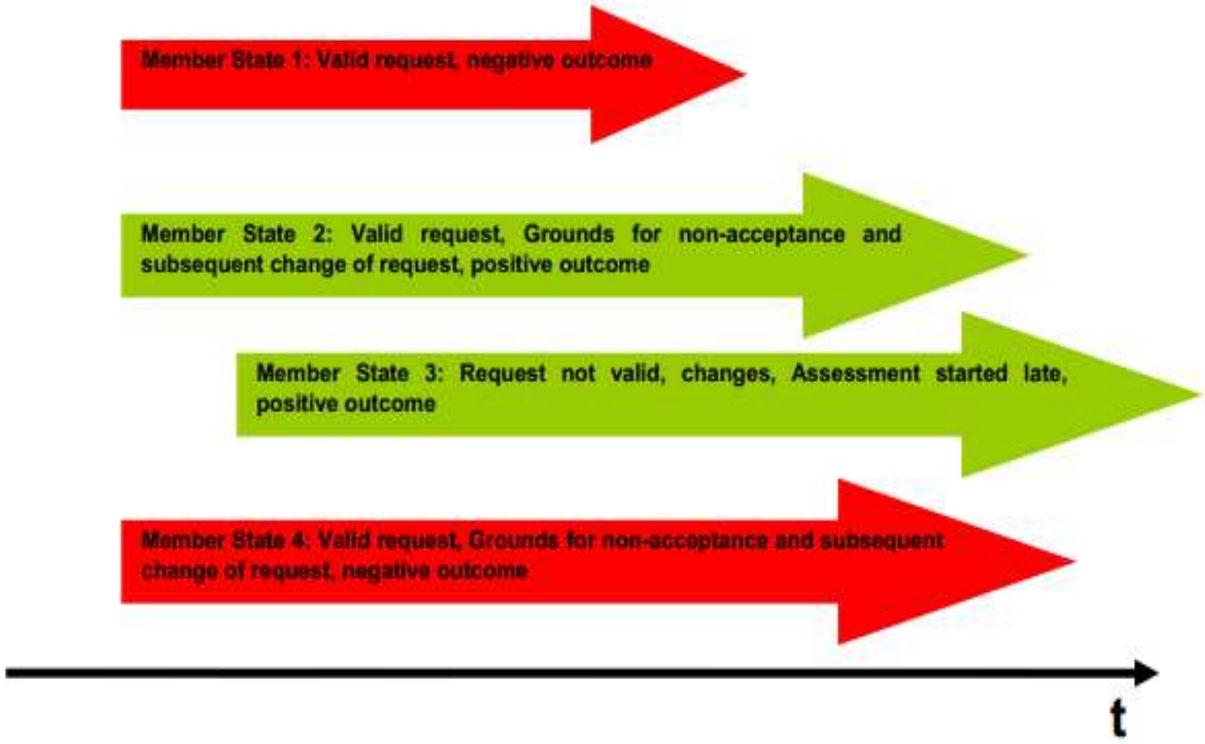

Figure 3: Submission of request for authorisation in 4 Member States (7)

These delays increased by 90% which was about 152 days between the finalised protocol and the 'first patient in'.

The next issue was a question of the "*inconsistent implementation of the Clinical Trials Directive*". (7)

Although one of the intensions of the Directive 2001/20/EC was to harmonise the conduct of clinical trials within the European Union, the implementation into the respective national legislation differed. This applied inter alia to the definition of substantial amendments, the details of the SUSAR-reporting and the scope of the CTD.

Substantial amendments were one of the issues, because this term was differently interpreted by the Member States. In order to be compliant sponsors notified more substantial amendments than were necessary in a multi-national trial. This led to "*a three-fold increase of number of substantial amendments*" (7) after the CTD came into force.

If a suspected unexpected serious adverse reaction occurred during a clinical trial, the sponsor had to report this to the CA and the EC of the Member States.

But this reporting "*led to a multitude of different regimes in the Member States, which (…) led in turn to multiple reporting of the same SUSAR, lack of reporting and unreliability of the Community data on SUSARs*". (7) Although the number of clinical trials did not raised considerably, the SUSAR reports increased by a factor of six.

The scope of the Directive 2001/20/EC covered all interventional trials, but "interventional" was interpreted differently. Therefore in a non-interventional trial no additional diagnostic

or monitoring procedures should be applied to the patients and epidemiological methods should be used for the analysis of collected data. This borderline between non-interventional and interventional created "*a situation where a trial is considered "non-interventional" in one Member State, while it is considered as "interventional" in another and thereby falls within the authorisation regime of the Clinical Trials Directive.*" (7)

"*Regulatory framework not always adapted to the practical requirements*" (7) was another key issue.
The past showed that the actual risk of a subject depended on different factors. "*Different types of trials carry different risks and thus require different regulatory safeguards.*" (7) But the provision in the Directive was a general risk-approach which induced high costs (e.g. insurance) without an obvious improvement of the patients' safety. Further the concept of a single sponsor was impractically in terms of multi-national trials. In particular non-commercial sponsors had difficulties "*to take responsibilities for clinical trials performed in another Member State.*" (7)

The fourth key issue concerned the "*adaptation to peculiarities in trial participants and trial design*". (7)
Clinical trials were performed in different groups, like paediatric clinical trials and clinical trials in emergency situations. These aspects were not adequately addressed in the CTD. Informed consent was one of the requirements for the authorisation of a clinical trial. But informed consent in emergency situations could usually not be obtained by the person concerned.
Clinical trials in emergency situation are reflected in international guidelines (e.g. ICH E6) which demonstrate the need for such kind of trials. "*Indeed, it would be a very serious setback for clinical research if medicinal research in emergency situations proved to be impossible in Europe.*" (7)
Some but not all Member States regulated the issue with clinical trials in emergency situations. "*However, these legal requirements lead to a situation where there are divergent standards for good clinical practices in emergency situations in the EU.*" (7)

The last issue was about "*ensuring compliance with good clinical practices ("GCP") in clinical trials performed in third countries*". (7)
In one quarter of clinical trials conducted in the European Union was also at least one third country included. Most of the 'first in men trials' were conducted in non-EU states and 65% of the information submitted in pivotal clinical studies for obtaining a marketing authorisation EU-wide were generated in non-EU countries. Different reasons were stated

for rolling out trials in third countries: more available subjects and therefore more simple recruitment, lower costs and fewer formalities.
"*There is a continuing risk that medical research and pharmaceutical products in the EU are based on clinical research in third countries not complying with international standards of safety and ethics.*" (7)

3.2.2 Summary of the answers to the consultation paper in 2009

106 respondents, 60 of them non-commercial, provided the European Commission with their answers to the public consultation paper of 2009. Many respondents used this consultation for further comments. In the following the responses to the above mentioned key issues of the concept paper are pointed out.

One of the first general comments concerned the ICREL-study. The number of participants and the outcome of the ICREL-study were criticised.
The response to the first key issue demonstrated, that the outcome of the assessment of a clinical trial application mostly differed. "*Respondents stressed that, if the ultimate decision was not always divergent, it was because sponsors withdrew applications.*" (9) The same happened with the Ethics Committees, the respondents stressed this issue. Although the item with the Ethics Committees was not mentioned in the consultation paper and called it a "*main challenge today when rolling out a clinical trial*". (9)

The second key issue concerned the divergent implementation of the Directive into national law.
The respondents confirmed the challenge with the substantial amendments, the SUSARs and the scope of the Directive 2001/20/EC. The different implementations of the SUSAR-reporting requirements was even stressed as the "*least harmonised [aspect] in the area of clinical trials legislation in the Union*" (9) which "*created a false sense of security*" (9). Also the burdensome annual safety report was highlighted as crucial. The term "non-interventional trial" required to be regulated.

A lot of respondents confirmed the third key issue "*that the CTD did not sufficiently differentiate between the risks posed by clinical trials."* (9)
Other issues were mentioned with the topics: compassionate use, off-label use mainly in paediatric research, radiotracer, etc. Various respondents required more guidelines with respect to the actual risk occurring in a trial, for instance "*a Commission guidance document 'on acceptable risk' "*. (9)

The key issue concerning paediatric clinical trials and clinical trials in emergency situations and the issue with obtaining informed consent was confirmed by the respondents.
First of all clinical trials with children are basically classified with a high risk; "*long-term measurement was more important than short-term reporting*". (9) Various ideas for an approach were suggested by the respondents based on the other legislations worldwide.
"Most respondents agreed that the situation [with emergency trials] as established by the CTD was unsatisfactory." (9)
The forms for receiving informed consent should also be adjusted.

The last key issue, concerning clinical trials in non-EU countries, induced that "*many respondents criticised the problem description as being founded on prejudice and not fact- and evidence-based*". (9)
It was criticised that pharmaceutical companies were blamed for having "*double standards*" (9) or conducting the trials in third countries with another quality. On the contrary some respondents stressed that the quality in some third countries could be superior to the quality in trials in the EU. The outcome was that the conditions in third countries were divergent.

3.2.3 Concept paper for public consultation in 2011

This consultation was to deepen the outcome of the public consultation in 2009 and to present "*a 'preliminary appraisal' of which option appears to be the most suitable one to address some of the key concerns of the Clinical Trial Directive*". (8)

The consultation paper started with the issue concerning the submission and assessment of a CT-application. A single submission via an EU-portal was suggested, from which the submitted information would be forwarded to the MS. Three options for a clinical trial assessment procedure were presented:

- "single submission with separate assessments"
- "single submission with subsequent central assessment"
- "single submission with subsequent 'coordinated assessment procedure' " (CAP)

The latter option CAP would be like the decentralised procedure for authorisation of a medicinal product. A leading Member state would be available for the assessment procedure and finally every concerned Member State would come to an individual decision including national ethical aspects. The appraisal clearly outlined that the ethical scope was a national issue.
The coordinated assessment procedure would cover defined aspects of the application, i.e. risk-benefit, quality and labelling of the medicine ('part a'). Ethical and local aspects would

be part of a national assessment (‘part b’). Each concerned Member State would have the opportunity for a justified ‘opt out’. Stakeholders should give their opinion on whether the CAP should be generally mandatory, mandatory or optional for multinational clinical trials. The timelines for a coordinated assessment procedure and for the assessment of substantial amendments would be leaned on the current given timelines.
After classification in a ‘pre-assessment’ as “type A trial”, the timelines for low-risk trials would be shorter.

As already stated in the first public consultation paper the implementation of the classification of a non-interventional trial was not harmonised in the Member States although the term was defined in the Directive.
“*Rather than limiting the scope of the Clinical Trials Directive through a wider definition of ‘non-interventional trial’, it would be better to come up with harmonised and proportionate requirements which would apply to all clinical trials*” (8) which was described as a ‘preliminary appraisal’ in the concept paper of 2011.
The same occurred with the ‘preliminary appraisal’ that academic/non-commercial sponsors should not be excluded from the scope of the clinical trials legislation. “*It is difficult to see why rules designed to protect the safety and rights of participants and the reliability and robustness of data should apply to some types of sponsor and not to others. (..) Beside, it is difficult in practice to establish whether a sponsor is acting in a ‘non-commercial’ or a ‘commercial’ context.*” (8) Harmonised rules and adapted requirements for clinical trials would be appropriate and should be independent from the type of sponsor.
“*More precise and risk-adapted rules for the content of the application dossier and for safety reporting*” (8) were further points for consultation, for example the possible risk occurring in a trial compared to the risk occurring in normal practice. It was suggested to integrate these rules “*in Annexes to the basic legal act*” (8) enforced by the Commission.

A clear definition of the used medicinal products would be necessary to discriminate whether a medicinal product is an investigational one or an auxiliary one. Therefore definitions for an ‘investigational medicinal product’ and for an ‘auxiliary medicinal product’ were suggested in the consultation paper taking into account the “*rules for dossier requirements, reporting, and labelling*”. (8)

Subjects in clinical trials are insured. Insurances and indemnities are linked to high costs and hence burdensome especially for academic sponsors. The proposals were either to exempt clinical trials with a low risk for subjects from the obligatory insurance as the available health insurances would be sufficient; or the implementation of a national obligation for indemnity.

The next item for consultation was about the limitation of conducting a clinical trial only by a single sponsor. The ‘preliminary appraisal’ was to keep the idea of having one single sponsor. It was explained that the ‘responsibility’ and the ‘liability’ of a sponsor were mixed up due to the fact that the liability is a national matter and is not harmonised amongst the Member States. “*Regarding the ‘responsibility’ of the sponsor, the main problem seems to stem from the divergent requirements amongst Member States for conducting clinical trials.*” (8) The condition for permitting co-sponsorship would be a clear differentiation of responsibility and liability in conjunction with a true harmonisation of the requirements among the Member States.

