Opinion of the European Economic and Social Committee 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 Directive 2001/20/EC'

COM(2012) 369 final — 2012/0192 (COD)

(2013/C 44/17)

Rapporteur: **Ms KÖSSLER**

The Council and the European Parliament decided, on 7 September and 11 September 2012 respectively, to consult the European Economic and Social Committee, under Articles 114 and 168(4) of the Treaty on the Functioning of the European Union, 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 Directive 2001/20/EC

COM(2012) 369 final — 2012/192 (COD).

The Section for the Single Market, Production and Consumption, which was responsible for preparing the Committee's work on the subject, adopted its opinion on 4 December 2012.

At its 485th plenary session, held on 12 and 13 December 2012 (meeting of 12 December), the European Economic and Social Committee adopted the following opinion by 105 votes to one with five abstentions.

1. **Conclusions and recommendations**

1.1 The EESC recognises that clinical research is an essential and continually developing area of scientific endeavour with the goal to understand diseases and develop medicines for patients.

1.2 In the context of scientific progress in clinical research and the development of innovative therapies, the protection of subjects from unreasonable risks and burdens has to be fully taken into account and the welfare of the individual subjects must take precedence over all other interests.

1.3 During its life-time, the regulation will be the system by which developing and novel trial designs will be appraised. Given how science and technology are developing and their impact on the way trials will be conducted and the products tested in clinical trials in the future, it makes sense that strong provision is made to periodically assess and if necessary amend the regulation.

1.4 The EESC calls for the establishment of a single EU governance area for clinical trials, where patients can enter into different clinical trials in different Member States independent of their country of origin/residence, and which respects the universal ethical, scientific and technical principles by which clinical trials are assessed.

1.5 The EESC welcomes and strongly defends the implementation and use of a single portal for both multinational and single country clinical trials without the need to further code data into any of the national systems. This will alleviate the administrative burden created by the current directive and ensure harmonisation of the submission requirements by national authorities. In addition, the single portal will ensure a streamlined process for the clinical trial life cycle as it will facilitate the possibility of including additional Member States in a clinical trial.

1.6 The EESC supports the coordinated assessment procedure being subdivided into two parts as proposed by the regulation. It will create a clear and understandable system under which there will be no duplication of assessments by the bodies concerned, giving patients the earliest possible access to a clinical trial at approximately the same point in time in all concerned Member States.

1.7 The EESC calls for explicit inclusion in the regulation of assessments by the independent ethics committee (in line with the requirements of the Paragraph 15 of the Declaration of Helsinki, Chapter II of the Proposal and Directive 2001/20/EC). The ethical assessment is a critical part in the authorisation process of clinical trials to ensure patients' rights are respected. An approval of a clinical trial should not be granted until an independent ethics committee has issued a favourable opinion.

1.8 The EESC calls for the EU to support and facilitate cooperation and the exchange of scientific information among Member States within a network connecting ethics committees designated by the Member States. The EESC recognises that EurecNet exists but calls for a formal, patient centred body to be established to replace EurecNet. Provisions concerning the Ethics Committees' Network should be included in the regulation.

1.9 The EESC strongly supports the distinction introduced by the regulation for low-intervention clinical trials.

1.10 The EESC welcomes the intention to strengthen the safeguards for the processing of personal data as long as there is an appropriate balance between the rights of individuals and the safe and secure use of patients data for health research.

1.11 The EESC supports the creation of a Clinical Trials Coordination and Advisory Group (CTAG) as set out in Article 81.

1.12 While clinical trials are most frequently conducted for medicinal products, it is also worth noting that in some cases, clinical trials - or clinical performance studies - may also be done in the area of medical devices and in vitro diagnostics, and the Commission's recent proposals on a Medical Devices Regulation ([1]) and an In vitro Diagnostic Medical Devices Regulation ([2]) include requirements for clinical performance studies. Especially in the context of personalised medicine, joint trials with a pharmaceutical and a diagnostic medical device are likely to increase. It should thus be ensured that the requirements and application processes for medicinal products and medical devices are compatible and reduce duplication as far as possible.

