

EUROPEAN SOCIETY OF CARDIOLOGY

POSITION PAPER ON THE PROPOSAL FOR A REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL ON CLINICAL TRIALS ON MEDICINAL PRODUCTS FOR HUMAN USE, AND REPEALING THE DIRECTIVE 2001/20/EC

Introduction

The European Society of Cardiology (ESC)* welcomes the publication of the *Proposal for regulation on clinical trials on medicinal products for human use, and repealing the 'Clinical Trials Directive' 2001/20/EC*.

The ESC stresses that the development of pharmaceutical products and the improvement of medical treatment strongly rely on innovative clinical research - of which clinical trials are an essential component - in order to tackle effectively societal challenges in health. This is notably the case for cardiovascular disease (CVD), the N°1 killer in Europe. Each year, CVD is responsible for the death of 1.9 million EU citizens in the 27 member states. CVD is estimated to cost the EU economy €195.5 billion a year.

The ESC acknowledges that, through the innovative nature of medicinal products and medical treatment, clinical research and clinical trials are key to strengthening knowledge and innovation as drivers of future growth, as highlighted in the 'Europe 2020 strategy for smart, sustainable and inclusive growth'¹. However, regulatory barriers to properly conduct clinical research in Europe currently abound and it can be mind-bogglingly difficult to conduct clinical trials. There is a clear need to facilitate academically driven, well-organised clinical research projects in Europe, while maintaining the necessary regulations to ensure that these possibilities are used in the best interest of the citizens (and potential patients) of Europe.

The ESC gladly acknowledges that some of the recommendations expressed in its written response to the European Commission Concept Paper submitted for Public Consultation in May 2011 have been taken in consideration in the present proposal. This position paper will reaffirm the views of the ESC in this important field.

* The European Society of Cardiology (ESC) represents over 75,000 cardiology professionals across Europe and the Mediterranean. Its mission is "to reduce the burden of cardiovascular disease in Europe". The ESC provides an array of scientific and educational activities, such as the production and continuous updating of Clinical Practice Guidelines, the organisation of educational courses and initiatives, pan-European surveys on specific disease areas. It also organises the ESC Congress, the largest medical meeting in Europe, as well as subspecialty congresses, in conjunction with its constituent bodies. The ESC edits and publishes 9 of the world's leading journals on cardiology.

¹ COM(2010) 2020, 3.3.2010

BACKGROUND

Impact of the 2001/20/EC Directive

In 2004, the ESC conducted a survey amongst its community of clinical researchers. The objective of the survey was to understand and assess the potential impact of the 2001 Clinical Trials Directive on CVD-related research in Europe.

10,009 scientists, all involved in cardiovascular research, were identified from the ESC database. They were asked 6 questions on the way the 2001 Clinical Trials Directive affected or could affect their research. 42% of respondents feared that the directive would decrease the number of investigator initiated projects by 25 to 75% in their research centres. The reasons identified for the decrease were the administrative load generated by the directive (76%), the costs related to it (56%), the overall approval process (49%) and finally the delays generated by the additional red-tape (41%).

These figures are actually confirmed by the explanatory memorandum of the *Proposal for a Regulation on Clinical Trials on medicinal products for human use, and repealing directive 2001/20/EC*, showing a fall of 25% of European clinical trials between 2007 and 2011.

One of the main obstacles to medical research generated by the 2001 Clinical Trials Directive is related to the obligation of a unique sponsor, bearing the legal responsibilities of the trial. While such a system may be well suited for industry-led clinical research, it proved detrimental to investigator-led research or research initiated in academic institutions because it places an obligation for onerous administration, pharmacovigilance, adverse event reporting, archiving, good clinical practice, drug packaging, site visits, etc. Many organisations of the non-commercial sector are unprepared to accept this role.

