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ASSESSMENT OF THE FUNCTIONING OF THE “CLINICAL TRIALS DIRECTIVE” 2001/20/EC

PUBLIC CONSULTATION PAPER

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1. INTRODUCTION

In its Communication of 10 December 2008 to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on “Safe, Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector”¹, the Commission announced that an assessment would be made of the application of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use² (“**Clinical Trials Directive**”).

This assessment would consider, in particular, various options for further improving the functioning of the Clinical Trials Directive with a view to remedy shortcomings and unintended negative consequences while taking the global dimension of clinical trials into account.

2. CLINICAL TRIALS IN THE EU

2.1. Background

Clinical trials in the EU are defined as “investigations in humans intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy”.³

Clinical trials are an indispensable part of clinical research which, in turn, is essential to develop medicinal products, and to develop and improve medical treatment.

In the EU/EEA⁴, approx. 4 000-6 000 clinical trials are performed each year (cf. table 1). Approx. 64% of clinical trials are sponsored by the pharmaceutical industry and 36% are sponsored by other actors, such as academics.⁵ Those trials are aimed at improving the use of authorised medicines, but may also well be done with the intention of developing a medicinal product. Also the results of these

¹ COM(2008) 668 final.

² OJ L 121, 1.5.2001, p. 34.

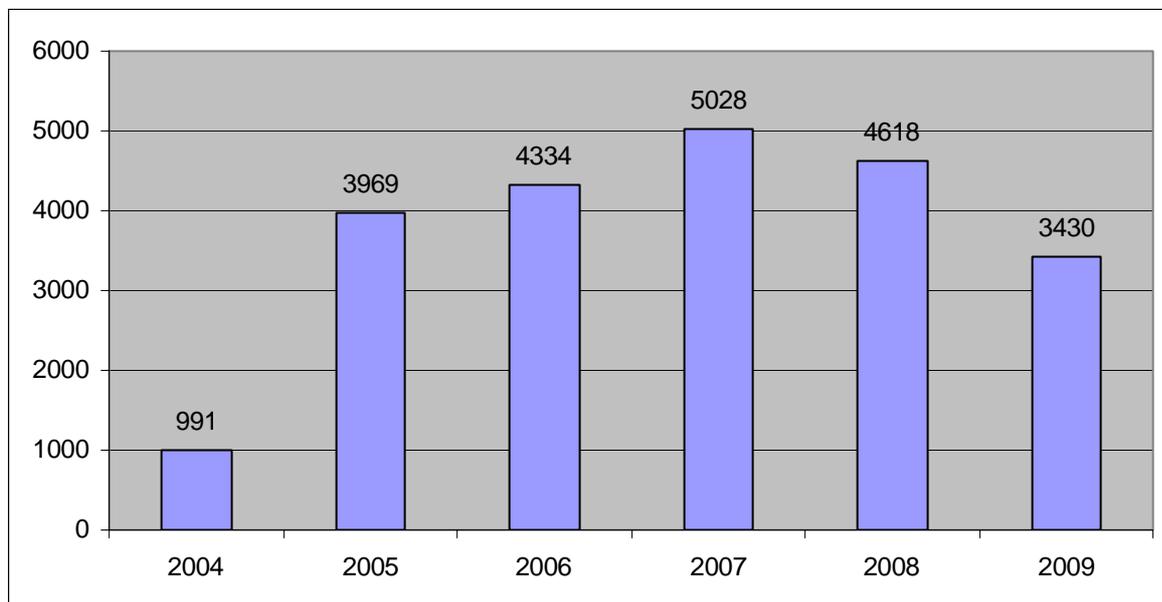
³ Article 2(a) of the Clinical Trials Directive.

⁴ For the purpose of this document, all references to EU or EU Member States shall include the EEA or EEA contracting States, unless indicated otherwise.

⁵ Source: EudraCT. When looking at clinical trial applications, the share of “commercial” sponsors is 80% (one clinical trial can imply up to 27 clinical trial applications - depending on the number of Member States concerned).

trials may subsequently be used in this context. In view of these figures, it is a fair assumption that approx. 60-80% of all clinical trials performed in the EU are intended to be subsequently used in the framework of marketing authorisation applications in the EU.

Table 1: Number of clinical trials applied for in the EU:⁶

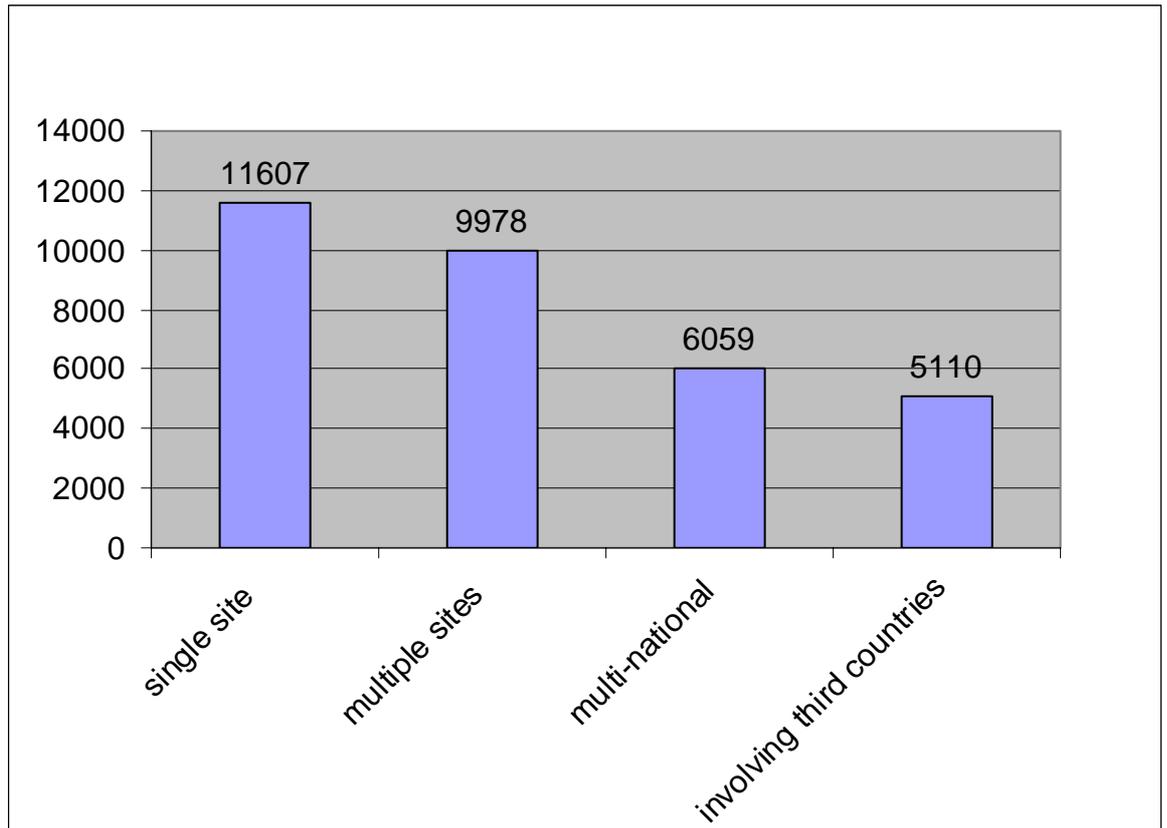


Approx. 25% of EU clinical trials are performed in more than one EU Member State (cf. table 2). This equals approx. 60% of all clinical trials applications in the Member States.