1.12.1 The EESC recognises that clinical trial data submitted in an application dossier for a marketing authorisation shall be based on clinical trials which have been registered prior to their start in a public register which is a primary registry of the international clinical trials registry platform of the World Health Organization, or an International Committee of Medical Journal Editors (ICMJE) approved registry.

2. **Gist of the Commission proposal**

2.1 In the recent years the number of applications for clinical trials in the EU fell significantly (by 25 % from 2007 to 2011), the costs for conducting clinical trials and the average delay for launching a clinical trial have increased. According to the European Commission, Directive 2001/20/EC has had many effects on the cost and feasibility of conducting clinical trials, which have led to a decline in clinical trial activity in the EU.

2.2 The aim of the current proposal is to make the conduct of clinical trials faster, easier and cheaper by laying down harmonised rules on the authorisation and conduct of clinical trials, in order to increase the attractiveness of the EU as a location for clinical trials, reduce costs of clinical testing and promote public health.

2.3 The proposal takes the form of a regulation replacing Directive 2001/20/EC. This legal form ensures that Member States base their assessment of an application for authorisation of a clinical trial on an identical text, rather than on diverging national transposition measures. It also allows actors to plan and conduct clinical trials, including multi-national clinical trials, on the basis of one regulatory framework.

2.4 The proposal covers the following main points: authorisation procedure for clinical trials, safety reporting, informed consent, manufacturing and labelling of the tested product, conduct of the trial, compensation for damage, responsibilities (investigator, sponsors, co-sponsor), EU contact person and inspections.

3. **General observations**

3.1 The EESC welcomes the revision of the European clinical trials legislation as an opportunity for Europe to demonstrate that it acts as a single coherent region in regulating and managing the conduct of clinical trials and is an attractive place for sponsors to conduct their clinical research and to provide access for patients to enter into clinical trials.

3.2 The EESC recognises that clinical trials in the EU are in decline (specifically academic research has significantly declined in the EU); this decline is not solely the fault of EU legislation but a number of confounding factors. The number of clinical trials has also fallen in the USA, and in later years the economic crisis may have contributed to the decline. However, EU legislation can help address the situation.

3.3 The EESC notes that the current proposal may slow the rate of that decline, but in its current state it will not fully arrest nor reverse it. It is, however, an opportunity to create a better environment for clinical research in the EU which could facilitate a more competitive framework for clinical research globally.

3.4 The EESC highlights that scientific research advances as our scientific and technical knowledge advances. To ensure the regulation continues to support European clinical research, a periodic review - fully empowered to result in any necessary amendment - of the regulation needs to be conducted. This is supported by the Commission's communication on 'An Integrated Industrial Policy for the Globalisation Era Putting Competitiveness and Sustainability at Centre Stage' ([3]), which states that 'systematic evaluations of legislation must become an integral part of smart regulation'.

([1]) COM(2012) 542 final.
([2]) COM(2012) 541 final.
([3]) COM(2010) 614 final.

3.4.1 The EESC requests that provisions should be laid down to assess and report on the implementation of this regulation after experience has been gained, with particular attention to the different types of clinical trials authorised and to scientific and technological progress.

3.4.2 The EESC calls for the introduction of the following Review Clause amendment: 'Five years after the entry into force of this regulation, and every five years thereafter, the Commission shall present a report to the European Parliament and the Council, on the operation of this regulation which shall include comprehensive information on the different types of clinical trials authorised pursuant to this regulation including defining plans for any appropriate amendments.'

3.4.3 In this report, the EESC requests the Commission to assess the impact of scientific and technological progress on the application of this regulation.

3.5 The EESC notes that as a result of the current disproportionate administrative requirements for the low intervention clinical trials, clinical research conducted by academia has declined in Europe. Low-intervention clinical trials are mainly conducted by academia, and are essential for the advancement and progression of medical practice.

3.5.1 The EESC supports the classification of low-intervention clinical trials in Article 5(2)(d) as it would reduce the heavy administrative obligations on sponsors, thus re-establishing patients' access to these low-intervention clinical trials.