Beyond the content of the actual directive, the nature of the legal tool chosen in 2001 to regulate clinical trials in Europe resulted in a regulatory fragmentation across the European Union (EU) member states. Directives give them a certain amount of leeway in the way they comply with the EU requirements. In the area of clinical research, it resulted in various national interpretations and systems. As a consequence, academic infrastructures of clinical research and investigators doing multinational studies in Europe are faced with various national legislative systems, in particular in the following areas: informed consent of patients, ethical review, data monitoring, reporting of adverse events, insurance, costs, funding, training, language, trial registration. All these are considered obstacles in the conduct of multinational studies.

Finally, the current directive does not allow joining third country-led trials, keeping European centres away from possible projects led, in particular, by the United States.

The overall impact of the 2001/20/EC Directive goes against the EU 2020 strategy, by reducing Europe's competitiveness and attractiveness when it comes to medical clinical research. Europe is now lagging behind the US in terms of research, scientific publication and consequently attractiveness to young researchers.

ESC POSITION

Reforming the Clinical Trials Directive

SCOPE

The ESC welcomes that the scope (Art. 1) of the Regulation is limited to clinical research on medicinal products and excludes clinical studies that do not involve an 'intervention'. Indeed, it is the ESC's opinion that the 2001 clinical trials directive is too burdensome for non-interventional clinical trials, which do not pose significant risk to subjects and thus require less stringent regulation. The 2001 provisions represented a prejudice for the development of clinical treatment research.

Concerning the definitions (Art. 2), the ESC would like to suggest:

- the inclusion of a definition for 'high-risk study' (such as the first use of a new antithrombotic agent for a specific indication). The definition of 'high-risk study' should read as follows: ***"A study on a new intervention that potentially has a high benefit but is also associated with significant risk and therefore needs close follow-up"***
- the definition of 'non-interventional study' should read as follows : ***"a clinical study other than a clinical trial or a low-interventional clinical trial"***

AUTHORISATION PROCEDURE & AUTHORISATION DOSSIER

- ▶ Submission of an Application, Assessment Report, Decision on the clinical trial (Artt. 5,6,7,8)

The ESC appreciates the European Commission's efforts to define strict timelines for the submission and assessment of applications as well as for the decision on the clinical trial.

Regarding aspects covered by Part I (Art. 6.1), the ESC welcomes the choice given to the sponsor to propose one reporting Member State, which will avoid lengthy approvals from all member states involved in multi-country trials.

Regarding aspects covered by Part II (Art. 7.1) the ESC contests the proposal to maintain an independent assessment by Member States for the following reasons:

- it shall complicate the conduction of international trials with the participation of several countries
- it will significantly reduce the advantages of a single reporting Members State for aspects covered under Part I as well as the advantages linked to the EU portal.

The ESC believes that the Member State appointed by the sponsor as 'reporting Member State' for the aspects covered under Part I, should be also the reporting Member States for aspects covered by Part II. Under these circumstances, the reporting Member State would draft one single report covering Parts I and II and would include, in the section addressing aspects covered by II, the possible local amendments which each Member State concerned will have communicated to the reporting Member State.

The same principle of one single reporting Member States should apply also to the provisions relating to the authorisation procedure for a substantial modification (Chpt. III).

Regarding the assessment criteria (Art.6), the ESC would like to underline the need to include '**the cost-effectiveness of the intervention**'.

Art.6 par 1(a)(ii) should be reworded as follows '***serious risk to subject health and public health posed by the medical condition..***' to safeguard the safety of individuals and of the wider society.

► Assessment of the application (Art.9)

The ESC fully agrees that the assessment of applications should be done by a reasonable number of independent and unbiased people who have the required qualifications and experience in the relevant field.

Moreover, the participation of patients in the different clinical trials phases (from design to post-marketing surveillance) is to be encouraged as it enables the development of more efficient trials that address issues expressed by those living with the condition.

► EU portal (Art. 77)

The ESC welcomes the creation of a single EU portal to submit applications. Such solution will simplify the administrative work of academic researchers and investigator led research project, notably for large-scale multi-national trials.

► EU database (Art. 78)

The ESC welcomes the creation of a dedicated database administered by the European Commission, which will contain the data and information submitted through the EU portal. However, the cardiology profession would like to recommend that all EU databases related to clinical trials (EUdraCT, EU Clinical Trials Register) and pharmacovigilance (EudraVigilance) are designed as to avoid any unnecessary duplication for the regulators, the users and the targeted public.