The lack of rules for clinical trials in emergency situations should be overcome by adaptation of the European legislation to the internationally available legal framework. It was suggested to have the possibility to conduct clinical trials in emergency situations bound to predefined conditions.

Good clinical practice is a basic requirement for conducting a clinical trial in the European Union. Due to the fact that globalisation goes forward, clinical trials are more often conducted in non-EU countries with different legal requirements.
“*[In] order to increase transparency of clinical trials performed in third countries the legislation could provide that the results of these clinical trials are only accepted in the context of a marketing authorisation process in the EU if the trials had been registered in the EU clinical trials database EudraCT and thus be published via the public EU-database EudraPharm.*” (8)

3.2.4 Summary of the answers to the consultation paper in 2011

The response to the public consultation paper in 2011 was higher than the response to the first public consultation paper in 2009, i.e. 143 respondents were counted whereas again most responses came from academia.
In general the concerned parties appreciated the second consultation partly because the communicated concerns on the part of the stakeholders were respected.
Only the issue with the Ethics Committees was not focused sufficiently, “*the “key problem”, namely a dual ‘approval’ by NCAs and ECs, had not been addressed.*” (10)

The possibility to submit a single application via an EU-portal was widely appreciated. But it was stressed inter alia that the required data should be standardised and not an accumulation of national peculiarities. The technical requirements should be realisable for non-commercial sponsors.

Nearly all respondents appreciated the basic principle of the coordinated assessment procedure. Still some concerns came up regarding e.g. determination of the reference MS, fear of increased opt-outs, possible influence on the scope of the EC review, and need for an 'appeal mechanism'.
Some further points were suggested to be included in 'part a' of the assessment in the CAP, like safety issues, non-IMPs, etc.
'Part b' should also include data protection besides all the other mentioned issues in the public consultation paper.
In case of disagreement between the Member States in the CAP, the limited possibility of a justified opt-out should be granted; the opt-out reason "*serious risk to public health*" (10) was stressed to be "*illogical*" (10) by many respondents. "*It was suggested that reference should be made instead to aspects of normal clinical practice in a MS, ethical issues, or to 'major issues with national specificities'.*" (8) But these issues should not lead to a general refusal of the application in all Member States. The question whether the CAP should be mandatory or not, was answered differently. The coordinated assessment procedure should be mandatory for trials conducted in more than one Member State. If the CAP would also be mandatory for trials conducted in one single MS, the CAP should still be manageable especially for non-commercial sponsors.
Most of the concerned parties appreciated the suggestion of appropriate and defined timelines for the assessment of an application for clinical trials.

The definition of the non-interventional trials was discussed and most of the stakeholders agreed with the proposal by the Commission to not widen the definition. Some of the respondents suggested rather defining the meaning of 'interventional trial' than 'non-interventional trial'.
The suggestion of a risk-based standard was answered inter alia with "*that risk in clinical trials refers to two separate issues: data reliability and subject safety.*" (10)
Stakeholders listed some more points to consider for a risk-based standard.
Several aspects and examples were highlighted for implementation of a definition for auxiliary medicinal products.

Respondents stressed that the issue with the insurance laid not basically in the costs. Rather the diverse liability coverage schemes existing in the Member States presented an issue, and therefore an exemption from insurance would not release a sponsor from its liability. A couple of respondents asked for harmonised liability coverage conditions within the European Union.

The concept of whether a single sponsor should be kept or multiple sponsors should be possible was ambivalent. Some stressed that with a single sponsorship discrepancies in responsibilities would not occur and were therefore preferable.
Others mentioned that "*large multinational companies, who conduct multinational trials through their national branches, are acting de facto on the basis of a co-sponsor model*". (10)

Rules for clinical trials in emergency situations were appreciated, but highlighted with several additional points to consider, like the exact wording of certain terms or the conditions for the informed consent process.

The 'ClinicalTrialsRegister' database should not be the only accepted database for registration of a clinical trials conducted in a third country, in order to obtain GCP-compliance. However, a registration in a database would not imply automatically GCP-compliance as some stakeholders mentioned in the response to the consultation paper. It was also stressed "*that bioavailability and bioequivalence studies should be excluded from transparency requirements*." (10)
Finally the respondents stated several additional issues for consideration regarding the Clinical Trials Directive, like "*Patient representation in ECs should be mandatory*" (10) and "*Patients should have access to the results of the clinical trials and to post-trial treatment*". (10)

3.3 Impact assessment report

The European Commission informed at the 2008 Pharmaceuticals Communication about an assessment of the CTD and its implementation and effects on the Member States and the stakeholders. (2)
Two public consultation papers were published and the responses were summarised (10) and used subsequently for the "*Impact assessment report on the revision of the "Clinical Trials Directive" 2001/20/EC*" (2), which was compiled by the European Commission and made public in 2012. This report accompanied the proposal of the European Commission for a Regulation on clinical trials on medicinal products for human use and summarised the impacts on the revision of the CTD. In the following the overview of the impact assessment report is described. (2)

3.3.1 Introduction

The Clinical Trials Directive was a new legislation and developed inter alia a better situation of the subjects' safety, but still it "*is the most heavily criticised piece of legislation of the entire EU acquis for pharmaceuticals*". (2)
The harmonisation failed and led to high criticism by all concerned parties. This failure influenced beside other things: the reduction of CT-applications, delay in starting the CT and rising costs in the EU.
The submission and the assessment of an application for a clinical trial were handled differently among the Member States. Accordingly the regulatory supervision (e.g. substantial amendments) was differently considered by the MS. The outcome of this caused delays in conducting clinical trials. Also an obligatory insurance for subjects was defined without calculating the actual risk that could happen to an individual in a clinical trial. The insurance and the additional administration induced a high rise of costs.
This impact assessment report aimed to name the issues with the CTD and summarised the recommended objectives for improvement by all concerned parties.
In the following the main objectives and suggestions for improvement are described.

3.3.2 Improving regulatory requirements (objective no. 1)

There were several options/suggestions in improving the CT into "*a modern regulatory framework for submission, assessment and regulatory follow-up of applications for clinical trials, taking into account the multinational research environment*" (2):

1. <u>No action but cooperation of the MS</u>
   With the "*voluntary harmonisation procedure (VHP)*" (2) Member States could jointly assess an application dossier for a clinical trial, but still every MS required a separate submission of the dossier and the ethical review would be handled on national level only.
   This option would not facilitate the current situation. The administrative costs would still be high and there would be no improvement in patient safety or gaining time.

2. <u>Single application but split assessment</u>
   An electronic portal should make a single submission possible. But the application would be assessed separately by the concerned Member States.
   This option would improve the current situation and would lead to less administrative cost. However, the costs for subsequent assessments would be equal

to the current situation. The concerned parties welcomed the option of a single submission but critically considered the aspect of separate assessments.

3. <u>One submission with cooperated assessment of aspects not related to ethics of the concerned MS</u>
   Ethical aspects would not be part of the assessment, but would be separately reviewed by each Member State.
   The advantage would be one single submission and one single opinion by the concerned MS without different additional requirements. This would reduce a lot of administrative cost, would support the early start of a clinical trial and would lead to identical conduct of clinical trials in the concerned Member States.

4. <u>One submission of aspects not related to ethics centrally assessed by the Agency</u>
   This option is similar to the central authorisation procedure for medicinal products in the EU. A rapporteur, member of a new established scientific committee, would assess the application and describe the decision in a report. This opinion would be effective in the complete EU. Each MS would be responsible for the ethical part and implement a national decision. The advantage would be the involvement of all MS and therefore a complete available expertise in assessing. There would be more time necessary for the assessment of the application. One critical point was the fact that the authorisation of a clinical trial and a medicinal product would be in the same institution.
   The administrative costs for the sponsors would decrease, but additional fees for implementation would rise. This would be a barrier for non-commercial sponsors. Also non-flexibility was named as a big issue by different pharmaceutical companies.

5. <u>Transferring the directive to a regulation</u>
   A regulation has the advantage that it is directly binding in all Member States and does not need to be implemented in national law.
   Therefore submitting an application would be facilitated for sponsors of a clinical trial. But "*if the legal form was a Regulation, requirements would still be interpreted differently by Member States bodies in the practical application, unless a cooperation mechanism is in place.*" (2) This could be achieved, if this option number 5 would be combined with the options number 3 or 4.
   However, the sponsors, both commercial and non-commercial, would appreciate a regulation.

6. Cooperated assessment with a regulation as the legal basis

   This option is the combination of number 3 (single submission with a cooperated assessment of the concerned MS without ethical aspects) and number 5 (directive transferred into a regulation). A regulation would facilitate the cooperation of the Member States because of a similar legislation.

3.3.3 Regard to practical aspects (objective no. 2)

There were six policy options which bore in mind practical aspects, concerning the insurance and the annual safety report "*in terms of operational objective (…) targeting in particular non-commercial sponsors who do not have access to the same (human and financial) resources as industry sponsors*" (2) to reduce the administrative burden and the costs .

1. No action

   The current situation would not be changed. The existing obligatory national insurance schemes would keep the current existing level of protection of subjects. The annual safety report would continue to help the competent authorities and ethics committees to monitor the IMPs' safety situation.

2. Non-interventional studies

   The CTD does not include non-interventional studies with authorised medicinal products. One of the requirements for a NIT is that there are no additional procedures (e.g. diagnostics, measurements) conducted in comparison to the usual manner.

   If this requirement would be excluded from the definition, this "*option would broaden the scope of non-interventional studies (…). This would mean that any study using authorised medicinal products for their authorised indication, even with additional intervention, would fall outside the scope of the Clinical Trials Directive if the subjects are not assigned prospectively, for example by randomisation.*" (2)
   In conclusion only phase IV studies would fall under this option (authorised IMP used in an authorised indication). This would not support the ambition of harmonisation through the Union. The large part opposed this proposal.

3. Non-commercial sponsors as an exception

   NCS would be excluded from the scope of the Regulation and therefore their trials would not be regulated on a European legal basis. This was discussed several times, to free the non-commercial sponsors from administrative and additional financial issues. But this would lead to a non-protection of the subjects by EU-law and the outcome of the trials might not be used because of non-robustness.
   One critical point is the possible influence on the public health by published data of non-EU-regulated trials.
   Anyway, the majority of the concerned parties opposed this option.

4. Authorised medicinal product as an investigational medicinal product

   Trials with authorised medicinal products normally bear low risks. This aspect would be respected and would induce facilitation for conducting these trials.
   Therefore the obligatory insurance and the annual safety report would be needless without having a cognisable influence on the safety of subjects. The institutions in which such trials would take part, mostly have an own liability insurance or something similar. So the subjects would be still protected.
   Due to the fact that authorised medicinal products are continually reviewed by the periodic safety update report, the annual safety report for such a clinical trial would be obsolete. This option was appreciated by all concerned parties.

5. National insurance

   With this option the obligatory insurance of participants of clinical trials would be subject to a "*national indemnification mechanism*" (2). A sponsor would have the possibility to take part in the national system where a trial would be conducted or would acquire an own insurance on the insurance market. This type of indemnification mechanism is already available in the Nordic MS. Actually the damage of subjects caused in clinical trials is very low. Following the costs for a national indemnification mechanism would be low.
   Still this option was opposed by most of the stakeholders. One of the concerns was "*the risk of divesting liability to the state*". (2)

6. Low-risk trials

   A national insurance mechanism would only apply to low risk trials. Thus, if a clinical trial is planned with an authorised medicinal product, there would be no need for a separate insurance. The general health insurance available for patients would be sufficient. Following, the insurance costs would decrease for trials with authorised medicinal products.

3.3.4 Compliance with GCP (objective no. 3)

Clinical trials conducted in non-EU countries are not always GCP-compliant per se.
Five options are described in the impact assessment report for "*ensuring compliance with GCP of clinical trials conducted in non-EU countries but referred to in the EU in the context of another clinical trial or of an application for a marketing authorisation*" (2):

1. No action

   This option would not change the current situation. Inspections outside the EU were conducted but limited to capabilities.
   To leave the situation as it is would not support the aim of improvement.