Table 2: Multi-site and multi-national clinical trials in the EU; clinical trials involving also third countries:⁷

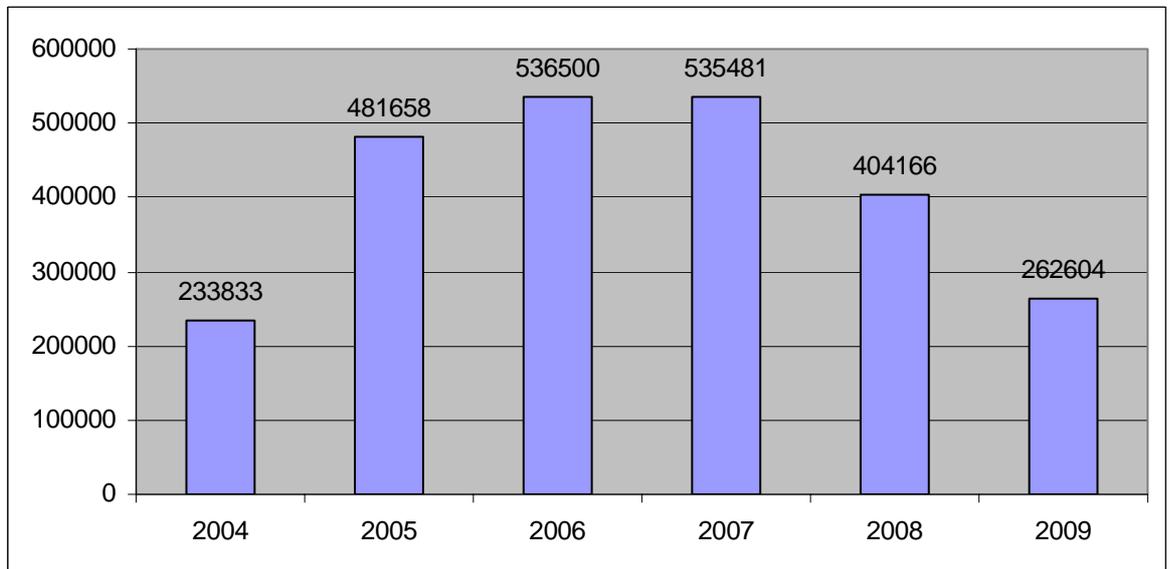
⁶ Source: EudraCT. Please note: These figures are clinical trials (i.e. per EudraCT number), *not* clinical trial applications in the Member States (Clinical trial applications are approx 45 000 since 2004). 2004-figures only as of 1 May 2004. 2009-figures only until end Sept. 2009.

⁷ Source: EudraCT. Please note: These figures are clinical trials (i.e. per EudraCT number), *not* clinical trial applications in the Member States (Clinical trial applications are approx 45 000 since 2004). 2004-figures only as of 1 May 2004. 2009-figures only until end Sept. 2009.



Each year, in the EU, there are approximately 500 000 clinical trials participants planned for inclusion in the clinical trials performed in the EU (cf. table 3).

Table 3: N° of planned clinical trials participants in EU:⁸



The risk-profiles of clinical trials vary considerably. They range from “first-in-human” trials of new molecules to the assessment and improvement of treatment with (a combination of) authorised medicines used in the authorised indication.

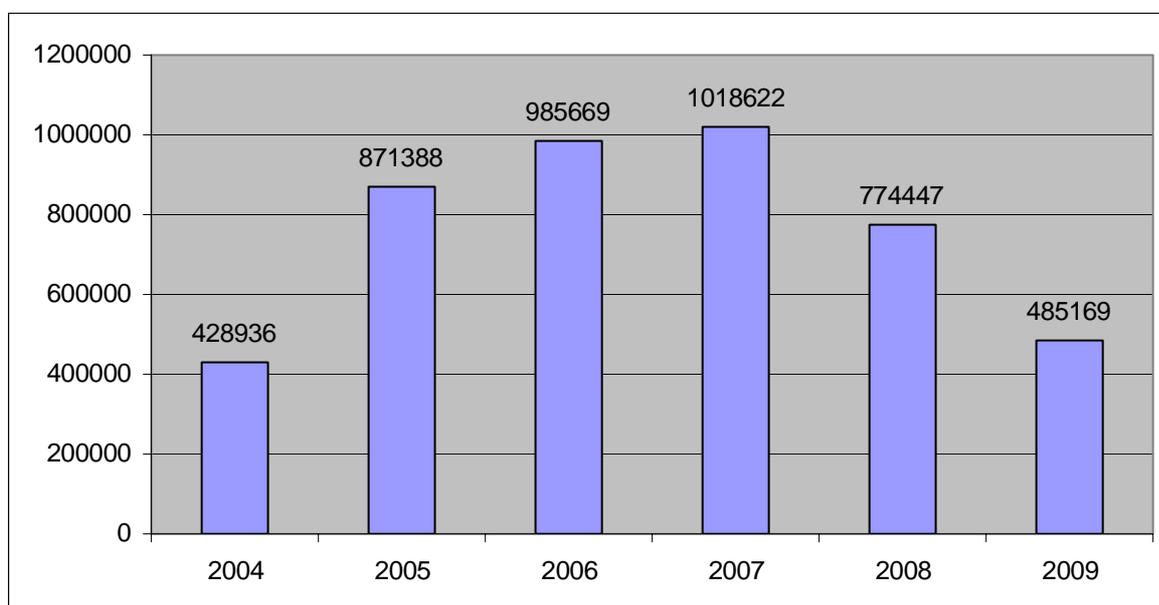
⁸ Source: EudraCT. Please note: 2004-figures only as of 1 May 2004. 2009-figures only until end Sept. 2009.

Indeed, in many cases, a clinical trial involves risks which are close to those of “usual medical care”.

Globalisation has had important impacts on clinical trials: About one quarter of all clinical trials in the EU are also performed in third countries (cf. table 2) with considerable degree of inclusion of 3rd country clinical trials participants (cf. table 4).

In response to this, international guidelines have been agreed on a variety on matters, including GCP⁹, structure and content of clinical trial reports¹⁰, choice of control groups, statistical principles, etc.¹¹ Many of the challenges in the regulation of clinical trials are faced by all regulators and legislators worldwide.¹² To this is added the challenge of achieving assurance of compliance with GCP of clinical trials performed in third countries. This latter aspect is being discussed in detail below.

Table 4: Total number of clinical trials participants planned (for clinical trials with at least one clinical trial site in the EU):¹³



⁹ http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm.

¹⁰ <http://www.emea.europa.eu/pdfs/human/ich/013795en.pdf>.

¹¹ See, for example, <http://www.emea.europa.eu/htms/human/ich/ichefficacy.htm>.

¹² As regards the U.S., reference is made to the ongoing efforts in the „Clinical Trials Transformation Initiative“ (<https://www.trialstransformation.org/>).

¹³ Source : EudraCT. Please note : 2004-figures only as of of 1 May 2004. 2009-figures only until end Sept. 2009.

2.2. The Clinical Trials Directive

Prior to the entry into force of the Clinical Trials Directive, the rules for performing clinical trials varied significantly in the Community as they were based on differing regulatory approaches in the Member States. Since 2004, clinical trials performed in the EU are regulated by the Clinical Trials Directive. The primary purpose of this Directive is to ensure:

- The protection of the health and safety of clinical trial participants;
- The ethical soundness of the clinical trial;
- The reliability and robustness of data generated in clinical trials; and
- Simplification and harmonisation of the administrative provisions governing clinical trials in order to allow for cost-efficient clinical research.¹⁴

This should be achieved while promoting high-quality research in the EU and the competitiveness of the European pharmaceutical industry.

Moreover, the conduct of clinical trials involves considerable inward investment to the Community in addition to trials funded by EU-sponsors.

Subsequently to its entry into force, the Clinical Trials Directive has been complemented with a Commission Directive¹⁵ setting out the principles of Good Clinical Practice (“GCP”). Moreover, there is a multitude of implementing guidance documents published in EudraLex, Volume 10,¹⁶ including the Guideline on “Good Clinical Practice – ICH E6”. This guideline has been agreed in the framework of the International Conference for Harmonisation (“ICH”) and is *de facto* recognised worldwide as *the* applicable standard for GCP.

