EUROPEAN PARLIAMENT

IMPA Impact Assessment

Initial appraisal of a European Commission Impact Assessment

European Commission proposal on clinical trials

Impact Assessment on the Revision of the Clinical Trials Directive 2001/20/EC
(SWD (2012) 200, SWD (2012) 201 (summary))
accompanying the Commission Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM (2012) 369).

- **Background**

This note seeks to provide an initial analysis of the strengths and weaknesses of the European Commission's Impact Assessment accompanying the Commission proposal on Clinical Trials.

- **Identification of the issue at stake**

A strong clinical research sector and efficient clinical trials infrastructures are important factors for the development of innovative health products and for the evidence-based evaluation of the effectiveness of novel or established medicinal products. Clinical trials allow for improving public health at large and can also be beneficial for individual patient health in the concrete setting of a clinical trial, if access to a medicine or to a medical treatment is only possible through a participation in a clinical trial. Conducting clinical trials also entails considerable investment and growth in the EU.

Clinical trials are currently regulated by the Clinical Trials Directive 2001/20/EC, the aim of which is to ensure the rights and safety of the subject, and to ensure that the data generated in a clinical trial is reliable and robust. However, this Directive seems not to have achieved the harmonisation of administrative requirements for clinical trials across Europe and is identified by the European Commission as 'the most heavily criticised piece of legislation of the entire EU acquis for pharmaceuticals' (I.A., p. 17). The fragmentation of the authorisation process is especially criticised as being too burdensome, multiplying bureaucracy and costs, and undermining Europe's position in clinical research.

- **Problem definition**

The definition of the problem in need of EU intervention is very much focused on the shortcomings of the existing Clinical Trials Directive and their consequences: a decrease in the number of applications for clinical trials in the EU, increased costs, and increased delays for launching a clinical trial.

Nevertheless, the Commission briefly indicates that there are other factors than regulation contributing to the reported problems in the sector. Industry, generally, conducts less research because of the economic slowdown since 2009. For the same reason, there is less public funding available. Moreover, it has become more difficult to recruit patients because of increasingly narrowly defined patient profiles. In general, costs in terms of salaries, hospital services, etc., have increased. The conclusion drawn by the Commission is that it would be wrong to attribute

the decline of clinical activity solely and exclusively to the Clinical Trials Directive, but that this Directive does have important adverse and direct effects on the cost and feasibility of clinical trials conducted in the EU.

The concrete problems to be addressed by the proposed legislation are therefore more narrowly defined in the IA:

1. Both for mono-national, as well as for multinational clinical trials, there are separate submission requirements both with the national competent authorities of the member states and with one or more Ethics Committees within the Commission, and their assessments diverge. The same requirements apply to the regulatory follow-up of applications for clinical trials. These procedures cause important costs and delays. These adverse effects are expected to worsen in the future, as the share of clinical trials performed in more than one member state is going to increase.

2. Regulatory requirements that are not adapted to practical considerations and needs cause greater difficulties with conducting clinical trials. According to the Commission, the disproportionate burden imposed by the Clinical Trials Directive is most obvious in the case of the obligatory insurance/indemnity requirement and of the obligatory annual safety report in the context of pharmacovigilance.

3. In view of the trend towards the globalisation of clinical research, there is a need for more reliable, quantifiable data on clinical trials performed in non-EU countries, in particular on the degree of compliance with 'good clinical practice'.

• Objectives of the legislative proposal

Closely linked to the problem definition, the IA sets out in a succinct and clear way a list of general objectives, followed by operational objectives.

Objective No 1 - A modern regulatory framework for submission, assessment and regulatory follow-up of applications for clinical trials, taking into account the multinational research environment. The operational objectives linked to the first general objective are: reducing administrative burdens and operational costs, and reducing delays for the launch of a clinical trial, as far as they are caused by regulation.

Objective No 2 - Regulatory requirements which are adapted to practical considerations, constraints and needs, without compromising the safety, well-being and rights of participants in clinical trials and without compromising data robustness. The operational objectives are reducing administrative burdens and operational costs as regards the two key regulatory requirements: the annual safety report and the obligatory insurance/indemnification.