PROTECTION OF SUBJECTS AND INFORMED CONSENT (Art.10 & Chpt. V)

The ESC welcomes the introduction of clear provisions on the involvement of patients and notably for the protection of minors and of incapacitated subjects (including the possibility to withdraw from a trial), as well as for the conduct of clinical trials in emergency situations.

SAFETY REPORTING (CHPT.7)

The creation of a European database to report all adverse events experienced during clinical trials is a significant step forward in the field of drug surveillance and is warmly welcomed by the cardiology profession. The European scope of the database will allow quicker dissemination of the information to national and European regulators, but also to the scientific community, as opposed to the co-existing national systems currently in force in each EU member state. It will also supplement the Eudravigilance database, which is only covering clinical trials related to market authorization applications or recently approved drugs, for post-marketing surveillance.

INVESTIGATIONAL AND AUXILIARY MEDICINAL PRODUCTS, MANUFACTURING, LABELLING (CHPT. 9 & 10)

The ESC acknowledges the efforts made to bring together the rules related to medicinal products intended for research and development trials, which were excluded from the scope of the 2001/20/EC Directive. This approach will help to simplify, clarify and streamline the rules for conducting clinical trials.

The ESC also welcomes the clarification concerning the definition of “investigational medicinal products” and of “auxiliary medicinal products” contained in Chapter IX of the proposal.

SPONSORS, CO-SPONSORSHIP, EU CONTACT PERSON (CHPT. 11)

The revision of the “sponsor” concept is favorably welcomed by the cardiology community. The newly introduced concept of “co-sponsorship” will alleviate the tasks and responsibilities that previously had to be supported by the investigator-led and academic researchers, by allowing some of these tasks to be shared among co-sponsors.

The possibility to have, for the first time, sponsors of clinical trials located in third countries will allow European researchers to work with the best teams of researchers, outside the European Union, and to share the credits of the cooperation, notably in the area of scientific publication.

Several national groups have successfully set up clinical trial units that operate across borders in Europe and have taken on the role of trial sponsor. Examples comprise e.g. the AFNET which cooperates with the European Heart Rhythm Association (EHRA). The new regulation should foster the further development of these academically driven units, including support from the EU.

LEGAL FORM OF REGULATION

The ESC welcomes the proposal to take the form of a regulation to replace the existing directive. This legal form will ensure a higher level of harmonization and consistency across Member States; it will contribute to simplify, clarify and streamline the rules for conducting clinical trials by providing a unique set of rules. It is expected that the regulation will consequently reduce extra costs generated by discrepancies of the regulatory framework for clinical trials experienced within the EU in the implementation of the 2001/20/EC Directive.

The Regulation is also a better suited legal instrument for multi-country research, which is increasingly relevant for the development of personalized medicine. Research in this field requires large geographical territories to be able to enrol a sufficient number of patients. The choice of the regulation positively addresses a critical aspect of clinical research for Europe to be able to compete with other regions of the world.

FURTHER RECOMMENDATIONS

► Gender, Age and Ethnic issues

The ESC recommends that clinical trials enrol a significant proportion of women, young and elderly subjects as well as individuals of different ethnic origins to guarantee that clinical trials populations reflect the diversity of real life populations. In addition, clinical trials should systematically allow for an analysis of the results by gender, age and ethnic origin.

In the specific case of gender, differences in the clinical presentation of some diseases (such as CVD) have been demonstrated and some therapeutic options may not be equally effective and safe in men and women. Underrepresentation of women in cardiovascular research has been clearly established in the past and as a consequence, safety and efficacy of several drugs have been evaluated predominantly in male populations. According to a study² realized between 2006 and mid 2009, women are underrepresented in cardiovascular research: in the 62 randomized clinical trials published during this period, only a third of enrolled participants were women. The percentage of women enrolled in each trial ranges between 15 and 60. In addition, only half of the trials reported the analysis of the results by gender.