3.6 The EESC calls for a regulation that will ensure the formation of a single EU governance area for clinical trials, which allows access for patients to information on clinical trials and to enter into different clinical trials consecutively in different Member States independent of their country of origin/residence, and which respects that the ethical, scientific and technical principles, by which clinical trials are assessed, are universal. Such principles were agreed by the International Conference on Harmonisation Guideline for Good Clinical Practice and they are consistent with principles that have their origin in the World Medical Association's Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. The EESC believes that the regulation should make reference to the Helsinki Declaration not only in the recitals but also in Article 9.

3.7 The EESC proposes that a step-change that will make a radical difference in the attractiveness of Europe as a clinical trials destination and grant European patients access to the most innovative treatments would be the introduction of a single, borderless EU area for the conduct of trials.

3.8 The EESC emphasises the need that, to assist with the implementation of the timelines under the tacit approval mechanism, clarification is required in the text that the trial may start on the notification date unless the Member State has provided grounds for not accepting the clinical trial. However, the timelines under the tacit approval mechanism mentioned in the proposed regulation are clearly to be regarded as too short and therefore they should be extended.

3.9 The EESC recognises that a mechanism is needed to help ethics committees to share expertise and knowledge and to learn from each other. The platform for such a network needs to be coordinated and funded at the EU level. The EESC recommends that patient involvement should be mandatory as adequate patient representation will ensure that decisions reflect patients' interests and realities, reflecting as well the involvement of patients in the assessment process as enshrined in Article 9.

3.10 The EESC recommends that cooperation amongst ethics committees should be increased to support Member States achieving greater efficiencies, economies of scale and the avoidance of duplication of effort. This regulation should facilitate the creation of sustained structures involving all the relevant authorities of the Member States, building on existing pilot projects and consultation of a wide range of stakeholders. This regulation should therefore provide a basis for continued Union support for such cooperation. It will provide the basis to improve efficiency in the assessment of the aspects listed in Article 6(1) and Article 7(1).

3.10.1 The EESC recognises that clinical trial insurance represents huge costs for sponsors, and in a few years' time can lead to further increases in the cost of drugs. However, the European Commission's attempt to reduce costs of liability insurance for sponsors should not lead to a deterioration of the security of the participants in the event of a claim, which might happen in case of the elimination of compulsory insurance. The EESC opposes a general elimination of a compulsory insurance, yet it agrees that in clearly defined cases exceptions should be allowed.

3.10.2 The establishment of a compensation mechanism requires a more detailed specification, in particular with regard to how and by whom this mechanism would be financed. Setting up national compensation mechanisms poses a risk of different financial coverage in individual Member States. Also different systems of medical and product liability insurance, as well as different liability rules in the Member States may lead to a possible deterioration in the event of damage to the subjects.

3.11 Simplification of **safety reporting**, and more particularly its **centralisation** at European Medicines Agency, will be a major achievement and should decrease unnecessary administrative workload related to pharmacovigilance while maximising EU capacity to detect pertinent events in time.

3.11.1 The EESC recommends not introducing specific disease categories or types of medicinal products in the regulation. The regulation should focus on ensuring the safety of participants and the reliability of the data generated. If specific diseases have their own classification within the regulation, there is a major concern that there would be an overload of new classifications introduced which would create confusion for sponsors and National Competent Authorities. There is a serious risk that an extensive classification system would in fact be contrary to the objective of the regulation, namely; simplification and harmonisation.

3.12 The EESC supports the creation of a Clinical Trials Coordination and Advisory Group (CTAG) as a key step to ensure true harmonisation of clinical research throughout Europe. To maximise the functioning of this group the meetings should be limited only to the parties named in Article 81. However, it should be ensured that there is a possibility for stakeholders, relevant to this regulation, to submit questions or topics for discussion by this advisory group. This would allow for increased transparency and an enhanced balance between all stakeholders involved in a clinical trial, including patients.

3.12.1 Therefore the EESC calls for the inclusion of the following text in Article 81(5): 'Upon request of a relevant stakeholder group, the Commission shall submit one or more questions which are relevant under Article 81(2) to the CTAG for discussion at the earliest possible meeting and, if necessary, convene the CTAG for that purpose. If the Commission refuses to submit a question to the CTAG or to convene the CTAG as requested by a stakeholder group the Commission shall inform the requester in writing about its refusal and specify the reasons thereof. Where the CTAG discusses a question under this provision, the Commission shall ensure that the requester concerned is informed about the outcome of the discussion.'