Objective No 3 - Addressing the global dimension of clinical trials when ensuring compliance with 'good clinical practice'. The operational objective is ensuring compliance with the 'good medical practice' of clinical trials conducted in non-EU countries, but referred to in the EU in the context of another clinical trial or of an application for a marketing authorisation.

• Range of the options considered

Corresponding to the objectives, the IA contains a sufficiently broad range of policy options, all assessed for their impacts. No policy options were discarded from the outset.

For Objective 1

Option 1/1	No action at European level and reliance on voluntary cooperation of Member States (baseline option),
Option 1/2	Single submission with separate assessment,
Option 1/3	Single submission with joint assessment by Member States of issues not related to ethical aspects,
Option 1/4	Single submission with central assessment by the European Medicines Agency (EMA) of issues not related to ethical aspects,
Option 1/5	Choice of legal form: Regulation,
Option 1/6	Combination of policy option 1/3 (joint assessment) and 1/5 (legal form of Regulation) - *preferred option*.

For Objective *2*

Option 2/1	No action at European level (baseline scenario),
Option 2/2	Enlarging the scope of non-interventional trials,
Option 2/3	Excluding non-commercial sponsors,
Option 2/4	Removing regulatory requirements on the basis of the knowledge of the investigational medicinal product,
Option 2/5	Insurance/ Optional 'national indemnification mechanism',
Option 2/6	Combination of policy options 2/4 and 2/5 - *preferred option*.

For Objective 3

Option 3/1	Leaving the situation as it is (baseline option),
Option 3/2	Facilitation 'good clinical practice' inspections by increasing transparency,
Option 3/3	Inspections of non-EU countries' regulatory systems for clinical trial,
Option 3/4 '	Good clinical practice' inspections by the Agency in non-EU countries,
Option 3/5	Combination of policy options 3/2 and 3/3 - *preferred option*.

These options are compared for each objective. Advantages, drawbacks and possible synergies are clearly explained.

- **Scope of the Impact Assessment**

The IA concentrated on the expected social and economic impacts of the various policy options. The assessment is balanced, giving equal weight to the options. For social impacts, the focus is only on the impact on public health and patient health and safety. The possible impact of the proposal on employment in the sector has not been examined.

As regards economic impacts, the IA calculates for each option administrative costs, other compliance costs (delays), and implementation costs in the Member States and in the European Medicines Agency and Commission.

The Commission states that the options discussed would not have a direct or noteworthy indirect environmental impact (IA, p. 39).

For the baseline scenarios, the Commission also briefly sets out the expected further development of the situation in the absence of new EU measures. The conclusion is that, if no action at EU level is taken now to reach the objectives, the situation will deteriorate further, both in terms of public health and in terms of costs (IA, p. 44).

The IA does not provide a specific analysis of impacts on sectoral competitiveness, the focus merely being on administrative and other compliance costs. The analysis could usefully have

been complemented by a sectoral perspective, focusing on the impact of the proposal on the pharmaceutical sector.

- **Subsidiarity**

The legal base for the proposed Regulation is Article 114 TFEU. Larger clinical trials are often performed in more than one Member State, and rules at EU level, inter alia on authorisation and performance of clinical trials, are necessary for the functioning of the internal market of medicinal products. The Commission also explains the limits concerning the harmonisation of ethical aspects (in particular the need to obtain 'informed consent' from the subject), as well as the exclusion of rules establishing who is 'legal representative' of the subject and rules on liability for damages.

The national parliament in Poland has issued a reasoned opinion, raising issues with respect to the subsidiarity principle.

- **Budgetary or public finance implications**

Annexes 6, 7 and 8 of the IA contain a calculation of the expected implementation costs for the Commission and the European Medicines Agency. These costs are related to the financing of the single submission point, to the technical support and the role of the Commission of a 'facilitator of the joint assessment, and to the 'systems inspections'. Annex 6 also looks at possible financing strategies for the single submission system (cross-subsidy from fees for marketing authorisation activities, a separate fee for all applicants or support from the EU budget).