2. More transparency

   Today the Clinicaltrialregister.eu is available for clinical trials conducted in more than one MS, but it is not applicable for clinical trials conducted solely in non-EU countries. The aim of this option is to have all data followed from clinical trials publicly available. This would lead to more transparency and would support GCP inspections. An advantage would also be the possibility of the society to observe the clinical trials. Most of the stakeholder appreciated this option; although more costs would arise for maintaining the register.

3. Inspections in non-EU countries (regulatory framework)

   If a clinical trial should be used for an authorisation of a medicinal product, this trial had to be conducted according to good clinical practice. Non-EU countries' regulatory infrastructure would be inspected and this would ensure more compliance.
   The costs would rise and it must be determined who would be responsible for conducting the inspection – the EMA or the European Commission.

4. Inspections in non-EU countries (GCP in clinical trial sites)

   The EMA would inspect non-EU clinical trials sites and would be independent of the inspectors of the Member State. Only the trial sites are part of the inspection and not the general regulatory framework of the non-EU country. The maintenance of all these inspections is going to be challenging. This is a big issue, because most of the first in men studies and the pivotal clinical trials are conducted outside the EU. "*Between 2005 and 2009, these pivotal clinical trials 67 were spread over 44 034 sites in 89 countries*" (2) and the application for a marketing authorisation of a medicinal product is mostly some years after the conduction of clinical trials. Following, this option was determined to be impracticable.

5. Combination

   The combination of the options number 2 (more transparency) and number 3 (inspections in non-EU countries) would be another possibility to improve the current situation.

   This combination would strengthen the GCP-compliance. The costs would rise for this purpose and the need for more inspectors would have to be considered.

3.3.5 Conclusion

In the following the final selections of the above listed policy options are described.
In terms of the objective no.1 the option 'Cooperated assessment with a regulation as the legal basis' was adjudged to be the effective one. It would be the combination of a regulation as the legal basis and the joint assessment with one single application. This would support a reduction of the administrative burdens and to further harmonise the clinical trial conditions in Europe.
In terms of the objective no. 2 the option 'Low-risk trials' was mostly agreed. It would be the possibility to have no obligatory insurance system for clinical trials with known IMP (i.e. authorised medicinal products). Normally these kind of clinical trials have a low risk of damage; the available general insurances of the institutions would be adequate. This would reduce a lot of costs. For clinical trials with IMP a national insurance system would cover the patients' protection.
In terms of the objective no. 3 the option 'combination' was a good compromise of all stated options. All clinical trials would have to be available in a register independent from the location of the clinical trial site. If a clinical trial, conducted in a non-EU country, would be part of a future marketing authorisation application for a medicinal product, then this country would be inspected concerning their regulatory framework.

4 The Clinical Trials Regulation (EU) 536/2014 – Key Changes

A Regulation is directly binding in all European Member States. It does not need to be transposed into national law; therefore different implementations into national legislation do not occur. A Directive needs to be implemented into national law by each Member State. With this adaption to national law, the transposition into a national legal text can tremendously differ from the original one, depending on the available national legal framework, the willingness of the MS to perform changes and to which extent the national text is modified. These different transpositions of the original text occurred with the implementation of the Directive 2001/20/EC within the Member States.

Hence the European Commission published the first proposal for a Regulation on July 17, 2012. (5) The Rapporteur Glenis Willmott (Committee on the Environment, Public Health and Food Safety (ENVI) of the European Parliament) published the final Draft Report on the proposal of the Commission on January 31, 2013 with 66 amendments to the Articles and eight amendments to the annexes (11).

Accordingly, the Council of the European Union published an amendment of the proposal of the Commission for a Regulation on October 29, 2013. (12)

Finally, the Commission, the Council and the Parliament came to an agreement and compiled the Clinical Trials Regulation negotiation on the December 17, 2013. (4) This final legislation text was adopted by the Parliament on April 4, 2014 and signed by the Council on May 16, 2014and got published in the Official Journal of the European Union on the 27th May 2014 with the number ‘536/2014’ (1) and 20 days after publication the Regulation enters into force.

To provide an overview over the changes in the Regulation development process in relation to the Clinical Trials Directive, two tables in this master thesis are attached in section 8 of the Appendix; one shows the Articles of the Regulation (EU) 536/2014 besides the Articles in the Directive 2001/20/EC (table 2) and the other shows the impact of the Parliament and the Council on the final legislation text compared to the proposed text of the Commission (table 3).

4.1 Content of the Clinical Trial Regulation (EU) 536/2014

The Regulation (EU) 536/2014 on clinical trials of medicinal products for human use starts with 85 recitals followed by 19 chapters with 99 Articles closing with seven annexes, presented on 76 pages.

In the following the important chapters of the Regulation (EC) 536/2014 are summarised. (1) These summaries are reviewed and are compared to the different proposals of the Commission, Parliament and the Council to find out who of them had the most influence on the important Articles of the Regulation.

4.1.1 Chapter I – General provisions

The first Article states the scope of the Regulation, i.e. "*This Regulation applies to all clinical trials conducted in the Union. It does not apply to non-interventional studies*". (1) Besides the scope, Article 2 is about the definitions. In the Directive 2001/20/EC only 16 terms were defined. Now the Regulation defines 35 terms and six more terms are referred to Article 1 of the Directive 2001/83/EC.
In the following some of the most important new or changed definitions are described. From now on the terms 'clinical study' and 'clinical trial' are clearly defined: 'clinical study' is the general term. A study is then classified as a 'clinical trial', if it fulfils at least one of the conditions laid down in Article 2 paragraph 2. (1)
The conditions are:

"*(a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;*

(b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or

(c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects." (1)

A 'low-intervention clinical trial' is a subtype of a 'clinical trial'. To classify a trial as low-intervention, all conditions set out in Article 2 paragraph 2 (1) have to be met, which are:

"*(a) the investigational medicinal products, excluding placebos, are authorised;*

(b) according to the protocol of the clinical trial,

(i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or

(ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and

(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned" (1)

In the Directive 2001/20/EC the term 'non-interventional trial' was used. This term is changed to 'non-interventional study' and is therefore not regulated by the Regulation.
The prior definition of an 'investigational medicinal product' is split in 'investigational medicinal product' including placebos and in 'authorised investigational medicinal product' independent from the intended labelling.
A substantial amendment was not precisely explained but it was a significant change to an authorised clinical trial stated in Article 10 (a) of the Directive. (13) In the Regulation, the term 'substantial modification' is established and defined in Article 2 of the Regulation.
The definition of the 'Principal investigator' is now specified in addition to that of 'investigator'.

It is interesting to see that the Parliament as well as the Council agreed with the proposal for the scope of the Regulation by the Commission.
The Commission stated in the Explanatory Memorandum to their proposal of the Regulation that the scope "*is essentially identical to that of the Directive 2001/20/EC*". (4)
The exclusion of 'non-interventional studies' is justified by the Commission, because these types of trials "*are post-authorisation safety studies initiated, managed or financed by the marketing authorisation holder*" (4) according to the Directive 2001/83/EC.
Next to non-interventional studies the narrow scope of the Regulation excludes, also all the other studies or trials in clinical research, like studies comparing surgical procedures. Some of the Member States included those types of studies within their scope of the CTD interpretation when they implemented the Directive 2001/20/EC (e.g. Belgium). The respective MS will have to decide how to handle these studies in future but there is a danger that there will be discrepancies between the clinical studies conducted in different countries, whereas only clinical trials with medicinal products are equally regulated in the European Union. So the assurance of robustness and reliability of the compiled data, the rights and safety of humans in a clinical study are limited to trials with medicinal products, which fall within the scope of the Regulation.

A critical question is: Is it politically and ethically correct to have only one type of studies in humans regulated identically EU-wide?

The Council and the Parliament did not agree with all proposals of the definitions, e.g. the Council enforced the deletion of two market authorisation status-related conditions in the definition of the term ‘clinical trial’. The Council is also responsible for having defined the terms further and for integrating new terms like ‘principal investigator’, ‘investigators brochure’ and ‘early termination of a clinical trial’. The Parliament included the terms ‘Ethics Committee’ and ‘clinical study report’, but not with its proposed definitions.
In the second summary of the answers of the consultation paper in 2011 most of the stakeholders argued for a definition of a non-interventional trial (10); this issue is respected in so far that the definition in the Regulation is now “*’Non-interventional study’ means a clinical study other than a clinical trial*”. (1) This is not a useful definition, because it is only a clarification that non-interventional studies do not fall within the scope of the Regulation (EU) 536/2014.
Fully agreed by the Parliament and the Council is the definition of ‘substantial modification’, which was one of the heavily criticised issues in the Directive. Some of the Member States differently implemented Article 10 (a) of the Directive 2001/20/EC; hence the Member States interpreted a ‘substantial amendment’ not always in the same way. This was a challenge for any sponsor if a substantial amendment occurred in their clinical trial. Due to the fact that the Regulation is directly binding for all Member States and therefore does not have to be implemented in national law, this shall not be longer a big issue.

4.1.2 Chapter II – authorisation procedure

From Article 4 to Article 14 the authorisation procedure for a clinical trial is described. It starts with the general remark that any clinical trial (not study, regarding the scope) has to be authorised prior conducting and has to be reviewed by the concerned Ethics Committee of the Member States.
Every Member State is responsible for having their national EC complying with the assessment procedure stated in the Regulation.

The applicant submits the application dossier to all concerned Member States via the EU-portal (according to Article 80). The basis for the application dossier is Annex I of the Regulation. With this submission the applicant also suggests one of the MS as the reporting Member State (rMS). Clear rules are stated in Article 5 for entitling the reporting Member State in case of non agreement between all concerned Member States (cMS).

To compare the authorisation procedure in the Regulation with the procedure fixed in the Directive 2001/20/EC, the current authorisation procedure in the Directive is described below:

According to Article 6 paragraph 5 and Article 9 paragraph 4 of the Clinical Trials Directive the timelines for assessing a valid application are defined.

Ethics Committee have to give their opinion within 60 days. This also applies to the competent authority. Both bodies have to give a separate statement.

"*The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion*". (13) If in a Member State the EC has give a positive opinion about a CTA and the CA has not raised any concerns during the stated timeline, an implicit approval with respect to the CA is possible.

In the following, the authorisation procedure in the Regulation is presented. Further, Figure 4 and 5 shall illustrate the procedure:

After the submission of the dossier by the applicant, the rMS has to validate the submitted dossier within 10 days. All cMS have the possibility to comment on the dossier's completeness no later than 7 days after submission.

The rMS shall "*[take] into account considerations expressed by the other Member States concerned*" (1) during the whole authorisation procedure.

If the dossier is incomplete or the trial falls out of the scope of the Regulation, the applicant gets a maximum of 10 days for a reply. The reporting Member State informs the sponsor about the outcome 5 days after receipt of the reply.

After a positive outcome of the validation, the assessment procedure starts ('validation day'). The assessment procedure is divided in two parts – Part I and Part II.

The reporting Member State is responsible for the assessment of Part I, but according to Article 4 a "*review by the ethics committee may encompass aspects addressed in Part I of the assessment report*". (1)

The dossier of Part I have to contain all required data of Chapter V ('Protection of subjects and informed consent'), Chapter IX ('Manufacturing and import of IMPs & AMPs) and Chapter X (Labelling). The details of the required documents are listed in Annex I of the Regulation.

The timeline for the assessment, the finalisation and the conclusion of Part I is 45 days since the end of the validation date.

If more than one Member State is involved in the application procedure, the timeline stays the same but the procedure differs and is divided in three phases:

1. ‘Initial assessment phase’

The reporting Member State is responsible for the first assessment. The timeframe for this procedure is 26 days. The draft of this assessment will be subsequently sent to the concerned Member States via the EU-portal.

2. ‘Coordinated review phase’

The rMS and the cMS review the draft within 12 days.

3. ‘Consolidation phase’

In the next 7 days the reporting Member State consolidates the last phase of the draft (with respect to the comments of the cMS) and provides the applicant and all cMS with the final assessment via the EU-portal. This day is classified as the reporting day (see Figure 3).
During the assessment phase the need for clarification or for sending additional documents by the sponsor can occur. Only the rMS can request for these information. In this case the rMS determines an extension up to additional 31 days: the sponsor has to send the responses not later than 12 days, all Member States involved coordinate the reply of the sponsor within another 12 days and finally, after a consolidation phase of seven days, the rMS reports the outcome of the assessment (see Figure 5).
The reporting Member State may also extend the timeline up to 50 days for an assessment in case of clinical trials with advanced therapy IMP, as well as biotech products developed by recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, hybridoma and monoclonal antibody methods (Regulation No 726/2004, Annex 1).
Besides the Part I application dossier, the applicant can also submit Part II of the application dossier at the same time. Part II of the application has to be assessed by every single concerned Member State on its own regarding their national requirements.
The dossier regarding Part II has to be compliant with amongst others the requirements concerning Chapter V (i.e. informed consent and protection), eligibility of the subjects and the trial site, compliance with the indemnification, etc.
The cMS assesses the documents with respect to the requirements on its territory within 45 days. If further information is needed, the cMS can extend the timeline up to 31 days. The sponsor has to submit the reply latest after 12 days of knowledge except the cMS grants less days. During the next maximum 19 days the cMS states its conclusion via the EU-portal to the sponsor and all concerned Member States.
After the assessment phase of Part I and Part II of the application dossier, the final single decision of every involved MS has to be notified within 5 days after the reporting day. This day is named the notification day.