In terms of substance, these Community rules aim at establishing *inter alia*:

- Harmonised procedures for the application and authorisation by the National Competent Authority (“NCA”) and Ethics Committee of a clinical trial;
- Harmonised provisions on the requirements for a clinical trial, including the rules for protection of the clinical trial participants;¹⁷
- Harmonised rules on reporting adverse events, and in particular suspected unexpected serious adverse reactions (“SUSARs”) during the clinical trial;

¹⁴ Cf. Whereas 10 of the Clinical Trials Directive.

¹⁵ Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (OJ L91, 9.4.2005, p. 13).

¹⁶ http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm

¹⁷ The Clinical Trials Directive defines clinical trials participants as „subjects“, cf. Article 2(i) of the Clinical Trials Directive. For the purpose of this document, the term “participants” shall be used.

- Rules on the manufacturing, importation and labelling of the investigational medicinal product (“**IMP**”); and
- Rules on inspection of clinical trials sites.

The Clinical Trials Directive does not address the question of whether and how the result of a clinical trial can be used, for example in an application for a marketing authorisation of a medicinal product. Instead this is regulated in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use¹⁸ (the “**Community Code for medicinal products**”). The Community Code for medicinal products provides that all clinical trials performed in the EU and submitted as part of a marketing authorisation application must comply with the Clinical Trials Directive. If the clinical trials have been performed in third countries, they must comply with rules and principles which are equivalent to those laid down by the Clinical Trials Directive. There are, however, allegations that these clear requirements are not always respected.

The Clinical Trials Directive provides for a database – **EudraCT** – which contains protocol-related information on clinical trials performed in the EU or contained in a Paediatrics Investigation Plan (“**PIP**”). This information is submitted in a dedicated form by the sponsor together with the request for authorisation of a clinical trial to the NCA of the Member State concerned, who submits this information to EudraCT. EudraCT is managed by the EMEA.

2.3. Sponsors involved in clinical trials

Clinical trials are performed under the responsibility of a sponsor. The types of sponsors vary greatly and range from large multinational pharmaceutical companies to small local pharmaceutical companies (often SMEs) and from large research organisations with well-organised structures to small, disseminated and cooperative structures with a lower level of dedicated resources. Note, that these structures are often interlinked: for example, research organisations may carry out clinical trials for pharmaceutical companies and clinical research and their publications may influence the development of medicinal products.

2.4. Authorisation by national competent authorities and Ethics Committees; inspections and surveillance

Clinical trials are subject to an authorisation by the NCA and the Ethics Committee of the Member State where the clinical trial is performed (hereinafter referred to as “**Member State concerned**”).

Clinical trials authorisation involves considerable resources on the part of the NCAs of Member States. Large Member States have approx. between 10 and 16

¹⁸ OJ L 311, 28.11.2001, p. 67, as amended.

staff¹⁹ (medical, pre-clinical, pharmaceutical assessors, data-entry staff and managerial staff); smaller Member States have approx. 3-6 staff.²⁰

The Clinical Trials Directive is based on the concept of one Ethics Committee opinion per Member State concerned. However, several Member States maintain a decentralised system where the single Ethics Committee opinion is based on the opinion of several local committees. As a consequence, in the EU there are approx. 1 900 Ethics Committees²¹ involved in the assessment of clinical trials.

Apart from this *ex-ante* control, regulatory compliance is verified by means of inspections of clinical trials sites by NCAs. Since the entry into force of the Clinical Trials Directive, there have been approx. 1 200 inspections in the Community.²² Clinical trials in third countries are only inspected in the framework of marketing authorisation procedures. For examples, in the case of centralised authorization procedures for medicinal products, the Committee for Medicinal Products for Human Use (“CHMP”) has requested, in 2008, 45 inspections. Twenty-one inspections were performed in the EU, eight in North America and 16 in other third countries.

2.5. Achievements but also shortcomings

The Clinical Trials Directive has brought about important improvements in safety and ethical soundness of clinical trials in the EU, as well as in the reliability of clinical trials data. This has been confirmed in a large number of fora. For example, in the Commission/EMA clinical trials conference in October 2007²³ a large majority of attendees acknowledged that the Clinical Trials Directive had resulted, overall, in a better protection of clinical trial participants.²⁴

Moreover, the Clinical Trials Directive has greatly improved cooperation of NCAs, who meet regularly in three settings: the “Ad-hoc group on the implementation of the 'Clinical Trials Directive' 2001/20/EC”, which is chaired by the Commission, and the inter-governmental “Clinical Trials Facilitation Group”, which is organised and chaired by Member States, and the “GCP Inspectors Working Group”, which is organised and chaired by the EMA.

Consultation item n°1: Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of Clinical Trials Directive?

¹⁹ DE: 33, FR: 18, UK: 10, SE: 16 (Source: Documentation submitted to the Heads of Medicines Agencies for their meeting on 10/11 July 2008).

²⁰ EE: 1, LV: 6, AT: 5, NO: 6, MT: 2, LT: 4, IE: 5, HU: 4, CY: 4 (Source: Documentation submitted to the Heads of Medicines Agencies for their meeting on 10/11 July 2008).

²¹ ICREL, p. 95.

²² EMA, Annual 2008 Report on the GCP Inspectors Working Group Activities, 2 December 2008 (Doc. Ref. EMA/INS/GCP/594196/2008)

²³ EMA/565466/2007: http://www.eortc.be/services/doc/EUCTD/EC-EMA_report_CT_20071003.pdf

²⁴ Commission-EMA conference report, p. 26.

Notwithstanding this progress, during the above-mentioned Commission/EMA conference, there was also a widespread criticism that the Clinical Trials Directive has led to a significant decline of the attractiveness of patient-oriented research and related studies in the EU, which greatly reduces competitiveness in Europe in the field of clinical research thus having a negative impact on the development of new and innovative treatments and medicines.

This negative effect has also been discussed in a range of publications drawing a picture of an increase in bureaucracy and costs, and a reduction of important research activities.²⁵ The High Level Group of Independent Stakeholders on Administrative Burdens (“Stoiber Group”) has highlighted, in its Recommendations of 5 March 2009,²⁶ the negative impact of the Clinical Trials Directive in terms of administrative costs.

In order to gain a clearer picture, the Commission launched, already in 2008, a comprehensive study on “Impact on Clinical Research of European Legislation” (“ICREL”) as part of the 7th Framework Programme. ICREL was a longitudinal, retrospective, observational and comparative study to assess the impact of the Clinical Trials Directive on the number, size and nature of clinical trials, on workload, required resources, costs and performance. Mean differences between 2003 (i.e. prior to the entry into force of the Clinical Trials Directive) compared to 2007 were assessed. ICREL concluded that:

- with the exception of one Member State, there has been no decrease in clinical research activity in the EU;
- performing clinical trials, on the other hand, has become considerably more difficult and costly.

More details on the findings of the study can be obtained here: <http://www.efgcp.be/icrel/>.

Moreover, the European Science Foundation has worked, in the framework of the initiative “Forward look - Investigator-driven clinical trials” on a set of recommendations to strengthen clinical research in Europe, which address comprehensively the impact of the Clinical Trials Directive on investigator-driven clinical trials.²⁷

²⁵ Cf. the literature review in ICREL (pp. 25-43); However, there are also publications which take a more nuanced approach when discussing the negative impact of the Clinical Trials Directive (cf. Berendt et al., Effect of European Clinical Trials Directive on academic drug trials in Denmark: retrospective study of applications to the Danish Medicines Agency 1993-2006, BMJ, published online on 6 December 2007)

²⁶ http://ec.europa.eu/enterprise/admin-burdens-reduction/highlevelgroup_en.htm

²⁷ http://www.esf.org/index.php?eID=tx_nawsecuredl&u=0&file=fileadmin/be_user/publications/IDCT.pdf&t=1254483557&hash=04981b7ce045d7243538c81f143c840b

3. KEY ISSUE N°1 TO BE ADDRESSED: MULTIPLE AND DIVERGENT ASSESSMENTS OF CLINICAL TRIALS

3.1. The issue

The Clinical Trials Directive aims at harmonising the regulatory framework for clinical trials. This is critically important in the area of clinical trials because they are very often performed in more than one Member State, the results may be used in marketing applications for medicines throughout the Community, and IMPs may have been produced in a different Member State from that of the clinical trial.