The ESC supports the efforts of the European Medicines Agency, and in particular its 2005 guidelines on gender issues in the conduct of clinical trials³, and we urge them to adopt strict rules on the inclusion of women in clinical trials and a systematic gender analysis.

² Red Alert on Women's Hearts, Women and Cardiovascular Research in Europe, Stramba Badiale M, November 2009, European Heart Health Strategy, Work Package 6

³ Gender Considerations on the conduct of clinical trials (EMA/CHMP/3916/2005)

► Clinical trials involving imaging techniques

The rapid development of cardiovascular imaging techniques provides new tools for the diagnosis and therefore treatment of patients with CVD. However, these tools are under-used in clinical research where they could quickly identify patients to be enrolled in trials and offer improved methods for accurately evaluating outcomes.

The cardiology community recommends that the Clinical Trials Regulation proposal acknowledges the need for methodological, technological and operational support for the involvement of imaging techniques in European clinical trials, in order to provide a scientific rationale for evidence-based diagnostic imaging that has a positive impact on clinical outcomes.

► Consultation of health professionals

The ESC believes that health professionals could contribute greatly to the design of simpler non-registration trials, especially investigator driven clinical trials, and recommends the setting up an appropriate consultation structure at EU level for this purpose.

ANNEX I – SUGGESTED AMENDMENTS

Proposal for a Regulation

Article 2 – Paragraph 4

<i>Text proposed by the Commission</i>	<i>Amendment</i>
(4) 'Non-interventional study': a clinical study other than a clinical trial;	(4) 'Non-interventional study': a clinical study other than a clinical or low-interventional trial;

Proposal for a Regulation

Article 2 – Paragraph 4 (new)

<i>Text proposed by the Commission</i>	<i>Amendment</i>
	(4) ' High-risk study ': a clinical study on a new intervention that potentially has a high benefit, but is also associated with significant risk and therefore needs close follow-up;

Proposal for a Regulation

Article 6 – Paragraph 1 – subparagraph (a) – point (ii)

<i>Text proposed by the Commission</i>	<i>Amendment</i>
– the risk to subject health posed by the medical condition for which the investigational medicinal product is being investigated;	– the serious risk to subject health and public health posed by the medical condition for which the investigational medicinal product is being investigated;

Proposal for a Regulation

Article 6 – Paragraph 1 – subparagraph (e) (new)

<i>Text proposed by the Commission</i>	<i>Amendment</i>
	(e) The cost-effectiveness of the intervention.

Proposal for a Regulation

Article 7 – Paragraph 1 – subparagraph 2

<i>Text proposed by the Commission</i>	<i>Amendment</i>
The assessment of the aspects referred to in the first subparagraph shall constitute Part II of the assessment report.	The assessment of the aspects referred to in the first subparagraph shall constitute Part II of the assessment report and will be compiled into the assessment report by the reporting Member State.

Proposal for a Regulation

Article 8 – Paragraph 1

<i>Text proposed by the Commission</i>	<i>Amendment</i>
1. Each Member State concerned shall notify the sponsor through the EU Portal as to whether the clinical trial is authorised, whether it is authorised	1. Each Member State concerned shall notify inform the sponsor through the EU Portal reporting Member State as to whether the

subject to conditions, or whether authorisation is refused.	clinical trial is authorised, whether it is authorised subject to conditions, or whether authorisation is refused. The reporting Member State shall notify the sponsor.
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Proposal for a Regulation

Article 8 – Paragraph 2 – subparagraph 3

<i>Text proposed by the Commission</i>	<i>Amendment</i>
Where the Member State concerned disagrees with the conclusion on the basis of point (a) of the second subparagraph, it shall communicate its disagreement, together with a detailed justification based on scientific and socio-economic arguments, and a summary thereof, through the EU portal to the Commission, to all Member States, and to the sponsor.	Where the Member State concerned disagrees with the conclusion on the basis of point (a) of the second subparagraph, it shall communicate its disagreement, together with a detailed justification based on scientific and socio-economic arguments, and a summary thereof, through the EU portal to the Commission, to all Member States, and to the sponsor reporting Member State.