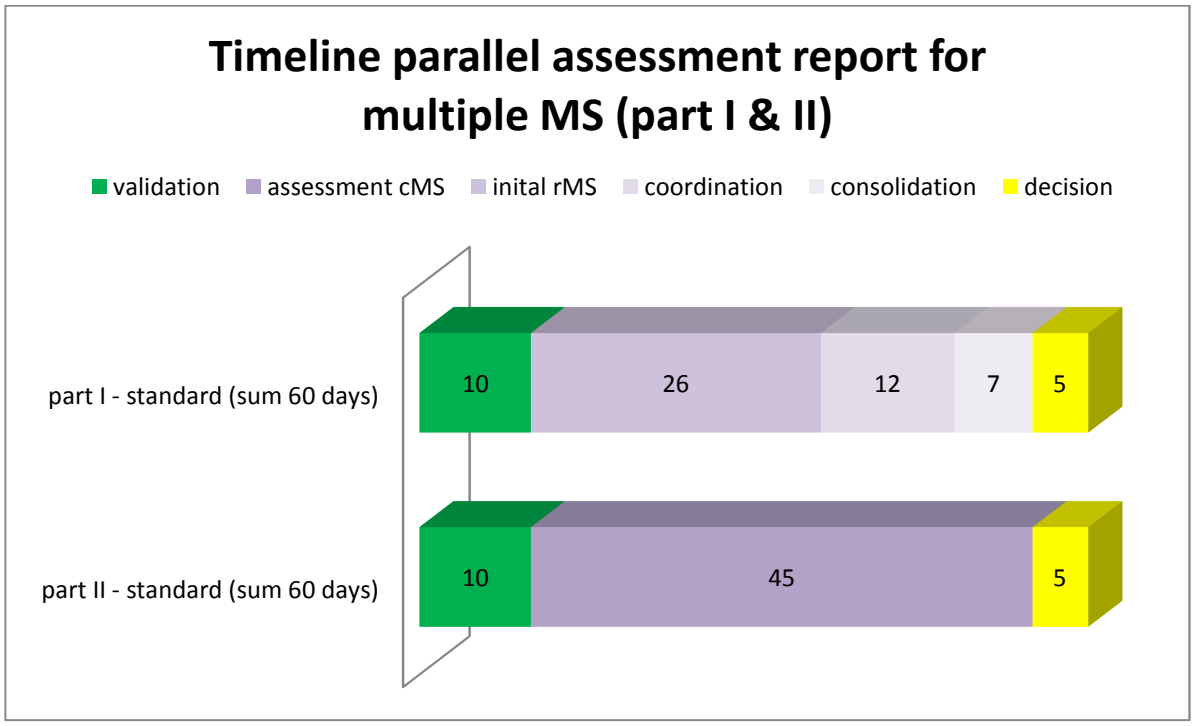

Figure 4: for the assessment procedure in multinational clinical trials with “standard” IMPs (1)

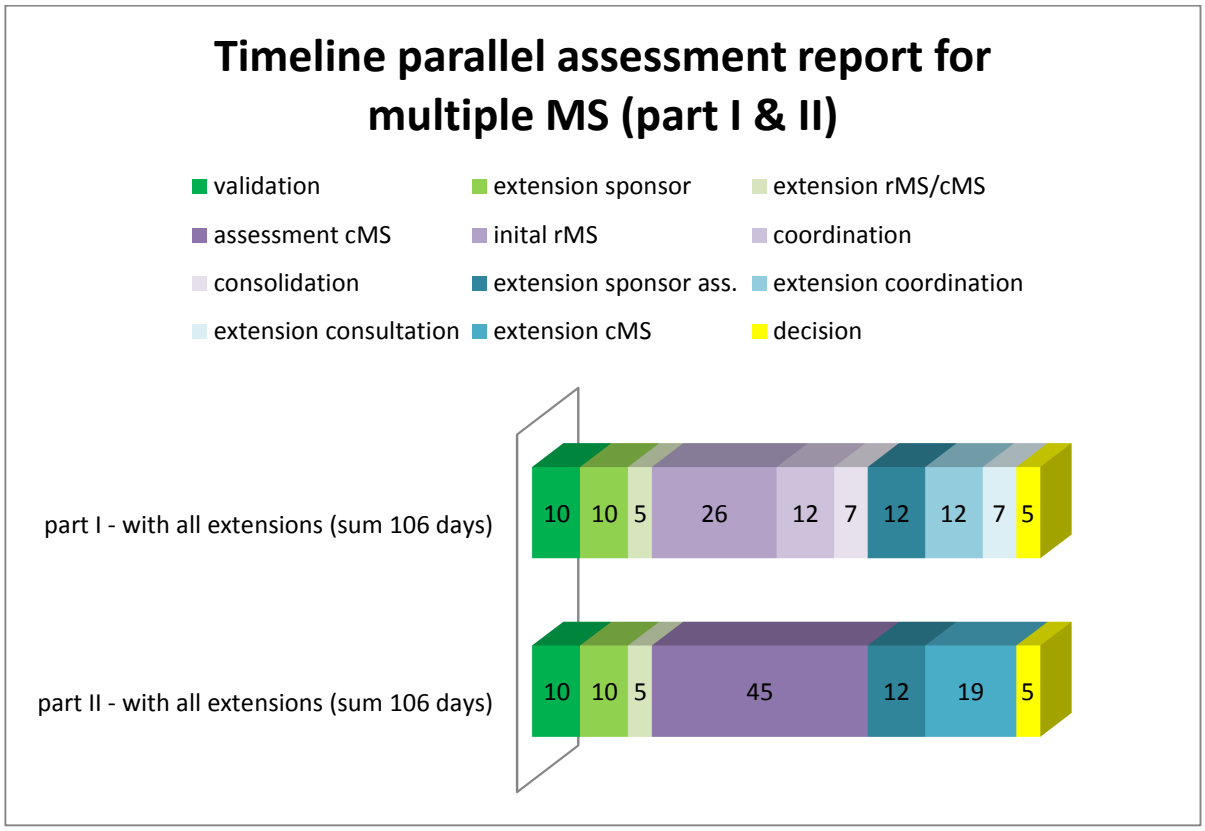

Figure 5: Timeline for the assessment procedure in multinational clinical trials with “standard” IMPs including extension of the validation phase and request for additional information (1)

If the sponsor does not provide the rMS or/and the cMS with the requested information within the given timeline (independent of the validation or assessment phase), "*the application deemed to have lapsed in all Member States*". (1)
The possibilities of the outcome of the assessment can be an approval, an approval under conditions or a refusal.
If the reporting Member State concludes to approve or to approve under conditions the application of Part I, then its decision "*shall deemed to be the conclusion of the Member State concerned.*" (1)
A refusal of the Part I application by the rMS leads to a refusal of Part I by all cMS.
If a cMS disagrees with the positive outcome of Part I assessed by the reporting Member State, this cMS can refuse an approval, this is called 'opt-out'. The refusal has to be justified according to Article 8 (2), (4) of the Regulation and has to be forwarded to the Commission and all concerned parties via the EU-portal. An appeal procedure has to be provided by the Member States.
If a concerned Member State does not notify its conclusion within the given timeline, the decision of the rMS concerning Part I applies to the concerned Member State.

A Sponsor has also the possibility to submit first a dossier concerning only Part I of the application. If the application for Part I gets approved, the sponsor may submit the dossier concerning Part II within the next 2 years providing that there are no "*new substantial scientific information that would change the validity of any item submitted in the [prior] application*" (1) of Part I.
The application can always be withdrawn by the sponsor till the reporting day, even a resubmission of a refused or withdrawn application is possible by submitting a new application.
Article 14 of the Regulation describes the possibility to add another Member State to an approved clinical trial. The added cMS has to provide the sponsor with its decision of the application within 52 days. If the additional Member State refuses the authorisation of that clinical trial, it "*shall provide for an appeal procedure in respect of such refusal*". (1)
The approval of the clinical trial expires within 2 years starting from the notification date unless the subjects have been recruited in the meantime.

The Regulation determines in Article 9 and 10 who has to assess and under what conditions Part I and Part II have to be assessed.
The Member States are responsible to have employees who "*do not have conflicts of interest, are independent of the sponsor, of the clinical trial site and the investigators involved and of persons financing the clinical trial, as well as free of any other undue influence*". (1) Therefore the involved employees have to declare annually their interest.

If a certain group of persons shall take part in the clinical trial, like minors or incapacitated persons, experts of these different vulnerable populations shall be involved in the assessment of the application.
Independent of the concerned population for a clinical trial, minimum one layperson shall be involved in the assessment of the application.

Annex I includes the necessary information for an application dossier. This Annex is based on 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)*". (14) To have this Annex now as a part of the Regulation is quite an improvement. The requirements are the same in every Member State, so this is a step forward to harmonisation. The Member States have to adhere to the law and cannot require different information for the same clinical trial. This is facilitation for every kind of sponsor.
The new authorisation procedure is comparable to the decentralised authorisation procedure (DCP) of a medicinal product. (15) The reporting Member State is similar to the Reference Member State (RMS) in the decentralised procedure. (16) But there are some differences between them. The applicant decides which RMS will be present in the DCP, whereas the applicant for a clinical trial authorisation can only suggest an rMS for the assessment procedure. The outcome of the assessment report Part I prepared by the rMS "*shall be deemed to be the conclusion of the*" (1) cMS, but this is not applicable to the CMS in a decentralised procedure. Another difference is that in the assessment of a clinical trial an independent Ethics Committees is supposed to be involved by the Member States, this is not foreseen in the DCP.
In the Explanatory Memorandum of the proposal of the Commission in 2012 the "*Regulation [did] (...) not regulate or harmonise the precise functioning of Ethics Committees*" (5), because "*it [was] up to Member States to organise, internally, the attribution of tasks to different bodies*". (5) This was extremely criticised and the Council enforced Article 4 into the Regulation. With this the Ethics Committees are not only integrated in the assessment procedure, they now have the power to refuse an authorisation. According to Article 4 the ECs are also empowered to review some aspects of the Part I, which does not include national requirements. It is up to national law whether some aspects of Part I have to be reviewed by the national ECs or not, but if an EC justifiably refuses the authorisation of a clinical trial in a Member State, which is the reporting Member State this decision will lead to a complete rejection of the trial for all participating Member States.

If the rMS comes to the conclusion "*that the clinical trial is not acceptable, that conclusion shall be deemed to be the conclusion of all Member States concerned.*" (1)
This is a very critical point which has to be considered by all Member States as soon as they adopt their national legislation to the Regulation.
The cooperation between the rMS and the cMS is another point to consider. The rMS is responsible for the assessment report and the appointed national authorisation body has to expand the timelines for the assessment and to ask for additional information. But the rMS shall also "*take into account [the] considerations expressed by the*" (1) cMS. The rMS is not legally obligated to accept or even to adopt the considerations of the cMS. The rMS can come into a conflict with any cMS if the considerations are not respected. However, this means that in the assessment report the rMS needs to justify when comments from cMS are ignored. The 'opt-out'-possibility for the cMS concerning the assessment of the Part I of the application has been widened by the Council. In the proposal of the Commission only two options to 'opt-out' an application for a clinical trial were provided (subject would receive an inferior treatment than the normal clinical practice in this Member State or an infringement of the national law), but finally the Regulation enables three possible reasons (subject would receive an inferior treatment, infringement of the national law or considerations as regards subject safety, data reliability and robustness) to 'opt-out' an application.