Therefore, the Clinical Trials Directive sets out common rules for the authorisation regime by the NCA. However, experience shows that these requirements are applied very differently by the respective NCAs of the Member States concerned. While the broad concepts are identical, when dealing with the details of the request for authorisations many different, conflicting points are brought up by the NCAs of the Member States concerned.

It has to be pointed out that there are relatively few clinical trials where the application of the regulatory framework leads ultimately to divergent decisions in different Member States. However, in practice, sponsors have to respond to the various required changes, adapt their protocol in view of diverging assessments by the NCAs or cannot pursue the envisaged clinical trial any further in one or more Member States.

To this adds that each clinical trial is subject to an assessment by two distinct bodies, the NCA and the EC of each Member State concerned. As the scopes of the respective assessments are not coherently separated in the Community, it is difficult for NCAs of different Member States concerned to cooperate in the assessment procedure. This adds to the complication of the authorisation of clinical trials by NCAs in the Community.

Consultation item n°2: Is this an accurate description of the situation? What is your appraisal of the situation?

3.2. Weaknesses

The following weaknesses have to be highlighted:

- First, the administrative costs for clinical trials, and thus clinical research, increase without added value. According to ICREL, staff needs in pharmaceutical companies for administrative work for submitting a request for authorisation of a clinical trial has doubled compared to the situation prior to the entry into force of the Clinical Trials Directive.²⁸ Indeed, it is very labour-intensive and costly to multiply largely identical administrative procedures for multinational clinical trials – and these costs increase even further if requirements differ for the different clinical trials. Sponsors spend a great deal of time retrieving the relevant information, modifying it, and writing the request for authorization. Large EU-based sponsors usually have dedicated departments

²⁸ ICREL, p. 130.

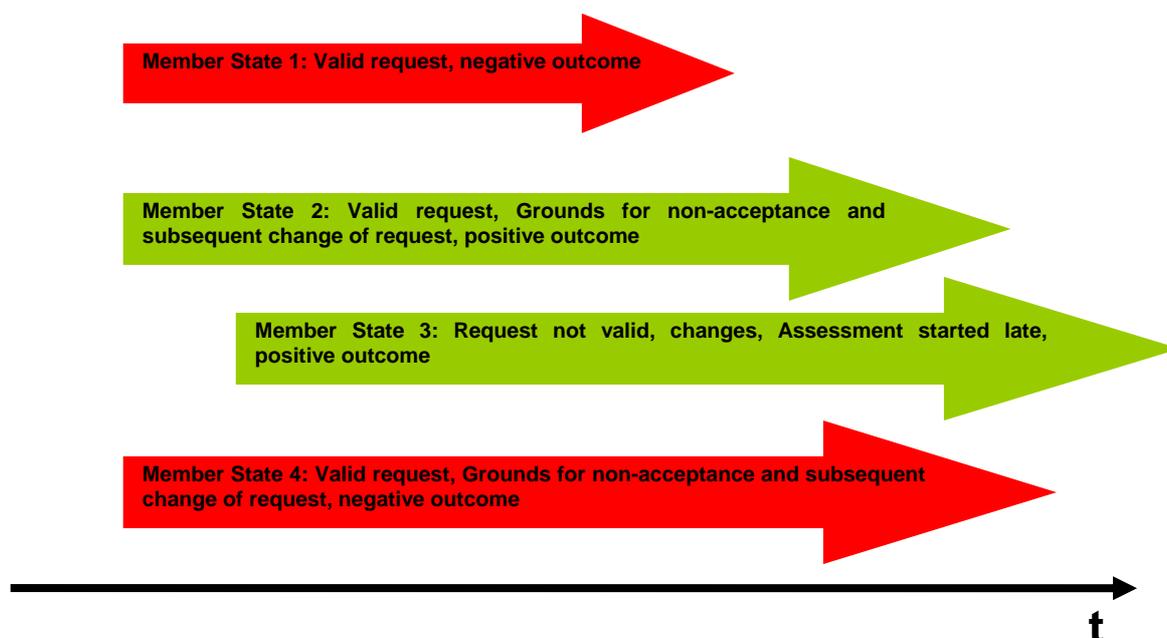
with the necessary resources to track differences in national requirements. However, for SMEs, academic sponsors, and third-country sponsors these costs can reach prohibitive levels. The negative consequences of the fragmentation of the authorisation regime have also been highlighted by the High Level Group of Independent Stakeholders on Administrative Burdens (“Stoiber Group”) in their Recommendations of 5 March 2009.²⁹

- Secondly, a “patchwork” of separate assessment procedures of clinical trials by the various national competent authorities of the Member States concerned does not necessarily ensure the highest-possible standard of the assessment, as the necessary specific expertise might not always be readily available in all the Member States concerned. This goes to the detriment of safety of the clinical trials participants.
- Thirdly, the inconsistent approach to the Clinical Trials Directive leads to longer delays for starting the clinical trial (“first patient in”), thus depriving patients of the results of clinical research. In order to roll out a clinical trial, based on one protocol, in every Member State planned, the sponsor has to wait – apart from the approval by the EC - for the authorisation from the NCA of each of the Member States individually. However, different national competent authorities may require additional information or advance differing reasons for non-acceptance (see, for illustrative purposes, the schema 1). This leads to a situation where the time-lag between the finalisation of the clinical trials protocol and the “first patient in” becomes unnecessarily long. Since the entry into force of the Clinical Trials Directive, this delay has increased by 90%³⁰ and is now reaching in average approx. 152 days. This, in turn, means that patients do not have access to new, innovative treatments, and the costs for the sponsor increase.

Schema 1: Example: Submission of request for authorisation in 4 Member States

²⁹ http://ec.europa.eu/enterprise/admin-burdens-reduction/highlevelgroup_en.htm

³⁰ ICREL, p. 128.



- Fourthly, NCAs in the Member States do not use resources efficiently. The available resources in NCAs are used in multiple assessment of the same information in different Member States. Indeed, the number of staff for scientific evaluation as well as administrative tasks has doubled compared to the situation prior to entry into force of the Clinical Trials Directive.³¹ This is not surprising considering that, for an identical clinical trial, the same assessment is presently being carried out (and the report drafted) separately by all national competent authorities of the Member States concerned.

Consultation item n°3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

3.3. Options to address the issue as regards the assessment by NCAs

3.3.1. *Reliance on voluntary cooperation of NCAs*

With regard to this option, it has to be highlighted that Member States, on the basis of a voluntary cooperation, have started to cooperate and to jointly assess requests for authorisation of clinical trials under the Voluntary Harmonised Procedure – “VHP”. This procedure was set up by Member States without the involvement of the Commission or the Community legislator. It is based on the concept of a voluntary parallel submission to all participating Member States of a dossier requesting authorisation of a clinical trial.³²

³¹ Source: ICREL (p. 79, 80).

³² http://www.hma.eu/uploads/media/VHP_public_CBB_22_Dec_08_hk_jan12.pdf

3.3.2. *Community-wide streamlining of NCA-authorisation process for clinical trials*

Today, the actual assessment of a request for authorisation of a clinical trial is done independently by the NCAs of the various Member States concerned. The legislation does not provide for a mechanism whereby the Member States concerned are obliged to reach a common finding as regards a clinical trial involving different Member States.

According to this option, this authorisation process would be changed so as to ensure a strong cooperation of Member States.