3.13 While supporting the Commission's intention to strengthen the safeguards for the processing of personal data, the EESC stresses that an appropriate balance between the rights of individuals and the safe and secure use of patients' data for health research is necessary. In particular, when patients participating in clinical trials have given broad informed consent which allows the use of samples and data for future research, it is necessary that good clinical practice and ethical principles for the use of this data is abided by.

4. **Specific observations**

4.1 The EESC strongly supports a single **EU governance structure for clinical trials** that must significantly facilitate the conduct of clinical research in the EU, and should be the benchmark and objective for amendment to and review of this regulation.

4.2 The EESC calls for inclusion in the regulation of the provisions concerning the **Ethics Committees' Network**.

4.2.1 The members of such network shall be designated by the Member States who shall communicate their names and contact details to the Commission. Those members shall participate in, and contribute to, the network's activities. The network shall be based on the principle of good governance including transparency, objectivity, independence of expertise, fairness of procedure and appropriate stakeholder consultations with meaningful patient involvement at all stages.

4.2.2 The objectives of the Ethics Committees' Network shall be to:

a) support cooperation between national and local ethic committees or bodies in the view of streamlining and harmonising processes conducting to issuance of ethics committee approvals;

b) support the analysis of the nature and type of information that can be exchanged;

c) avoid duplication of assessments;

d) safeguard that patients participating in clinical trials in the EU are protected according to the same universal ethical principles;

e) support pan-European harmonisation of qualifications and training of ethics committees' members.

4.2.3 The EESC supports the funding by the EU Research Programme for this Committee. Only those authorities and bodies in the network designated as beneficiaries by the participating Member States shall be eligible for Union aid.

4.3 The EESC recognises that **timelines** for adding a new Member State are not competitive and not in line with timelines of Part II assessment by Member States concerned defined in Article 7. As an additional Member State concerned may disagree with the conclusion of the reporting Member State for Part I only on the following grounds:

a) significant differences in normal clinical practice between the Member States concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal practice;

b) infringement of the national legislation referred to in Article 86, this assessment should also be possible in less than 10/20 days suggested, i.e. in ten days and the possibility to suspend the relevant time for obtaining those additional explanations should be in line with timelines of Part II assessment by Member States concerned defined in Articles 7 and 14(8).

4.4 With regard to the evaluation process, the EESC recommends that each Member State shall, in addition to the conditions laid down in Article 7(1), assess the application with respect to the fulfilment of the requirements for the protection of subjects. To avoid lengthy clinical trial authorisation procedures that would delay patients' access to clinical trials the EESC proposes the following amendment in **Article 7(2)** first sentence: 'Each Member State shall complete its assessment, **including the opinion of the national ethics committee**, within 10 days from the validation date **pursuant to Article 6(4)**.'

4.5 At the end of **Article 8(6)** the following sentence should be added: 'The sponsor may start the clinical trial forthwith on the notification date, unless the Member State concerned has communicated its disagreement in accordance with paragraph 2.'

4.6 In order to ensure patients' safety, the Committee asks urgently for an extension of the time limits provided for in the proposed regulation. In particular, the following periods should be extended: in Article 5(2) from 6 to 14 days, in Article 5(4) third paragraph from 3 to 7 days, in Article 6(4) from 10 to 25, from 25 to 35 and from 30 to 40 days, as well as in Article 17(2) from 4 to 10 days.

4.7 The protection standards in Articles 31 and 32 of the proposed regulation should be based on the provisions of Directive 2001/20/EC or at least foresee an opt-out option for the Member States with respect to the protection of vulnerable groups.

4.8 For documentation relating to **compliance with Good Manufacturing Practice (GMP)** for the Investigational Medicinal Product (Annex I, point 6), the EESC emphasises that the application shall contain a statement to confirm that all documentation relating to compliance with GMP for the investigational medicinal product(s) is on file and available for inspection to ensure maintenance of patient safety.

Brussels, 12 December 2012.

The President
of the European Economic and Social Committee
Staffan NILSSON