In the proposal of the Commission one of the legal aspects concerning the authorisation procedure stated in the Explanatory Memorandum was to have "*Clear timelines with a concept of tacit approval in order to ensure compliance*". (5) But in the further proposal this 'concept' was not reflected in the Articles 6-8.
In the Recital number 8 of the Regulation it is stated that the "*Directive 2001/20/EC introduced the concept of tacit authorisation. This concept should be maintained in order to ensure that timelines are adhered to.*" (1)
Nevertheless, a careful analysis of the Articles 6, 7 and 8 does not indicate a tacit approval in the assessment procedure. Only the validation itself (Article 5 paragraph 4) and the decision of the cMS concerning Part I (!) of the application dossier (Article 8 paragraph6) do fulfil the concept of a tacit approval. The Council had deleted Article 8 paragraph 6 as well as paragraph 8, second sentence in its amendment of the proposal. But the Commission enforced to keep these parts of the Article 8, otherwise there would have been no tacit approval at all. All other procedures are not connected with a tacit authorisation, e.g. if the rMS does not compile the assessment report of Part I within 26 days or the cMS does not finish the assessment report of Part II within 45 days. So this is a worsening of the situation as it has been with the Directive. In the Directive a "*sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the competent*

authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance". (13) The condition for a tacit approval is only a favourable opinion of the EC, not the authorisation of the competent authority. This discrepancy between the principle explained in the recitals and the wording of the regulation text needs further clarification but a strict following of the letter means that in the Regulation both bodies have to give their approval, no matter how long it might take, otherwise the conduct of a clinical trial is not possible.

Chapter II is clearly Council-oriented, because each Article has been modified by them. All amendments of the Council concerning the Articles 4-6 and 14 are adopted, only the timelines have been slightly changed. The Parliament announced 14 amendments concerning Chapter II (Articles 6, 7, 9, 10, 12 and 13), but only three amendments have been adopted, i.e. Article 9 paragraph 1 second paragraph ('*Persons assessing the application*'), Article 10 paragraph 4 (experts have to be involved for clinical trials in vulnerable populations) and Article 12 third sentence ("*The reasons for the withdrawal shall be communicated through the EU portal*"). (1)
The Timeline for an authorisation set in the Directive have been 60 days both for the ECs and the competent authorities (13), which was one of the complaints of the stakeholders (3). The Commission respected this concern and therefore published in its proposal in 2012 much shorter timelines for the validation and assessment. The Commission divided the timelines dependent on to the kind of trial. A low-intervention clinical trial should have been assessed within 10 days, a 'normal' clinical trial within 25 days and 'special' trials (e.g. the IMP is an ATMP) within 30 days. But the Council proposed longer timelines as it is in the Directive. Finally the Council determined the timelines and now in the Regulation the timeline for an authorisation is still 60 days excluding the possible extensions. So this concern of the stakeholders is not regarded by the Regulation.
During the validation phase the sponsor has the possibility "*to complete the application dossier*" (1) if the rMS finds the dossier incomplete. But during the assessment phase the reporting Member State "*may request additional information from the sponsor*" (1). It is not clear if with this 'additional information' any changes to the application incl. the protocol can be implemented by the sponsor. The Recital number 16 explains that the possible extension of the timelines is "*to allow the sponsor to address questions and comments raised during the assessment of the application dossier*" (1), but it is not clearly stated that this includes changing or adapting the application dossier according to the requests of the Member States.
If a Member State wishes to have any aspect changed of the provided data by the applicant, then the sponsor might have to withdraw the application and submit a new one, because amendments are not clearly conformable to law. This will need further clarification.

‘Low-risk trials’ were mentioned in the objective no. 2 of the impact assessment report (2). These trials are now regulated with the term ‘low-intervention clinical trial’. It is a trial which is only conducted with authorised medicinal products in the authorised indications except the investigational indication is evidence-proofed.
The conditions for a low-intervention clinical trial are set in Article 2 paragraph 3. In Recital no. 11 is stated that “*those clinical trials should be subject to less stringent rules*” (1) but there is no difference in the authorisation procedure for this type of trials after the Council enforced the deletion of the shorter assessment timeline for low-intervention clinical trials. The reason is stated in the same Recital no. 11, i.e. “*In order to ensure subject safety they should however be subject to the same application procedure as any other clinical trial*”. (1)
Low-intervention trials are conducted by a lot of non-commercial sponsors. If during the assessment phase the rMS asks for information, also the non-commercial sponsor has 12 days for response, just as every other applicant, but with the difference that most of the NCS do not have the organisational infrastructure to respond within 12 days. However, 12 days are very short to answer adequately, dependent on the raised issues, for every sponsor. So if the sponsor does not respond on time, “*the application deemed to have lapsed in all Member States*”. (1)

Article 9 states that “*At least one layperson shall participate in the assessment*” (1) as a result in the negotiations in December 2013. But who is a layperson? In the Recital no. 18 is stated, that this person should be a “*in particular a patient or [someone from a] patients’ organisation*” (1). But what type of competence is expected from this person? In the respective area of indication? In general? And does this patient have a right to vote? This will have to be clarified in national legislation and thus may lead to different conditions in the different concerned MS.

Article 14 describes the subsequent addition of a Member State to an approved clinical trial. The timeline of the assessment procedure is 52 days. This timeline is comparable to the timeline for the assessment procedure for an authorisation of a clinical trial (normally 60 days). This insignificant timeline shall prevent the sponsors from adding repeatedly another Member State to a clinical trial.

4.1.3 Chapter III – substantial modification of an authorised clinical trial

The term ‘substantial amendment’ (13) as stated in the Directive is changed in the Regulation to the term ‘substantial modification’ (1).

According to Article 15 of the Regulation a substantial modification of the authorised clinical trial has to be authorised as well. Therefore a dossier concerning a substantial modification of Part I or Part II or both parts has to be submitted via the EU portal. The required information for the application dossier is set out in Annex II of the Regulation.

The rMS of the prior authorised clinical trial shall be the same rMS for the assessment of an application that is submitted for a substantial modification of that clinical trial.

The authorisation procedure of the substantial modification is similar to the authorisation procedure of the clinical trial, only the timeframe differs (see Figure 6).

The validation phase for both Part I and Part II lasts generally 6 days, with a possible extension of further 10 days for the response of the sponsor and another 5 days for the conclusion of the rMS , in case of additional required data.

The assessment phase for both parts lasts 38 days.

If the substantial modification concerns Part I of the dossier and more than one MS is involved, then the assessment is divided in different phases, similar to the phases stated in the authorisation procedure of a clinical trial – i.e.

- the ‘initial assessment phase’ with 19 days for the rMS,
- then the ‘coordinated phase’ with 12 days for rMS & cMS and
- finally the consolidation phase with 7 days for the rMS.

If any objection arises, the assessment phase for both Part I and Part II can be extended up to 31 days only by the rMS. The 31 days extension for the assessment is split in the same different phases as the extended phase of the assessment for the authorisation of a clinical trial (see Figure 5).

For special medicinal products, like ATMPs, the extension can be up to 50 days in order to obtain the assistance of experts but only for the assessment of Part I.

The “*[notification of the assessment] shall be done by way of a single decision within five days from the reporting day*” (1), only if a substantial modification concerns Part I or both parts of the application.

The outcome of a substantial modification concerning solely Part II of the application has to be notified “within 38 days from the validation day” (1).

If the outcome of the assessment procedure of either Part I or Part II is negative, then the concerned Member State has to enable an appeal procedure.

If the rMS or the cMS do not give a response within the given timeline to the sponsor, the application for “*the substantial modification shall be deemed to be authorised*” (1).

If the sponsor does not provide the rMS or cMS with the required data within the given timeline, "*the application shall be deemed to have lapsed in all Member States concerned*" (1).

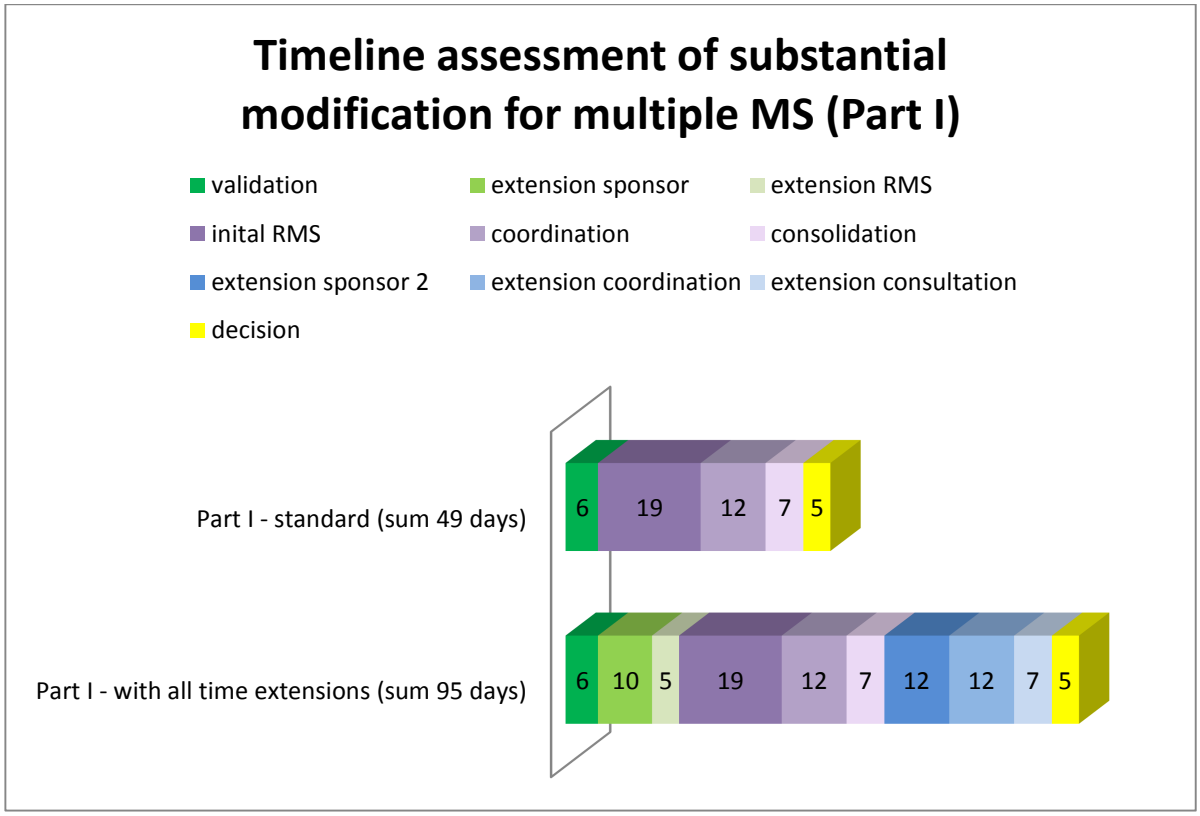

Figure 6: Timeline for the assessment of a substantial modification for multiple MS (Part I) with a "standard" IMP for Part I (1)

Substantial amendments under the Clinical Trials Directive are defined differently by most of the Member States. This issue was heavily criticised by the stakeholders (7). Now the information laid down in Annex II of the Regulation are mandatory for the application dossier of a substantial modification, which is based on paragraph 3 of the CT-1- Guideline. (14) This is an improvement in harmonisation and facilitates the handling with a substantial modification for any sponsor. Another improvement is the fact that the "*concept of tacit authorisation*" (1) is implemented for the procedure of a substantial modification.

One discrepancy can be found in the assessment of a substantial modification to a clinical trial with special medicinal products (e.g. ATMPs). If such a clinical trial has to be modified in Part II, no cMS has the possibility to extend the timeline in order to obtain support by an expert. This is also true for the assessment procedure of Part II to get a clinical trial authorised.

The timeline for the assessment of a substantial modification in a low-intervention clinical trial does not differ from the 'normal' clinical trials.

The Parliament did not suggest any amendment for Chapter III of this Regulation. The Council made again a lot of amendments in Chapter III, with implementing longer timelines for the assessment procedure.

4.1.4 Chapter IV – application dossiers

In this Chapter the application dossiers for a clinical trial and for a substantial modification are described. In each case a list of the necessary documents and information is available in the Annex of the Regulation. Annex I has to be considered for a clinical trial application and Annex II has to be used in case of a substantial modification of an authorised clinical trial.
If nonclinical data are provided in the application dossier, these data have to be GLP-conform, i.e. the nonclinical studies have to be done under good laboratory practice according to EU-law.
As soon as the Regulation is applicable, clinical data submitted in the dossier have to be registered in a public register which is a primary or partner registry of the WHO ICTRP[1] prior conducting the trial. "*Data from a clinical trial started before [the Regulation is applicable] shall only be submitted in an application dossier if that clinical trial is registered in a public register [as mentioned above] of if the results of that clinical trial have been published in an independent peer-reviewed scientific publication.*" (1)
If the data are from a clinical trial conducted outside the scope of EU law (i.e. Directive 2001/20/EC and the Regulation), the provided data have to be "*in accordance with principles equivalent to those of this Regulation as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial*" (1) otherwise those data should not be part of the application dossier.
Delegated acts in order to update the Annexes I and II are adopted by the European Commission.