3.3.2.1. Streamlining the procedures

Different degrees could be considered:

(a) According to this option, the Member States concerned would have to get to a common agreement as to whether the clinical trial can be authorised for the Member States concerned. The authorisation decision would then be issued either by the NCAs individually or by the Community for the Member States concerned. To ensure added value in terms of resources for assessments in Member States, one would have to ensure that:

- The assessment is done only by one of the Member States concerned, hereinafter referred to as reference Member State;
- The reference Member State would draw up the assessment of the clinical trial. The other Member State concerned would be consulted and could assist in this assessment, for example by providing additional expertise with regard to certain products or product categories;
- The assessment of the reference Member State would be applicable for the clinical trial in all Member States concerned. In case of disagreement by another Member State, a clear decision making procedure would have to be established.

This option would ensure that the application is based on an identical interpretation and application of the Clinical Trials Directive. It would build on experiences with a similar approach in the “decentralised procedure”/“mutual recognition procedure” for marketing authorisations. In particular, in case of disagreement amongst Member States, a sort of “arbitrage procedure” would have to be set up.

(b) According to this option, there would be an authorisation of a clinical trial for the entire Community. This assessment would be performed by one body. The authorisation would be issued – as regards the issues assessed by the NCAs – at

Community level drawing on the scientific expertise of the EMEA and decision-making powers of the Commission in close cooperation with Member States.

The authorisation would be valid throughout the Community and the clinical trial could be rolled out in the entire EU without additional follow-up authorisations of additional Member States concerned.

This option would thus be a genuine one-stop shop for authorisations of clinical trials performed in the Community while at the same time closely involving NCAs.

Regarding medicinal products falling within the scope of the Community authorisation, this option would lead to a “connection” and “continuum” between the authorisation process for clinical trials throughout the development process of a medicinal product, and the marketing authorisation of a medicinal product.

3.3.2.2. Scope for streamlining

As regards the scope of such an authorisation procedure (which could be optional, the choice whether to opt for this procedure being left to the sponsor) there are a number of options that could be considered. The scope could cover:

- All clinical trials performed in the Community;
- Only some clinical trials performed in the Community: To limit the number of such procedures, it could be considered to restrict the scope of this policy option according to various criteria, such as
 - Whether the clinical trial is intended to be multinational, i.e. performed in more than one Member State concerned, or involving a significant number of Member States; or
 - Whether the IMP has certain characteristics, for example those for which a marketing authorisation issued by the Community is obligatory.³³

Consultation item n°4: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

³³ Cf. the Annex to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L136, 30.4.2004, p. 1), as amended (<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:02004R0726-20090420:EN:NOT>)

3.4. Options to address the issue as regards the assessment by Ethics Committees

Ethical issues clearly fall within the ambit of Member States and should remain there. Notwithstanding this, it is worthwhile considering how cooperation and exchange amongst national Ethics Committees, as well as procedural best practices, could be promoted in order to improve the ethical review of a clinical trial.

3.4.1. *One-stop shop for submission of assessment dossier*

This option would introduce a one-stop shop as regards the submission of the request for authorisation of a clinical trial to the NCA and Ethics Committee. It would thus reduce the administrative burden of multiple submission of information to separate actors, while maintaining the role of independent ethics review in accordance with international guidelines and principles.

3.4.2. *Strengthening networks of national Ethics Committees involved in multinational clinical trials*

This option would mean working towards a stronger cooperation of Ethics Committees within the process of assessments of requests for clinical trials application. This could build on their existing networks in the EU. It would allow Ethics Committees to assess requests for authorisation of clinical trials, thereby exchanging views, best practices and experiences at an operational level. This would not mean that any national committee could be “outvoted”: Concerning ethical issues, Member States could “opt out” as regards the final result of an assessment of a request for authorisation of a clinical trial.

3.4.3. *Clarifying the respective scope of assessment of NCA and Ethics Committees*

According to this option the Clinical Trials Directive would be revised to ensure that there is legal clarity of the respective scope of assessment by NCAs and Ethics Committees in the Member States. It would mean a clearer identification of their respective roles and responsibilities in order to avoid “overlaps” in the assessment process of clinical trials by the NCAs, thus facilitating their cooperation.

<p>Consultation item n°5: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?</p>

4. KEY ISSUE N°2 TO BE ADDRESSED: INCONSISTENT IMPLEMENTATION OF THE CLINICAL TRIALS DIRECTIVE

4.1. The issue

As set out above, the Clinical Trials Directive aims at an exhaustive harmonisation of the regulatory framework for clinical trials. However, while Community

legislation strives for harmonisation, it has achieved this aim only to a limited extent. This is due to the inconsistent application of the Clinical Trials Directive.

There are multiple examples of inconsistent application of the Clinical Trials Directive. Three prominent examples shall be set out in more detail:

4.1.1. Example 1: Substantial amendments

The aim of the legislation was to limit changes to those which are substantial in terms of, for example, safety for the participant. However, there are many differences between Member States in the interpretation of what could be considered as a “substantial amendment”. This leads to a situation whereby the company regards something as a substantial change more often than it actually should in order to avoid problems of non-compliance. As a result more notifications are made than are necessary. Today, each year, approx. 21 000 substantial amendments are notified to the national competent authorities every year.³⁴ This is a three-fold increase of the number of substantial amendments compared to 2003, i.e. prior to the entry into force of the Clinical Trials Directive.

4.1.2. Example 2: Reporting of SUSARs

According to the Clinical Trials Directive, all relevant information about suspected unexpected serious adverse reactions (“**SUSARs**”) have to be reported to the NCA and the EC of the Member State concerned.

Member States must see to it that these SUSARs are reported to a Community database.

While these provisions seem straightforward, they have led to a multitude of different regimes in the Member States, which has led in turn to multiple reporting of the same SUSAR, lack of reporting and unreliability of the Community data on SUSARs. Moreover, the number of SUSARs received diverges disproportionately amongst some Member States.³⁵

The different reporting regimes impact on data quality either by duplicate reports being generated or by some reports not being submitted at all, thus reducing the NCAs' ability to monitor safety data and thereby address potential risks for clinical trial participants.

Today, in average, each national competent authority receives approx. 5 700 SUSAR reports per year.³⁶ This is a 6-fold increase compared to 2003, while the number of clinical trials has not changed significantly since 2003. This development may have a variety of explanations –

³⁴ Source: ICREL (2007: 20 986 substantial amendments)

³⁵ ICREL, Supporting Statistical Report CA, p. 121, Figure CA 102 (http://www.efgcp.be/downloads/icrel_docs/ICREL_Statistical_Report_CA.pdf)

³⁶ ICREL, p. 81. Large Member States receive approx. 45 000 SUSAR reports per year (DE: 40 000, FR: 50 000).

however, one cannot exclude the possibility that this development is due to multiple reporting and over-reporting.

4.1.3. *Example 3: Scope of the Clinical Trials Directive*

The Clinical Trials Directive only applies to “interventional trials”, not to so-called “non-interventional”³⁷ ones. Non-interventional trials are those where the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation; the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice; the prescription of the medicine is clearly separated from the decision to include the patient in the study; no additional diagnostic or monitoring procedures are applied to the patients, and epidemiological methods are used for the analysis of the collected data.

Non-interventional trials are going to be covered in the future by the revised Community legislation on pharmacovigilance. A proposal to this effect has been submitted by the Commission to the Community legislator in December 2008.³⁸

The purpose of excluding non-interventional trials from the scope of the Clinical Trials Directive is that non-interventional trials typically have a lower risk than interventional trials. Moreover, this restriction is meant to exclude medical activities which are normal clinical practice and, as such, part of the general medical surveillance of a patient.

The results of observational trials cannot be used as basis in a request for a marketing authorisation.

Thus, the “borderline” between interventional and observational trial is critical. This “borderline” is defined in the Clinical Trials Directive and further elaborated in guidance documents published by the Commission.

However, in the daily application of the definition and the guidelines, there are frequently cases where the borderline is drawn differently in individual Member States. This holds in particular with regard to the last qualifying of the abovementioned definition (“*no additional diagnostic or monitoring procedures are applied to the patients, and epidemiological methods are used for the analysis of the collected data*”).