Proposal for a Regulation

Article 8 – Paragraph 3

<i>Text proposed by the Commission</i>	<i>Amendment</i>
3. Where, regarding Part I of the assessment report, the clinical trial is acceptable or acceptable subject to conditions, the Member State concerned shall include in its decision its conclusion on Part II of the assessment report.	3. Where, regarding Part I of the assessment report, the clinical trial is acceptable or acceptable subject to conditions, the reporting Member State concerned shall include in its decision assessment report its the conclusions of each concerned Member State on Part II of the assessment report.

Proposal for a Regulation

Article 8 – Paragraph 4

<i>Text proposed by the Commission</i>	<i>Amendment</i>
4. Where the Member State concerned has not notified the sponsor of its decision within the time periods referred to in paragraph 1, the conclusion on Part I of the assessment report shall be considered as the decision of the Member State concerned on the application for authorisation of the clinical trial.	4. Where the Member State concerned has not notified the sponsor reporting Member State of its decision within the time periods referred to in paragraph 1, the conclusion on Part I of the assessment report shall be considered as the decision of the Member State concerned on the application for authorisation of the clinical trial.

Proposal for a Regulation

Article 14 – Paragraph 3

<i>Text proposed by the Commission</i>	<i>Amendment</i>
The additional Member State concerned shall notify the sponsor through the EU portal by way of one single decision as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether the authorisation is refused within the following time periods:	The additional Member State concerned shall notify the sponsor through the EU portal reporting Member State by way of one single decision as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether the authorisation is refused within the following time periods:

Proposal for a Regulation

Article 14 – Paragraph 4 – subparagraph 3

<i>Text proposed by the Commission</i>	<i>Amendment</i>
Where the additional Member State concerned disagrees with the conclusion on the basis of point (a) of the second subparagraph, it shall communicate its disagreement, together with a detailed justification based on scientific and socio-economic arguments, and a summary thereof, through the EU portal to the Commission, to all Member States, and to the sponsor.	Where the additional Member State concerned disagrees with the conclusion on the basis of point (a) of the second subparagraph, it shall communicate its disagreement, together with a detailed justification based on scientific and socio-economic arguments, and a summary thereof, through the EU portal to the Commission, to all Member States, and to the sponsor reporting Member State .

Proposal for a Regulation

Article 14 – Paragraph 9

<i>Text proposed by the Commission</i>	<i>Amendment</i>
3. Where, regarding Part I of the assessment report, the clinical trial is acceptable or acceptable subject to conditions, the additional Member State concerned shall include in its decision its conclusion on Part II of the assessment report.	3. Where, regarding Part I of the assessment report, the clinical trial is acceptable or acceptable subject to conditions, the additional reporting Member State concerned shall include in its decision assessment report its the conclusions of the additional Member State on Part II of the assessment report.

Proposal for a Regulation

Article 14 – Paragraph 10

<i>Text proposed by the Commission</i>	<i>Amendment</i>
4. Where the additional Member State concerned has not notified the sponsor of its decision within the time periods referred to in paragraph 3, the conclusion on Part I of the assessment report shall be considered as the decision of the additional Member State concerned on the application for authorisation of the clinical trial.	4. Where the additional Member State concerned has not notified the sponsor reporting Member State of its decision within the time periods referred to in paragraph 1, the conclusion on Part I of the assessment report shall be considered as the decision of the additional Member State concerned on the application for authorisation of the clinical trial.

Proposal for a Regulation

Article 78 – Paragraph 1

<i>Text proposed by the Commission</i>	<i>Amendment</i>
1. The Commission shall set up and maintain a database at Union level (hereinafter, the 'EU database'). The Commission shall be considered controller of the database.	1. The Commission shall set up and maintain a database at Union level (hereinafter, the 'EU database'). The Commission shall be considered controller of the database and will be responsible for avoiding unnecessary duplication between the existing European databases on clinical trials and on pharmacovigilance.