This Chapter is one of the few chapters in which the Parliament has enforced its amendments to the proposal of the Commission. The Parliament is responsible for the inclusion of the requirement that every conducted clinical trial has to be registered in a public database that is free of charge and linked to the WHO ICTRP "*In order to increase transparency in the area of clinical trials*" (1) which is described in the Recital no. 25 of the Regulation.

[1]WHO ICTPR = World Health Organization International Clinical Trials Registry Platform. This platform "*is to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base.*" (21)

Annex I and Annex II are both based on the CT-1 Guideline. (14) Many aspects are adopted from this Guideline.
A Guideline can be characterised as a "soft law". (17) This means that the Guidelines are not legally binding but they are handled as an "anticipated expert opinion". (17) The authorities are not forced to accept these Guidelines and therefore some Member States did not fully assess the application according to the CT-1 Guideline, which was criticised by the sponsors.
A big step towards harmonisation has been done by integrating the CT-1 Guideline into the Annexes I and II of the Regulation which is directly legally binding for all Member States.

4.1.5 Chapter V – subjects in clinical trials

Article 28 lays down the general conditions that all have to be met when conducting a clinical trial.
Some requirements are e.g. the informed consent given by the subject or by "*his or her legally designated representative*" (1), only a "*qualified medical doctor*" (1) or dentist is responsible for an adequate medical care and subjects should not be influenced in their decision of taking part in a clinical trial because of e.g. financial interest.
Any subject can quit a clinical trial without giving any reason at any time.
The informed consent is set out in Article 29 of the Regulation and describes the framework for preparing an informed consent. This Article does not affect the national provisions concerning incapacitated persons and minors.
In case of a low-intervention clinical trial solely conducted in one Member State, it is possible to simplify the informed consent, but it is associated with several conditions (Article 30). To have incapacitated subjects, minors, pregnant or breastfeeding mothers integrated in a clinical trial, several requirements are necessary in addition to the conditions set out in Article 28.
In emergency situation the conduct of a clinical trial can be justified, if certain criteria are met. The informed consent of the person in an emergency situation is the key issue and therefore the clear procedures are set out in Article 35.

Chapter V has been changed to a considerable degree. Most of the changes are determined by the Council. The Council added four conditions in Article 28 and six new sections in Article 29. The Articles 33 ('*Clinical trials on pregnant or breastfeeding women*') and 34 ('*Additional national measures*') have been newly included by the Council into the proposal of the Commission. The Article 35 ('*Clinical trials in emergency situations*') is an

improvement over the Directive. The Directive does not regulate a clinical trial in an emergency situation. (7) The Council has enforced diverse amendments to the Article 35. Chapter V has been significantly changed during the Triage negotiations in December 2013. The Article 29 (‘*informed consent*’) paragraph 2 (d) and (e) and paragraph 4-6 and the Article 30 (‘*Informed consent in cluster trials*’) have been introduced during the Triage negotiations. The Article 30 facilitates especially the conduct of low-intervention clinical trials in a single Member State for non-commercial sponsors, who often conduct such kind of trials for academic research. The administrative burden of the informed consent is therefore reduced for this kind of trials.

4.1.6 Chapter VI - duration of a clinical trial

As soon as a clinical trial is authorised, any action that is done, has to be notified to all concerned Member States via the EU-portal.
This means in detail that the start, the first visit and the end of the recruitment of the subjects, any interruption and the end of the trial have to be notified to all Member States within 15 days.
If an interruption occurs due to safety reasons all MS have to be informed “*without undue delay but not later than in 15 days of the date of the temporary halt or early termination. It shall include the reasons for such action and specify follow-up measures*” (1).
The end of a clinical trial in a particular MS and of the trial in total has to be notified to all Member States irrespective of the location of the site (i.e. the last Member State or the end of a trial in the last third country).
Independently from the result of the trial, within one year after the end of it a summary of the results of the trial has to be submitted to the EU database for all concerned Member States and one for laypersons. The summaries have to be prepared according to Annex IV for the Member States and according to Annex V for laypersons. A full clinical study report has to be provided to the EU database “*30 days after the day a marketing authorisation has been granted, the procedure for granting marketing authorisation has been completed or the applicant for marketing authorisation has withdrawn the application*” (1). The Commission is able to update the Annexes IV and V with delegated acts according to Article 39.

This Chapter VI has been amended mostly by the Council. But the Parliament succeeded in adding a few amendments (i.e. Article 37 paragraph 4-8).
The sponsor shall now notify to all concerned Member States if any action was done concerning the conduct of a clinical trial. In the Directive only the end of a clinical trial has to be declared by the sponsor and if the trial has been early terminated (CT-1 Guideline (14)). The CT-1 Guideline includes the "*clinical trial summary report*" (14) which is part of the declaration for the end of the trial. In the Regulation now the sponsor has to compile a summary of the trial for the Member States concerned and a summary for laypersons "*In accordance with international standards*" (Recital no. 37 (1)). These summaries and the permanent updates of the status will increase the administrative burden for the sponsors, especially for non-commercial sponsors but substantially increase transparency.
The Parliament has committed the sponsor to submit a clinical study report to the EU database in Article 37 (according to Annex I, Part I, module 5 of the Directive 2001/83/EC) and therefore makes the result publically available. The Parliament wants to have more transparency, and "*For the purpose of this Regulation, in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted, the procedure for granting themarketing authorisation has been completed, the application for marketing authorisation has been withdrawn*" (1) as stated in the Recital number 68.
Is the clinical study report really not '*considered commercially confidential*' if the application has been withdrawn? This has to be considered critically, especially if the sponsor plans to submit an updated application for a marketing authorisation.

4.1.7 Chapter VII – safety reporting

Articles 40 to 46 are about the safety reporting of adverse events during a clinical trial. If a suspected unexpected serious adverse reaction (SUSAR) occurs during a clinical trial, this event has to be reported via the EudraVigilance database, which is already available. The investigator is responsible for recording any adverse event and for documenting it according to the protocol. He has to inform the sponsor about any serious adverse event "*without undue delay*" (1) but latest within 24 hours as defined in the protocol. Equally the sponsor has to report any suspected unexpected serious adverse reaction to the agency as soon as possible but latest within seven (life-threatening) or 15 days depending on the seriousness of the reaction. SUSARs occurring in a clinical trial site outside the European Union have to be reported in the same way. The sponsor provides the European Medicines Agency with an annual report regarding the safety of the IMP used in the clinical trial. The information

that has to be provided to the Agency is stated in Annex III of the Regulation, both for the SUSAR reporting and the annual safety report.
Member States have to assess the SUSAR and the annual reports; it is up to their national legislation to involve Ethics Committees in the assessment.

The Council has noticeably influenced Chapter VII. The Commission had proposed that the investigator should report any adverse event to the sponsor as fixed in the protocol. There was no timeline specified for the reporting by the Commission. In the proposal the sponsor should report the SUSAR "*without delay"* (5) to the database, but again the Commission did not give any timelines. The Council enforced to keep the given timelines as stated in the Directive 2001/20/EC. The Council was also responsible for deleting the Article 41 in the proposal of the Commission, as in this Article the sponsor had to provide the marketing authorisation holder with an annual report, if an authorised medicinal product was used within its authorisation in the clinical trial.
The Ethics Committees stated in the ICREL-study that it is an administrative burden to review the SUSAR reports in addition to the competent authority. (3) The Commission has respected this issue and included in Article 44 paragraph 3 the option in which ECs "*shall be involved in the assessment (...) if it has been provided for in the law of the Member State concerned*". (1) So the Member States can now decide on their own territory, if Ethics Committees shall participate in the assessment.
All the information on a SUSAR that the sponsor has to submit to the EudraVigilance database is now harmonised by including Annex III into the Regulation which was the "*least harmonised*" (9) legislation noticed by the stakeholders stated in the public consultation paper in 2009. Annex III is based on the Guideline called "*Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')*". (18)
The Commission handled the complaint of the stakeholders and made the required data mandatory for SUSAR reporting, which is an improvement compared to the Directive.
The issue raised by the stakeholders about the annual safety report and its administrative burden for the sponsors (9) has not been respected in the Regulation. Still the sponsor has to compile an annual safety report.

4.1.8 Chapter XII – damage compensation

This Chapter contains only Article 76 with three paragraphs. Member States have to "*ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk*". (1) This shall be sufficient for low-intervention clinical trials in a Member State, "*if any possible damage that could be suffered by a subject (...) is covered by the applicable compensation system already in place.*" (1)

This Chapter has been completely changed by the Council.
The Commission proposed in Chapter XII two Articles, the first concerning damage compensation and the second was about a national indemnification mechanism.
The Council amended to delete both Articles and added instead of them Article 76 with the first two paragraphs, which are now stated in the Regulation. The third paragraph concerns a national compensation system and is included in the Regulation during the Triage negotiations. Still fees for a damage compensation system are not regulated.
It is to appreciate that the Commission respected the concerns raised by the stakeholders that the insurance for the subject should be risk-adapted. (10)
The national indemnification mechanism should have been free of charge for clinical trials which would have not been used "*for obtaining a marketing authorisation for a medicinal product.*" (5) The deletion of this option leaves the situation as it is now in the Member States. The indemnification mechanism would have been a further step to harmonisation (with respect to the condition for the patients' protection) and a cost reduction, especially for investigator-initiated trials, which usually do not aim to obtain a marketing authorisation for an IMP.

4.1.9 Chapter XIV to Chapter XIX – summary

Chapter XIV includes three articles which specify the EU portal and the EU database.
The European Medicines Agency (EMA) is responsible for arranging and maintaining the EU portal and the database "*in collaboration with the Member States and the Commission*". (1) The EU portal shall be the submission tool. All the information according to the Regulation submitted via the portal shall be saved in the EU database.

The EU database shall not contain the same information laid down in the EudraCT & EudraVigilance database in terms of duplication.
The EU database has a lot of functions: it allocates a "*unique EU trial number*" (1) for any clinical trial, it is the single portal for all trial related information and it supports the xEVMPD with the data available in the EU database. It facilitates the "*cooperation between the competent authorities of the Member States*" (1); the sponsor can communicate with the Member States via this database. The information provided in the EU database shall be searchable in an easy way so that citisens can use this database as well. Therefore the "*user interface of the EU database shall be available in all official languages of the Union*". (1)
If incorrect information is available on the database the responsible parties have to change it within a maximum of 60 days.
The Management Board of the Agency is responsible for the functionality of the EU database and has to inform the Commission when it is ready for operation, after an independent audit. Then the Commission has to publish this information.

Chapter XV is about the cooperation inside of the European Union. In Article 83 the Member States are committed to arrange "*one national contact point in order to facilitate the functioning of the procedures set out in Chapters II and III*". (1) The Commission will list all national contact points and publish this list. For this purpose the 'Clinical Trials Coordination and Advisory Group (CTAG) has been established consisting of all these national contact points. In Article 85 their tasks are described, e.g. "*to support the exchange of information between the Member States and the Commission*". (1)

Chapter XVI describes the possibility to demand fees for activities done by the Member State, but Article 87 limits the Member States for charging multiple fees for the assessment done by the different bodies.

Chapter XVII is about implementing and delegated acts. The Commission is empowered to adopt delegated acts "*for a period of five years*" (1) as soon as the Regulation has entered into force and has to compile a report concerning the delegated powers. The Parliament and the Council have the authority to oppose delegated acts by the Commission.