This creates a situation where a trial is considered as “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.

³⁷ Also referred to as “observational” trials.

³⁸ COM(2008) 665 final (Chapter 4).

Consultation item n°6: Is this an accurate description of the situation? Can you give other examples?

4.2. Weaknesses

The following weaknesses have to be highlighted:

- Insufficient patient protection: For example, an incoherent regime of transmitting and processing information on SUSARs leads to an increased risks of undetected factors influencing the risk-benefit balance;
- Increase of administrative costs: The divergences in application have created an important increase of administrative costs for sponsors. ICREL has shown that staff needs to perform administrative tasks have increased significantly with the entry into force of the Clinical Trials Directive: In particular, “academic”/“non-commercial” sponsors have experienced increases by approx. 90%.³⁹

Consultation item n°7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

4.3. Options to address this issue

A number of options could be envisaged to address this issue:

4.3.1. *Reviewing the Clinical Trials Directive with a view to clarifying provisions, where necessary*

This option would imply a legislative procedure whereby the Clinical Trials Directive would be amended with a view to clarifying certain provisions, such as, *inter alia* the rules on:

- the procedures and modalities of reporting SUSARs to the Community database ‘Eudravigilance – Clinical Trials Module’;
- the follow-up and assessment to the annual safety report (“ASR”) on the part of the NCA (and Ethics Committee);
- the *regime* for notifying substantial amendments to the NCA/EC if the respective body had not been involved in the assessment of the aspect amended; as well as timelines for assessment of the substantial amendment by the NCA.

4.3.2. *Adopting the text of the Clinical Trials Directive in the form of a Regulation*

This option would be mean repealing the Clinical Trials Directive and re-adopting its content in the form of a Regulation. Unlike a Directive, which only binds Member States as to the result to be achieved while

³⁹ ICREL, p. 144.

leaving to them the choice of form and methods,⁴⁰ a Regulation would remove national transposition measures, thereby ensuring that NCAs and Ethics Committees base their assessment on an identical text, rather than on diverging national transposition measures.

Moreover, the legal form of a Regulation would make it possible to address the submission process for the request for authorisation and notification of a substantial amendment in greater detail in a binding manner.

Consultation item n°8: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case-by-case basis?

5. KEY ISSUE N°3 TO BE ADDRESSED: REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS

5.1. The issue

The Clinical Trials Directive, and its implementing guidelines, has brought in regulatory obligations and restrictions which, in some cases, are widely considered as not matching practical considerations and requirements.

5.2. Examples

5.2.1. Requirements not always risk-commensurate

Clinical trials as defined in the Clinical Trials Directive are very varied: The actual risk of a clinical trial for the participant in that trial depends on a wide range of factors, including:

- extent of knowledge and prior experience with the IMP;
- patient population is involved;
- whether or not the IMP is already authorised in the EU or elsewhere;
- whether the clinical trial is performed with an authorised medicine in approved indications or for other therapeutic uses; etc.

Thus, the risk for a clinical trial participant varies considerably depending on the actual circumstances of the clinical trial. Different types of trials carry different risks and thus require different regulatory safeguards.

The Clinical Trials Directive does not discriminate sufficiently in this respect. Too often, it applies the “broad brush”, and adopts a “one-size-

⁴⁰ Cf. Article 249 3rd paragraph of the Treaty establishing the European Community.

fits-it-all” approach. This undifferentiated approach is visible in several areas. Examples include insurance requirements, safety reporting (including SUSAR reporting and yearly reporting of suspected serious adverse reactions – “SARs”), labelling of the IMP, and monitoring of clinical trial sites and respective data collection process.⁴¹

Consultation item n°9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

5.2.2. *Requirements not always adapted to the practical circumstances*

To this adds that the Clinical Trials Directive establishes requirements which, albeit theoretically justified, are difficult to meet in practice. The most important aspect concerns the concept of a single sponsor. The Clinical Trials Directive is based on the concept of one single sponsor per (multi-national) clinical trial. This concept is meant to ensure that national competent authorities have a unique addressee for requests for information regarding a multi-national clinical trial. While this is a very legitimate objective, in practice, the solution of a “single sponsor” creates major difficulties: It is difficult for sponsors, in particular “academic”/“non-commercial” sponsors, to take responsibilities for clinical trials performed in another Member State. Equally, it is difficult for national competent authorities to enforce the Clinical Trials Directive vis-à-vis sponsors located in another Member State.⁴²

Consultation item n°10: Do you agree with this description? Can you give other examples?

5.3. Weaknesses

The consequences of these shortcomings are increased costs for conducting clinical research in Europe, while these costs are not necessary in order to achieve the objective of the Clinical Trials Directive, i.e. patient safety, ethical soundness of the clinical trial, and quality of research.

Moreover, these issues create disincentives to conduct clinical research in the EU. This consequence is felt in particular by so-called “academic”/“non-commercial” sponsors. While no clear definition exists, “academic”/“non-commercial” sponsors usually do not hold a marketing authorisation and do not intend to apply for it (as is the case with pharmaceutical companies). Clinical trials sponsored by “academic”/“non-commercial” sponsors are not necessarily performed with the intention to generate data to support an application for a marketing authorisation of a medicinal product.

The long-term consequence is that patients are deprived of innovative treatments and the competitiveness of European clinical research is reduced.

⁴¹ These issues have been voiced in numerous for a in recent years. Cf. also the report of the Commission/EMA clinical trials conference in October 2007, p. 19, 25 and 31.

⁴² Report of the Commission/EMA clinical trials conference in October 2007, p. 17.

5.4. Options to address this issue

5.4.1. *Review of existing implementing guidelines*

Following the adoption of the Clinical Trials Directive, the Commission and the Agency, in close cooperation with Member States and stakeholders, have developed – in accordance with the mandate given by the co-legislator – implementing guidelines on the various provisions of the Clinical Trials Directive. These guidelines are very technical and extensive and published in Volume 10 of “EudraLex - The rules governing medicinal products in the European Union”.

This option would involve a revision of some of these implementing guidelines in order to ensure that the implementing rules would be more risk-adapted. This would address the following aspects in particular:

- The rules for safety reporting;
- The rules for labelling of the IMP;
- The details of the rules for reporting of SUSARs;
- The content of the clinical trial application.

However, this option would not address issues which are directly vested in Community legislation, such as requirements for insurance, the requirement of a single sponsor per trial, and certain rules for reporting.

Therefore, this option could also be complementary to a more far-reaching change of applicable rules, thus addressing regulatory shortcomings in the interim.

Consultation item n°11: Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?

5.4.2. *Review of the existing Directive and adaptation of the requirements to practical necessities*

This option would consist in reviewing the Clinical Trials Directive in order to adjust it to experiences.

The advantage of this option would be that issues can be addressed which are grounded in the legislation itself, i.e. areas where changes to implementing guidelines would not have effect.

Consultation item n°12: In what areas would an amendment of the Clinical Trials Directive be required in order to address the issue? If this was addressed, can the impacts be described and quantified?

5.4.3. *Review of the existing Directive and excluding clinical trials of “academic” sponsors from the scope of the Directive*

This option would mean an outright exclusion of so-called “academic” sponsors from the rules of the Clinical Trials Directive. This would mean that national rules set by Member States would apply. This would also mean that, in accordance with the Community legislation set out above, results of these clinical trials cannot be referred to in the framework of an application for a marketing authorisation in the EU.

Consultation item n°13: Would you agree to this option and if so what would be the impact?

6. KEY ISSUE N°4 TO BE ADDRESSED: ADAPTATION TO PECULIARITIES IN TRIAL PARTICIPANTS AND TRIAL DESIGN

6.1. The issue

Clinical trials are performed in many different settings, and with different groups of trial participants. This raises the question whether the various constellations are adequately addressed.