- **SME test**

According to the Commission, approximately 9% of clinical trials are run under the responsibility of SMEs, 'academic sponsors' never being considered SMEs (Annex 2, nr. 10). In the assessment of the economic impacts of the proposal, the IA occasionally takes possible effects on SMEs into account.

- **Impact on fundamental rights**

The Commission, having committed to examine the impact of legislative proposals on fundamental rights where such an assessment is relevant, makes a link between socioeconomic impacts with impacts on fundamental rights. Any increase/decrease of patient safety is a positive/negative impact on Articles 1 ('Human dignity') and 3 ('Right of the integrity of the person') of the Charter of Fundamental Rights of the European Union. Any reduction/increase of costs for conducting clinical trials has a positive/negative impact on Articles 13 ('Freedom of the arts and the sciences'), 35 ('Health care') and 16 ('Freedom to conduct a business') of the Charter. No further specific assessment of the impacts on fundamental rights is made.

- **Simplification and other regulatory implications**

The simplification potential of the proposal is dealt with briefly in the assessment of the various options, often under the heading 'other aspects'. The choice of the legal form of a Regulation, rather than a Directive, is also justified in the IA as a means to simplify the regulatory environment (IA, p. 51).

The IA explicitly refers to the recommendations of the High-Level Group of Independent Stakeholders on Administrative Burdens ('Stoiber Group') on pharmaceuticals legislation, dating from March 2009.

- **Relations with third countries**

Although the IA explains the trend towards the globalisation of clinical trials, the expected impact of the proposal on relations with third countries is not examined. The assessment of the impacts of the policy options relating to data on clinical trials performed in non-EU countries focuses on the cost of inspections.

- **Stakeholder consultation**

During the preparation of the proposal and IA, the Commission conducted extensive stakeholder consultations. The results of these are clearly and systematically presented throughout the IA, indicating stakeholders' preferences and objections.

- **Quality of data, research and analysis**

The IA is not directly based on externally conducted research. However, in 2008, the Commission launched a comprehensive study on the 'Impact on Clinical Research of European Legislation' (ICREL)[1].: This contains an assessment of the impact of the existing Clinical Trials Directive on the number, size, and nature of clinical trials, and on resources, costs and performance.

The IA contains a combined qualitative and quantitative assessment of all options, clearly presented in overview tables. The 'standard cost' method was used to calculate the administrative and other compliance costs, detailed and explained in the Annexes to the IA.

According to the calculations of the Commission, as a consequence of streamlining the authorisation procedure, administrative costs could be reduced by 271 million euro, and compliance costs reduced by 440 million euro per year across the EU. A saving of 34 million euro per year across the EU would be a consequence of removing the requirements for insurance and reducing the requirements for safety reporting for low intervention trials.

- **Monitoring and evaluation**

The IA contains a clear overview of indicators for monitoring and later evaluation of the legislation. However, the only clear timeline given for this monitoring and evaluation is seven years after the implementation of the Directive.

- **Commission Impact Assessment Board**

The Commission's IA Board first considered a draft version of the IA in January 2012 and formulated several recommendations for its improvement. An amended draft was considered by the Board by written procedure and further recommendations were made. These recommendations seem to have been largely followed-up, and as a consequence, the impact of the policy options was more clearly presented, the intervention logic for the proposal was better explained, as was the assessment of the national indemnification mechanism.

[1] http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf

- **Coherence between the Commission's legislative proposal and IA**

The legislative proposal and the IA submitted by the Commission appear to correspond. The former does not contain substantive elements that have not been addressed in the latter.

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This note, prepared by the Impact Assessment Unit for the European Parliament's Committee on Environment, Public Health and Food Safety (ENVI) analyses whether the principal criteria laid down in the Commission's own Impact Assessment Guidelines, as well as additional factors identified by the Parliament in its Impact Assessment Handbook, appear to be met by the IA. It does not attempt to deal with the substance of the proposal. It is drafted for informational and background purposes to assist the relevant parliamentary committee(s) and Members more widely in their work. This document is also available on the internet at: http://www.europarl.europa.eu/activities/committees/studies.html

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