Miscellaneous provisions are laid down in chapter XVIII. Subjects shall not charge for the participation in a clinical trial except it is conform to the national legislation.
Member States have to establish "*rules on penalties applicable to infringements of this Regulation and shall take all measures necessary to ensure that they are implemented*". (1)

Finally Chapter XIX is about the last provisions. Five years after the Regulation has come into force the Commission has to prepare a report concerning the impact of the Regulation, e.g. "*the competitiveness of European clinical research*". (1)

In the proposal from the Commission responsibility for building and maintaining the EU portal and the EU database laid with the Commission. As a result of the Triage negotiations the responsibility has been transferred to the EMA without any published justification. The Agency is also responsible for maintaining the EudraVigilance database. It is not a secret that the EMA has not coped sufficiently well with the development of complex databases up to now. But the application of this Regulation is dependent on the functionality of the EU portal and the EU database. As long as the functionality of these technical requirements is not confirmed by the Commission, this Regulation will not come into force. An incalculable time might go until the Regulation becomes applicable. The Agency is now the time factor for the application of the Regulation. The Commission has to publish the functionality of the EU database, "*when it is satisfied that the conditions referred to in paragraph 2 [of Article 82] have been fulfilled*" (1), i.e. the "*EU portal and the EU database have achieved full functionality*". (1)
The EU database will become a very complex system. It has to meet a lot of criteria. In the following some of the criteria are considered which could delay the finish of the EU database.
This EU database has to be simple in its structure, "*technically advanced and user-friendly*" (1). Besides the authority bodies and the applicants, every citisen shall have the possibility to use this database. The Parliament enforced to make the EU database publicly available, to have more transparency.
Thus, two points will not be transparent for the public: the communication between the Member States during the assessment phase and the "*Personal data in accordance with Regulation (EC) No 45/2001"* (1) have to be kept confidential. This is absolutely legitimate. But the transparency on the part of the applicants is a critical point.
In Article 81 paragraph 4 (b) is stated that "*commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product*" (1) are protected. In Article 81 paragraph 5 is also stated that the information in an application dossier for a clinical trial are protected as far as the decision has been made. In both cases the data are only protected if there is no "*overriding public interest in disclosure*" (1) otherwise all information is publicly available, no matter whether the clinical trial is authorised or the marketing authorisation is granted at that moment or not.

It is legitimately that the sponsors are worried, because it is not regulated who decides whether there is a public interest or not, or even if the applicant has the possibility to undertake the disclosure.

The EU database has also the function "*to enable the cooperation between the competent authorities of the Member States*" (1). This cooperation shall be enabled for the competent authorities and sponsors but the Ethics Committees are not mentioned. So each Member State has to decide on its own territory whether the Ethics Committees should get an access to the EU database as an assessor or if the competent authority would provide the EC only with the necessary information without a separate access to the EU database. So this EU database has to enable separate accesses with different access authorisations for the competent authorities, possible EC, sponsors and all citizen of the European Union.

The EU database shall award a "*unique EU trial number*" (1) for every clinical trial, comparable to currently available EudrCT number. The Council inserts this topic in the Regulation and is also responsible for the insert of the Article 82 "*Functionality of the EU portal and EU database"*. (1)

One of the most critical points, which will make a high demand on the EMA's time, is the fact that the "*user interface of the EU database shall be available in all official languages of the Union*". (1)

In the European Union we have 28 Member States with 24 different official languages and three different alphabets. (19) "*It should be left to the Member States to establish the language requirements for the application dossier. To ensure that the assessment of the application for authorisation of a clinical trial functions smoothly, Member States should consider accepting a commonly understood language in the medical field as the language for the documentation not destined for the subject*" ((1) Recital no. 26).

So every MS can decide in which language the applicant has to submit the dossier. Part I of the dossier of a multi-national clinical trial should to be accepted in English, otherwise a single submission of one dossier is not possible and again there would be no harmonised application dossier. But it is up to the MS if they also accept Part II of the dossier of a multi-national clincial trial (except patient-relevant documents like informed consent) in English. In terms of harmonisation the Member States shall cooperate with each other and find a solution which is acceptable for both the assessors and the applicants, basically for multi-national clinical trials.

The adaptation of the EU database to this requirement is a big challenge and will have an impact on the date when the Regulation will apply.

The Council included in the Regulation the obligation for the Commission to compile a report concerning the delegated acts five years after the Regulation applies.

The Articles 94 (Penalties), 97 (Review) and 98 (transitional provisions) second paragraph have been developed by the Triage during their Meeting.
The Parliament suggested in its amendment of the proposal to add an Article in Chapter XVIII (Miscellaneous Provisions) about a cooperation between the ECs, i.e. "*The Commission shall facilitate cooperation of ethics committees and the sharing of best practices on ethical issues including the procedures and principles of ethical review*" (11) but based on the Council's position it has not been adopted in the Regulation.

The transition period starts six months after the publication of the functionality of the EU database by the Commission. Then the sponsor can decide on which legal basis the application for an authorisation of a clinical trial shall be. If the sponsor decides to submit the application according to the Directive 2001/20/EC, then the clinical trial can be conducted in terms of the Directive for three years after the application date of the Regulation.
Sponsors should consider whether to make use of this option or not. If the duration of a clinical trial shall be for example five years, which is not unusual, then the trial will have to undergo a switch to the new legal basis. It is not clarified in the Regulation, how this aspect has to be handled. It could happen that the sponsor has to stop the trial and submit an application for an authorisation according to the Regulation. Even an adaptation to the Regulation might be a condition of the Member States. If a substantial modification (not substantial amendment!) occurs, the sponsor will have to submit the application via the EU portal. But this is only possible if the clinical trial is registered in the EU database. Who will be the rMS if the trial is authorised in more than one Member State? This is another issue that has to be considered by the EMA for maintaining the EU database.
Further, the transition period is difficult for the Member States. They have to assess the applications in a different way. The technical aspect as well as the content and the provided data are different. Following, the coordination of the applications during the transition period will be a challenge for the Member States.

5 Is the Regulation (EU) 536/2014 satisfying?

The application date of the Regulation is "*six months after the publication of the (…) [functionality of the EU portal and the EU database], but in any event no earlier than 28 May 2016*". (1) The transition period is one year, six months after the EU portal and the EU database is functioning. After this one year the trial can be continued for two more years according to the Directive 2001/20/EC, and then finally the Regulation applies. (1)

The main reason for changing the rules for clinical trials was to harmonise the legislation EU-wide. The introduction of the Directive 2001/20/EC was a big step towards harmonising the authorisation procedure and the conduct of clinical trials, but it has left room for improvement. The implementation of the Directive into national law has caused differences in the legislations of the Member States. The proposal of the Commission was to change the legal form into a regulation, a courageous step which was heavily criticised as going too far and limiting the MS' freedom of legislation. The Commission provided the Council and the Parliament with a detailed proposal for a Regulation on clinical trials with IMPs for consultation. While the European Parliament submitted a report with several amendments, ultimately, the Council has strongly influenced the final text of the Regulation whereas the Parliament could only enforce a few amendments to the proposal of the Commission.
The Regulation is basically an improvement and has a lot of advantages compared to the Directive. The first and most important advantage is the legal form, because the Regulation is directly binding for all Member States and does not have to be transferred to national law. Especially the Annexes support facilitation for the applications, a reduction of the administrative burdens for the sponsors and the idea for a further harmonisation within the European Union.

Currently under the CTD sponsors have the tough task to adapt their applications to the requirements of the Member States if they want to conduct a clinical trial in more than one Member State. Integration of the differing requirements from competent authorities and ethics committees in the different MS has to be handled by the sponsor and very often results in the requirement for a substantial amendment before the clinical trial can start. This means de facto a prolongation of the trial preparation timelines way beyond the 60 days requested by the CTD as was shown by the ICREL results. With the now approved coordinated assessment procedure the responsibility for integration and negotiation of the different MS positions falls under the responsibility of the rMS and has to be achieved in clearly defined timelines.

With separating the application dossier for the authorisation of a clinical trial in Part I and Part II the national characteristics, mainly ethical aspects including informed consent, have been respected. Also the possibility to submit one single application for several Member States via the fast electronic way is a success, "*in order to simplify the procedures for the submission of an application dossier*" ((1) Recital no. 4).
But some aspects of the Regulation have not improved or even changed the conditions for clinical trials for the worse:
Although the timeline for clinical trial authorisation is very strict, there is no time pressure for the Member States as the principle of tacit approval seems not to be established. Without the concept of the tacit approval, Member States have time for the assessment of an application, particularly in assessing Part II of the application.

The idea of the EU portal and the EU database is basically welcomed but the technical requirements will be very complex. Small research organisations might not have the capacity and the financial support to adapt their equipment.
The EU database is also a tool for transparency. All parts of the information in the database (e.g. application dossier, summary of the results, clinical study report if applicable) shall be public except confidential data (i.e. personal data, commercially confidential data, communication between MS, etc.). This enlarged transparency has to be considered critically, although the academia and the public demand for it. Many of the sponsors intend to obtain a marketing authorisation with the IMP used in a clinical trial. For this purpose, they have to compile amongst others a clinical study report, which has to be submitted to the EU database under the terms stated in Chapter IV. A clinical study report includes commercially confidential data. With the provision to publish this report, the European Union might get less attractive for non-EU sponsors.

The Regulation does not facilitate the language issue as it is bound to fundamental European rules. Every Member State can decide which languages are accepted for the application in its territory. Part I has to be assessed by all involved MS for a multi-national clinical trial and the rMS has to compile an assessment report. To have this report understandable for all cMS, this report should be in a language which fits all MS and therefore the MS should enable an agreement among each other. Unfortunately, Part II of the assessment is solely assessed by the cMS. In terms of keeping the European Union as an attractive place for conducting clinical trials, Member States should respect this and voluntarily agree on an application in English – at least for multi-national trials but ideally also for national trials as the sponsor may need to run the trial in more than one country if recruitment is not satisfactory.

Some concerns raised by the stakeholders have not been addressed in the Regulation, for example the administrative burden with the annual safety report. Actually it has increased with the obligation for the sponsor to submit two summaries after completion finish of the trial within one year.

"*In order to maximise the valuable contribution of [ ] non-commercial sponsors and to further stimulate their research but without compromising the quality of clinical trials, measures should be taken by the Member States to encourage clinical trials conducted by those sponsors*"((1)Recital no. 81) After the shorter authorisation timelines have been skipped by the Council there are not many advantages for low-interventional trials left. This Recital has to be appreciated but according to the Regulation, it is difficult to integrate those 'measures'. The possibility to use the national damage compensation system supports the non-commercial sponsors only for low-intervention trials in those countries where this possibility already exists.

However, if a non-commercial sponsor submits an application for authorisation of a clinical trial only in one Member State, then this Member State has the option to 'encourage' NCS through its national legislation. Some options for encouragement are shortening the timeline for the assessment of the application nationally in case of a low-intervention clinical trial or of charging lower authorisation fees.

"*The Commission (…) proposed patient involvement in the assessment of clinical trials (…). After all, it is patients who will bear the potential risks of the trial, and who will enjoy the potential benefits [and] that these patients should be experienced and knowledgeable, and their involvement should not be seen as tokenism.*" (11) This was stated by the Parliament in its Explanatory Statement of the amendment of the proposal for a Regulation.

The Parliament proposed to involve patients in the assessment procedure. But the Council did not agree and proposed the deletion of the third paragraph of Article 9 in the proposal of the Commission. (12) Finally the Commission, the Council and the Parliament came to an agreement in the Triage negotiations and the third paragraph of Article 9 in the final implies the involvement of a layperson (not particularly patients).

An EU-wide harmonised involvement of patients in the assessment procedure for authorising a clinical trial would have been a great chance for the Union, as patients, politics and the EU Parliament has called for it.

In conclusion the Regulation is a further but not the final step for harmonisation. A large number of aspects are still linked to national requirements. Now it is the task of the Member States in cooperation with the CTAG to configure the requirements of the Regulation in terms of harmonisation.

Beside the aim to harmonise the rules in the EU, a further aim is to get the EU attractive again for clinical research and conducting clinical trials. Whether the attractiveness returns to the EU or not, cannot be decided at the moment. As soon as the system is established the attractiveness can be measured. It depends on how the real processes will take place in the EU.

Last but not least it should be mentioned that the aim of any clinical trial should be essentially the interest of the population, who shall benefit from the results of a clinical trial someday. "*In a clinical trial the rights, safety, dignity and well-being of subjects should be protected and the data generated should be reliable and robust. The interest of the subjects should always take priority over all other interests*" (first Recitals (1)).