In this respect, one example relates to clinical trials in the paediatric population, where rules on clinical trials have to ensure the protection of individual children, while ensuring a favourable environment for clinical research in this area. This is crucial for the development of treatments and the assessment of the safety and efficacy of medicines in the paediatric population. With regard to paediatric clinical trials, there is a risk that clinical research to develop treatments and medicines for children is hindered or unnecessarily burdensome.⁴³ This could run counter to the key objective of the recent legislation on paediatric medicines, which is to ensure that medicines address specifically the need of the paediatric population.⁴⁴

Another example relates to clinical trials in emergency situations. The regulation of clinical trials is based on the concept of informed consent by the clinical trials participant. In practice, the information provided to a subject prior to their informed consent is extensive, covering several pages and lasting up to two hours.

However, in an emergency situation (for example, a stroke or a heart attack), it may not be feasible in practice to obtain informed consent. Since the entry into force of the Clinical Trials Directive on 1 May 2004, in the EU, 532 emergency

⁴³ 8.5% of all clinical trials applied for in the EU since 1 May 2004 involved paediatric population (Source: EudraCT).

⁴⁴ Cf. *whereas* no. 4 and 7 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.

clinical trials have been applied for, which represents 2.38% of all clinical trials performed since then in the EU.⁴⁵

This situation is not addressed in the rules for obtaining informed consent in the Clinical Trials Directive.

Since the entry into force of the Clinical Trials Directive there has been a debate in the EU about whether the Clinical Trials Directive was *de facto* aiming at a ban on clinical trials for medicinal products used in the context of an emergency situation, as it is usually not possible to obtain informed consent from the patient or the legal representative for practical reasons.

There is general agreement that, in principle, clinical trials of this kind are necessary in order to ensure a high level of human health, which is a fundamental policy aim of the Community (Article 152(2) EC Treaty). The need for clinical trials in emergency situations is also reflected in various international guidelines, such as in the World Medical Association's Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (as amended in 2008)⁴⁶ and the Guidelines on good clinical practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH E6).⁴⁷

Indeed, it would be a very serious setback for clinical research if medicinal research in emergency situations proved to be impossible in Europe.

In view of these considerations, some ten Member States have legislation in place allowing clinical trials in emergency situations. Other Member States have administrative guidelines on how to deal with these trials, in order to ensure that they can be performed. However, these legal requirements lead to a situation where there are divergent standards for good clinical practices in emergency

⁴⁵ Source: EudraCT.

⁴⁶ Point 29 („*Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.*”)

⁴⁷ Point 4.8.15 („*In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.*”)

situations in the EU. This was also acknowledged in the Commission/EMA clinical trials conference in 2007.⁴⁸

6.2. Option to address this issue – adapting the Clinical Trials Directive

Specific constellations in terms of clinical trial design and clinical trial participants could be considered in a review of the Clinical Trials Directive.

As regards paediatric clinical trials, the recent legislation on paediatric medicines⁴⁹ has introduced various measures specifically aimed at promoting clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants. Measures include ensuring transparency of clinical trials⁵⁰ in order to avoid unnecessary duplication of trials, and the creation of a “*European network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population*”.⁵¹

Consultation item n°14: In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

Emergency clinical trials could be addressed by introducing a regime which, on the one hand, ensures the safety and ethical soundness of clinical trials, while making it possible to perform emergency clinical trials where necessary.

In terms of substance, it is crucial to ensure a balance between the protection of the participant in terms of ethical soundness and the practical impossibility of obtaining informed consent prior to the start of the clinical trial. It is noteworthy that many countries have reached such a balance, which usually implies a waiver of the need to obtain informed consent from the clinical trial participant/its legal representative subject to very strict conditions.

Consultation item n°15: Should this issue be addressed? What ways have been found in order to reconcile patient’s rights and the peculiarities of emergency clinical trials? Which approach is favourable in view of past experiences?

⁴⁸ Conference report, p. 29.

⁴⁹ Cf. Regulation (EC) No 1901/2006.

⁵⁰ Information contained in the clinical trials database EudraCT is going to be publicly available in 2010. More information is available here: http://ec.europa.eu/enterprise/pharmaceuticals/clinicaltrials/clinicaltrials_en.htm

⁵¹ Article 44 of Regulation (EC) No 1901/2006; The EMA has set up an implementing strategy for this network (<http://www.ema.europa.eu/pdfs/human/paediatrics/54352307en.pdf>).

7. KEY ISSUE N°5 TO BE ADDRESSED: ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES (“GCP”) IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

7.1. The issue

Clinical trials are performed in the EU and in third countries. About 25% of all clinical trials performed in the EU do also involve at least one third country.⁵² 65% of all data/patients submitted in pivotal clinical studies in the framework of an application for an EU-wide marketing authorisation are generated in third countries.⁵³ U.S.-led research on this phenomenon shows that scientific articles reporting the results of clinical trials increasingly refer to clinical trials outside the U.S. and Europe.⁵⁴

Clearly, there can be valuable benefits in conducting trials in third, non-OECD countries. Global clinical research helps to respond to global questions about the safety and efficacy of medicinal products and medicinal treatment. Research in third countries is needed, so that specific situations can be taken into consideration. Moreover, clinical research in third countries allows capacity-building, and the sharing of know-how and knowledge.

The following are some of the many reasons for EU-based industry to conduct clinical research outside the EU:

- The quality of clinical trials conducted in non-OECD third countries is not intrinsically worse. Moreover, in recent years, intellectual property protection in third countries has been strengthened;
- In addition, the pharmaceutical market in non-OECD third countries is becoming increasingly attractive for pharmaceutical industries. This could create a need for conducting clinical trials in those countries for regulatory or scientific reasons;
- Also, in some non-OECD third countries, costs for staff and personnel (physicians, nurses, and study coordinators) may be lower. This is relevant, as clinical research costs are largely driven by human labour;
- Finally, conduct of clinical trials in non-OECD countries means access to more potential clinical trial participants.

⁵² Source: EudraCT.

⁵³ In the four years from 2005 to 2008, 4 146 pivotal clinical trials have been submitted to the EMEA as part of central marketing authorisations. This involved 179 741 patients recruited in the EU. Of the 4 146 pivotal clinical trials, 613 (involving 167 481 patients) had been performed in North America (CAN and U.S.), and 2 171 (involving 125 798 patients) in other third countries. These third countries include in particular Asia (406 clinical trials, 36 878 patients), Australia/New Zealand (150 clinical trials, 7 334 patients) and Central/South America (406 clinical trials, 46 588 patients). Only a very limited number of these pivotal clinical trials are conducted in non-OECD countries. (Source: EMEA).

⁵⁴ S. W. Glickman, *et. al.*, Ethical and Scientific Implications of the Globalization of Clinical Research, *N Engl J Med* 360; 8 February 19, 2009, p. 816.

However, any disregard of the rules that protect clinical trial participants is unacceptable and calls for determined action – independently of where the clinical trial has been performed. The Commission is committed to ensuring that the fundamental ethical rules for clinical trials are applied everywhere. Any weakening of the standards with regard to third countries would be in contradiction to the fundamental principles of human rights and dignity and their universal guarantee and protection, to which the EU is fully committed.

Indeed, there are also other aspects, closely linked to poverty, which may lead to increased recourse to non-OECD third countries in order to perform clinical trials. These include:

- Easier and faster recruitment, as a certain disease may have a higher morbidity or mortality in non-OECD third countries than in the EU;
- Less regulatory control and oversight, in particular as regards the ethical oversight of a clinical trial.