6 Resources

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7 Appendix

This table shows the Articles of the Directive in comparison to the Regulation. (1)

Article	Directive	Regulation
		Chapter I: General provisions
1	Scope	Scope
2	Definition	Definition
3	Protection of the clinical trial subjects	General principle
		Chapter II: Authorisation procedure for a clinical trial
4	Clinical trials on minors	Prior authorisation
5	Clinical trials on incapacitated adults not able to give informed legal consent	Submission of an application
6	Ethics Committee	Assessment report – Aspects covered by Part I
7	Single opinion	Assessment report – Aspects covered by Part II
8	Detailed guidance	Decision on the clinical trial
9	Commencement of a clinical trial	Persons assessing the application
10	Conduct of a clinical trial	Specific consideration for vulnerable populations
11	Exchange of information	Submission and assessment of applications limited to aspects covered by Part I or Part II of the assessment report
12	Suspension of the trial or infringements	Withdrawal
13	Manufacture and import of investigational medicinal products	Resubmission
14	Labelling	Subsequent addition of a Member State concerned
		Chapter III: Authorisation procedure for a substantial modification of a clinical trial
15	Verification of compliance of investigational medicinal products with good clinical and manufacturing practice	General principles
16	Notification of adverse events	Submission of application
17	Notification of serious adverse reactions	Validation of an application for authorisation of a substantial modification of an aspect covered by Part I of the assessment report
18	Guidance concerning reports	Assessment of a substantial

		modification of an aspect covered by Part I of the assessment report
19	General provisions	Decision on a substantial modification of an aspect covered by Part I of the assessment report
20		Validation, assessment and decision regarding a substantial modification of an aspect covered by Part II of the assessment report
21		Substantial modification of aspects covered by Parts I and II of the assessment report
22	Application	Assessment of a substantial modification of aspects covered by Parts I and II of the assessment report – Assessment of the aspects covered by Part II of the assessment report
23	Entry into force	Decision on the substantial modification of aspects covered by Parts I and II of the assessment report
24	Addresses	Persons assessing the application for a substantial modification
		Chapter IV: Application dossier
25		Data submitted in the application dossier
26		Language requirements
27		Update by way of delegated acts
		Chapter V: Protection of subjects and informed consent
28		General rules
29		Informed consent
30		Informed consent in cluster trials
31		Clinical trials on incapacitated subjects
32		Clinical trials on minors
33		Clinical trials on pregnant and breastfeeding women
34		Additional national measures
35		Clinical trials in emergency situations
		Chapter VI: Start, end, temporary halt, and early termination of a clinical trial
36		Notification of the start of the clinical trial and the end of the recruitment of subjects

37	End of the clinical trial, temporary halt and early termination of the clinical trial and submission of the results
38	Temporary halt or early termination of by the sponsor for reasons of subject safety
39	Update of the contents of the summary of results and summary for laypersons
	Chapter VII: Safety reporting in the context of a clinical trial
40	Electronic database for safety reporting
41	Reporting of adverse events and serious adverse events by the investigator to the sponsor
42	Reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency
43	Annual reporting by the sponsor to the Agency
44	Assessment by Member States
45	Technical aspects
46	Reporting with regard to auxiliary medicinal products
	Chapter VIII: Conduct of a clinical trial, supervision by the sponsor, training and experience, auxiliary medicinal products
47	Compliance with the protocol and good clinical practice
48	Monitoring
49	Suitability of individuals involved in conducting the clinical trial
50	Suitability of clinical trial sites
51	Traceability, storage, return and destruction of investigational medicinal products
52	Reporting of serious breaches
53	Other reporting obligations relevant for subject safety
54	Urgent safety measures
55	Investigator’s brochure
56	Recording, processing, handling and storage of information
57	Clinical trial master file

58	Archiving of the clinical trial master file
59	Auxiliary medicinal products
	Chapter IX: Manufacturing and import of investigational medicinal products and auxiliary medicinal products
60	Scope of this Chapter
61	Authorisation of manufacturing and import
62	Responsibilities of the qualified person
63	Manufacturing and import
64	Modification of authorised investigational medicinal products
65	Manufacturing of auxiliary medicinal products
	Chapter X: Labelling
66	Unauthorised investigational and unauthorised auxiliary medicinal products
67	Authorised investigational and authorised auxiliary medicinal products
68	Radiopharmaceuticals used as investigational medicinal products or as auxiliary medicinal products for a medical diagnosis
69	Language
70	Delegated acts
	Chapter XI: Sponsor and investigator
71	Sponsor
72	Co-sponsorship
73	Principal investigator
74	Legal representative of the sponsor in the Union
75	Liability
	Chapter XII: Damage compensation
76	Damage compensation
	Chapter XIII: Supervision by Member States, Union inspections and controls
77	Corrective measures to be taken by Member States
78	Member State inspections
79	Unions controls

	Chapter XIV: IT Infrastructure
80	EU portal
81	EU database
82	Functionality of the EU portal and the EU database
	Chapter XV: Cooperation between Member States
83	National contact points
84	Support by the Agency and the Commission
85	Clinical Trials Coordination and Advisory Group
	Chapter XVI: Fees
86	General principles
87	One payment per activity per Member State
	Chapter XVII: Implementing acts and Delegated acts
88	Committee procedure
89	Exercise of the delegation
	Chapter XVIII: Miscellaneous provisions
90	Specific requirements for special groups of medicinal products
91	Relation with other Union legislation
92	Investigational medicinal products, other products and procedures, free of charge for the subject
93	Data protection
94	Penalties
95	Civil and criminal liability
	Chapter XIX: Final provisions
96	Repeal
97	Review
98	Transitional provisions
99	Entry into force

Table 2: Comparison Articles of Directive and Regulation

This table shows the impact of the Council of the European Union and the European Parliament on the proposal of the European Commission concerning the final Regulation. An empty line means that the proposal of the European Commission has been adopted. (1) (12) (12)

Article	**Regulation**	**Influence of**
	Chapter I: General provisions	
1	Scope	
2	Definition	Council brought up 7 changes and 2 new definitions Parliament brought up 2 new definitions
3	General principle	
	Chapter II: Authorisation procedure for a clinical trial	
4	Prior authorisation	Included by the Council
5	Submission of an application	Strongly influenced by the Council
6	Assessment report – Aspects covered by Part I	Strongly influenced by the Council
7	Assessment report – Aspects covered by Part II	Influenced by the Council
8	Decision on the clinical trial	Strongly influenced by the Council
9	Persons assessing the application	Influenced by both Council and Parliament
10	Specific consideration for vulnerable populations	Influenced by both Council and Parliament
11	Submission and assessment of applications limited to aspects covered by Part I or Part II of the assessment report	Influenced by the Council
12	Withdrawal	Influenced by the Parliament
13	Resubmission	
14	Subsequent addition of a Member State concerned	Strongly influenced by the Council
	Chapter III: Authorisation procedure for a substantial modification of a clinical trial	
15	General principles	Influenced by the Council
16	Submission of application	
17	Validation of an application for authorisation of a substantial modification of an aspect covered by Part I of the assessment report	Strongly influenced by the Council
18	Assessment of a substantial modification of an aspect covered by Part I of the assessment report	Strongly influenced by the Council
19	Decision on a substantial modification of an aspect covered by Part I of the assessment report	Strongly influenced by the Council

20	Validation, assessment and decision regarding a substantial modification of an aspect covered by Part II of the assessment report	Strongly influenced by the Council
21	Substantial modification of aspects covered by Parts I and II of the assessment report	
22	Assessment of a substantial modification of aspects covered by Parts I and II of the assessment report – Assessment of the aspects covered by Part II of the assessment report	Influenced by the Council
23	Decision on the substantial modification of aspects covered by Parts I and II of the assessment report	Strongly influenced by the Council
24	Persons assessing the application for a substantial modification	
	Chapter IV: Application dossier	
25	Data submitted in the application dossier	Strongly influenced by both the Council and the Parliament
26	Language requirements	
27	Update by way of delegated acts	
	Chapter V: Protection of subjects and informed consent	
28	General rules	Strongly influenced by the Council and some changes occurred after the Triage negotiations
29	Informed consent	Strongly influenced by the Council and some changes occurred after the Triage negotiations
30	Informed consent in cluster trials	Included by the Triage
31	Clinical trials on incapacitated subjects	Influenced by the Council
32	Clinical trials on minors	Influenced by the Council
33	Clinical trials on pregnant & breastfeeding women	Included by the Council
34	Additional national measures	Included by the Council
35	Clinical trials in emergency situations	Strongly influenced by the Council
	Chapter VI: Start, end, temporary halt, and early termination of a clinical trial	
36	Notification of the start of the clinical trial and the end of the recruitment of subjects	Influenced by the Council
37	End of the clinical trial, temporary halt and early termination of the clinical trial and submission of the results	Strongly influenced by both the Council and the Parliament
38	Temporary halt or early termination of by the sponsor for reasons of subject safety	Strongly influenced by the Council
39	Update of the contents of the summary of results and summary for laypersons	Included by the Council

	Chapter VII: Safety reporting in the context of a clinical trial	
40	Electronic database for safety reporting	Strongly influenced by the Council
41	Reporting of adverse events and serious adverse events by the investigator to the sponsor	Strongly influenced by the Council
42	Reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency	Strongly influenced by the Council
43	Annual reporting by the sponsor to the Agency	Strongly influenced by the Parliament and some changes occurred after the Triage negotiations
44	Assessment by Member States	Strongly influenced by the Council
45	Technical aspects	Influenced by the Council
46	Reporting with regard to auxiliary medicinal products	
	Chapter VIII: Conduct of a clinical trial, supervision by the sponsor, training and experience, auxiliary medicinal products	
47	Compliance with the protocol and good clinical practice	Strongly influenced by the Council
48	Monitoring	Strongly influenced by the Council
49	Suitability of individuals involved in conducting the clinical trial	
50	Suitability of clinical trial sites	Influenced by the Council
51	Traceability, storage, return and destruction of investigational medicinal products	Influenced by the Council
52	Reporting of serious breaches	Influenced by the Parliament
53	Other reporting obligations relevant for subject safety	Strongly influenced by the Council
54	Urgent safety measures	Influenced by the Council
55	Investigator’s brochure	
56	Recording, processing, handling and storage of information	
57	Clinical trial master file	Strongly influenced by the Council
58	Archiving of the clinical trial master file	Influenced by the Triage
59	Auxiliary medicinal products	Influenced by the Council
	Chapter IX: Manufacturing and import of investigational medicinal products and auxiliary medicinal products	
60	Scope of this Chapter	
61	Authorisation of manufacturing and import	Strongly influenced by the Council
62	Responsibilities of the qualified person	Responsibilities of the qualified person

63	Manufacturing and import	Strongly influenced by the Council
64	Modification of authorised investigational medicinal products	
65	Manufacturing of auxiliary medicinal products	
	Chapter X: Labelling	
66	Unauthorised investigational and unauthorised auxiliary medicinal products	Influenced by the Council
67	Authorised investigational and authorised auxiliary medicinal products	
68	Radiopharmaceuticals used as investigational medicinal products or as auxiliary medicinal products for a medical diagnosis	
69	Language	
70	Delegated acts	
	Chapter XI: Sponsor and investigator	
71	Sponsor	Influenced by the Council
72	Co-sponsorship	
73	Principal investigator	Included by the Council
74	Legal representative of the sponsor in the Union	Strongly influenced by the Council
75	Liability	
	Chapter XII: Damage compensation	
76	Damage compensation	
	Chapter XIII: Supervision by Member States, Union inspections and controls	
77	Corrective measures to be taken by Member States	Influenced by the Council
78	Member State inspections	
79	Unions controls	Strongly influenced by the Council
	Chapter XIV: IT Infrastructure	
80	EU portal	Influenced by the Triage
81	EU database	Strongly influenced by both the Council and the Parliament
82	Functionality of the EU portal and the EU database	Included by the Council
	Chapter XV: Cooperation between Member States	
83	National contact points	
84	Support by the Agency and the Commission	Influenced by the Triage
85	Clinical Trials Coordination and Advisory Group	Strongly influenced by the Council
	Chapter XVI: Fees	
86	General principles	
87	One payment per activity per Member State	
	Chapter XVII: Implementing acts and Delegated acts	
88	Committee procedure	Strongly influenced by the Council

89	Exercise of the delegation	Strongly influenced by the Council
	Chapter XVIII: Miscellaneous provisions	
90	Specific requirements for special groups of medicinal products	Strongly influenced by the Council
91	Relation with other Union legislation	Strongly influenced by the Council
92	Investigational medicinal products, other products and procedures, free of charge for the subject	Influenced by the Council
93	Data protection	
94	Penalties	Included by the Triage
95	Civil and criminal liability	
	Chapter XIX: Final provisions	
96	Repeal	
97	Review	Included by the Triage
98	Transitional provisions	Included by the Triage
99	Entry into force	Strongly influenced by the Council

Table 3: Influence of the Council and Parliament

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

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