It is unacceptable and calls for determined action by the regulator, if clinical trials performed in these third countries exploit the particular vulnerability of their population.⁵⁵

The issue of third-country clinical trials has been discussed in several recent reports published by researchers and NGOs, such as:

- the study commissioned by the European Parliament - Directorate-General for External Policies of the Union: “Clinical trials in developing countries: How to protect people against unethical practices”;⁵⁶
- the “Final report of the expert meeting ‘Clinical trials and protection of trial subjects in low-income and developing countries’”;⁵⁷
- the report “Ethics for Drug Testing in Low and Middle Income Countries – Considerations for European Market Authorisations”;⁵⁸ and
- the report “Ethical concerns in clinical trials in India: an investigation” of the Centre for Studies in Ethics and Rights, Mumbai, India.⁵⁹

⁵⁵ This is also reflected in various written questions put forward by the European Parliament to the European Commission, cf. the most recent written questions E-1805/06 and E 0777/07 by Mr van den Berg, E-2357/07 by the Honourable Member and Mr van den Berg, E-1167/08 by the Honourable Member et al., E-2954/08 by Mr Holm, E 4953/08 by Ms Sinnott, and E-2703/09 by Dorette Corbey (all accessible via: http://eur-lex.europa.eu/RECH_questions_parlementaires.do)

⁵⁶ April 2009 - http://somo.nl/publications-en/Publication_3035/at_download/fullfile

⁵⁷ Wemos, January 2008.

⁵⁸ SOMO, February 2008.

⁵⁹ February 2009; http://www.fairdrugs.org/uploads/files/Ethical_concerns_in_clinical_trials_in_India_An_investigation.pdf

It is noteworthy that international rules for protection of clinical trial participants are in place and indeed largely accepted: there is a range of internationally-agreed documents setting out universally applicable principles for the protection of clinical trial participants, independently of where the clinical trial has been performed. These documents include:

- The Nuremberg Code of 1947 on medical experiments;⁶⁰
- The World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects;⁶¹
- The Council of Europe (“CoE”) Convention on Human rights and Biomedicine (“Oviedo Convention”);⁶²
- The International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences (“CIOMS”);⁶³ and
- The Good Clinical Practice Guidelines of the International Conference for Harmonisation (ICH E6).⁶⁴

Thus, there is no shortage of agreement on the general principles. The challenge is rather the practical application and, even more importantly, supervision and enforcement of those principles.

Consultation item n°16: Please comment? Do you have additional information, including quantitative information and data?

7.2. Weaknesses

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. Options to address this issue

The different options listed below are not mutually exclusive. Rather, they are alternatives which can apply cumulatively.

⁶⁰ <http://www.cirp.org/library/ethics/nuremberg/>

⁶¹ <http://www.wma.net/e/>

⁶² <http://conventions.coe.int/treaty/en/treaties/html/164.htm>

⁶³ http://www.cioms.ch/frame_guidelines_nov_2002.htm

⁶⁴ <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/3cc1aen.pdf>

7.3.1. *Supporting regulatory framework and capacity-building where necessary*

This option would rely on strengthened capacity-building in third countries where the regulatory framework for clinical trials, including its enforcement, is weak. Examples are the Community initiative “European and Developing Countries Clinical Trials Partnership” (“EDCTP”).⁶⁵

7.3.2. *Self-regulation by EU-based sponsors*

The option “self-regulation” would mean reliance on voluntary self-obligation of European sponsors to ensure that clinical trials performed in third countries are performed in accordance with international standards.

7.3.3. *Strengthening international cooperation in GCP inspection and mutual recognition of GCP rules*

This option would further strengthen international cooperation and efforts to align GCP requirements with international standards. Moreover, this option would strive for a stronger cooperation in inspection activities of clinical trial sites– including the possibility of mutual recognition of GCP inspections conducted by third countries with a regulatory framework complying with internationally agreed standards.

7.3.4. *Optional assessment of 3rd-country clinical trials by the EMEA*

This option would give to EMEA a mandate to assess a clinical trial to be performed in a third country, if such an assessment is requested by an international body, such as the World Health Organisation. This policy option would thus be conceptually similar to Article 58 of Regulation 726/2004 which provides the legal basis to evaluate medicinal products intended exclusively for markets in third countries.

7.3.5. *Strengthening a culture of transparency*

Transparency of clinical trials is crucial to ensure surveillance and monitoring. Under this policy option, sponsors requesting authorisation of clinical trials in the Community could be put under an obligation to make all clinical trials conducted by them available in a public register, such as the European clinical trials database EudraCT.

This transparency could contribute to compliance with GCP-standards worldwide and facilitate inspections by third country inspectors in third countries.

This transparency could be extended to publishing cases of non-compliance with GCP following inspection.

⁶⁵ <http://www.edctp.org/>. See also the contributions from various international bodies during the conference “Ethics, Research & Globalisation”, organised by the Commission in May 2007 (http://ec.europa.eu/research/science-society/document_library/pdf_06/erg-proceedings_en.pdf).

7.3.6. *Strengthening scrutiny of clinical trials results of which are submitted to the EU, or which are financed in the EU*

Compliance could also be ensured through strengthened scrutiny in the EU. To this end, one would have to rely on the possible “linkages” between a clinical trial performed in a third country on the one hand, and the EU on the other hand. Three such “linkages” can be identified:

- 1st “linkage”: The results – be they negative or positive – of a clinical trial performed in a third country are submitted in the process of an application for a marketing authorisation for a medicinal product in the EU: According to Community laws, the results of clinical trials related to the medicinal product submitted for marketing authorisation have to be submitted to the authorising authority. Pivotal clinical studies are described in more detail. In order to allow for better control and enforcement, one could require, in a legally-binding manner, additional information on the modalities of the clinical trials in terms of protection of participants. Indeed, EMEA is currently working on this issue and is planning to put forward concrete proposals.⁶⁶
- 2nd “linkage”: The results of a clinical trial performed in third countries, are submitted in the dossier of a request for authorisation of a clinical trial in the Community: According to Community rules the request for authorisation has to include summaries of all available data from previous clinical trials. The GCP compliance of these clinical trials has to be confirmed by the applicant in a statement of the CGP status of that clinical trial.⁶⁷ In order to allow for better control and enforcement, the applicant could be required, in a legally-binding manner, to submit additional information supporting the GCP-compliance of the clinical trials referred to in the application. To allow for time for inspections, the possibility of a “clock-stop” in the authorisation process could be introduced.
- 3rd “linkage”: Clinical trials performed in a third country are financed by the EU, for example through the 7th framework program: With regard to the funding of clinical trials through the 7th framework program, according the applicable Community rules ethical aspects are being assessed by the Commission. The Commission has published guidelines on this scrutiny with regard to clinical research in third countries.⁶⁸

Consultation item n°17: What other options could be considered, taking into account the legal and practical limitations?

⁶⁶ <http://www.emea.europa.eu/Inspections/docs/22806708en.pdf>

⁶⁷ Point 4.1.6.1.3. of the *Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial* (Revision 2, October 2005).

⁶⁸ ftp://ftp.cordis.europa.eu/pub/fp7/docs/developing-countries_en.pdf

Consultation item n°18: What other aspect would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?

The Commission invites comments on this consultation paper, and especially on the boxed “consultation items” by Friday evening, 8 January 2010 at the latest. Responses are sent preferably by e-mail to entr-pharmaceuticals@ec.europa.eu, or by post to Unit ENTR/F/2, BREY 10/114, BE-1049 Brussels.

Submitting parties should indicate whether they are stakeholder associations or private parties. In case of associations, please indicate clearly the type of stakeholder (sponsor, investigator, hospitals, IMP manufacturer, insurance company, etc.). In case of companies, please indicate whether the company falls within the Community definition of a small and medium enterprise (i.e. < 50m EUR yearly turnover and, cumulatively, <250 employees).

Contributions will be made publicly available on the ‘Pharmaceuticals’ website of the Commission⁶⁹ once the consultation period is over. If you do not wish your contribution to be made public please indicate this clearly and specifically in the submitted documentation. In this case, only an indication of the contributor will be disclosed.

Professional organisations are invited to register in the Commission’s Register for Interest Representatives (<http://ec.europa.eu/transparency/regrin/>) set up in the framework of the European Transparency Initiative with a view to providing the Commission and the public at large with information about the objectives, funding and structures of interest representatives.

⁶⁹ http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm