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*Committee on the Internal Market and Consumer Protection*

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**2012/0192(COD)**

22.3.2013

## **OPINION**

of the Committee on the Internal Market and Consumer Protection

for the Committee on the Environment, Public Health and Food Safety

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)0369 – C7-0194/2012 – 2012/0192(COD))

Rapporteur: Cristian Silviu Buşoi,

PA\_Legam

## SHORT JUSTIFICATION

### Objectives of the proposal

The Commission proposal revises the rules on clinical trials on medicinal products for human use. The current clinical trials Directive (2001/20/EC) brought important improvements in the safety and reliability of clinical trials in the EU. However, its divergent application and transposition, disproportionate regulatory requirements and resulting administrative burden have led to a decline of clinical trials in the EU.

The Commission proposes to revise the legislation by simplifying the authorisation and reporting procedures taking into account the risk-profile of the trials and improving transparency, while maintaining the highest standards of patient safety and robustness of data. The new legislation will take the form of a Regulation. This will ensure that the rules are applied in a uniform manner throughout the EU.

### General comments

The Rapporteur for opinion welcomes the proposal of the Commission and supports the general approach of a single submission portal managed by the Commission and the setting of tight and tailored timelines for assessment reports and authorisation decisions on the clinical trials. Increased cooperation and coordination within and between Member States and an efficient procedure for the addition of Member States will improve the conduct of multinational clinical trials and support innovative clinical research in the EU. The Rapporteur shares the Commission's views that the persons validating and assessing the application should be independent from the sponsor and the investigator, do not have conflict of interests and are free of any undue influence. The provisions related to the protection of patients and informed consent, are fair and appropriate.

### EU portal

It should be clarified that the single submission procedure applies to both multinational and single Member State clinical trials and that once the Member States notified their decision, the clinical trial can start.

It would be preferable as a general rule that the sponsor decides from the beginning of the procedure about the Member States where the clinical trial will be conducted, though the addition of a new Member State at a later stage should be possible. Therefore, in order to keep procedures simple and efficient it should be clarified that the extension of an authorised clinical trial to another Member State can be made only after the initial authorisation decision by all Member States concerned. Besides, when an application for a substantial modification concerning Part I of the assessment is under evaluation, the sponsor should wait for the end of this procedure before requesting the addition of a new Member State to that clinical trial.

## **Ethical review**

The role of ethics committees did not appear to be very clear in Commission's proposal. The Rapporteur for opinion tabled a few amendments to clarify that all ethical aspects covered by part I (e.g. anticipated health benefits versus risks for the subjects) and part II (e.g. informed consent) in an application should be assessed by the Member States prior their authorisation decision on the clinical trial.

## **Administrative burden**

The Commission is proposing relevant provisions to cut red tape. Further improvements could be made by requesting the update of the investigator's brochure only when necessary, e.g. when new safety information becomes available.

## **Patients groups**

Where relevant, the design of a clinical trial should take into account the diversity of the patient groups that the investigational medicinal product is intended to treat. Safety aspects specific to a gender or age group should be identified accordingly and included in the safety reporting.

In the assessment, it is important to take into account the view of at least one patient and preferably that patient should represent a patient's organisation for the disease for which the investigational medicinal product is intended.

## **Transparency**

Data and information on clinical trials should be accessible through the EU database in accordance with clear and established confidentiality rules. Solutions to increase the transparency of clinical trials' results should also be found. Navigation through the EU database should be possible in all EU official languages while the translation of the protocol and other related information would be disproportionate in terms of relevance, costs and feasibility.

## **Damage compensation**

The concrete use of national indemnification mechanisms instead of insurance systems should be further clarified in order to avoid inequalities for compensation damages between the Member States.

## **AMENDMENTS**

The Committee on the Internal Market and Consumer Protection calls on the Committee on the Environment, Public Health and Food Safety, as the committee responsible, to incorporate the following amendments in its report:

**Amendment 1**  
**Proposal for a regulation**

**Recital 1**

*Text proposed by the Commission*

(1) In a clinical trial the safety and rights of subjects should be protected and the data generated should be reliable **and robust**.

*Amendment*

(1) In a clinical trial the safety and rights of subjects should be protected and the data generated should be reliable, **robust and reflect the diversity of the population in terms of age and gender balance**.

**Amendment 2**  
**Proposal for a regulation**

**Recital 4**

*Text proposed by the Commission*

(4) Directive 2001/20/EC aimed to simplify and harmonise the administrative provisions governing clinical trials in the European Union. However, experience shows that a harmonised approach to the regulation of clinical trials has only been partly achieved. This makes it in particular difficult to perform a clinical trial in several Member States. Scientific development however, suggests that future clinical trials will target more specific patient populations, such as subgroups identified through genomic information. In order to include a sufficient number of patients for such trials it may be necessary to involve many, or all, Member States. The new procedures for the authorisation of clinical trials should stimulate the inclusion of as many member states as possible. Therefore, in order to simplify submission procedures, the multiple submission of largely identical information should be avoided and replaced by the submission of one application dossier through a single submission portal to all the Member States concerned.

*Amendment*

(4) Directive 2001/20/EC aimed to simplify and harmonise the administrative provisions governing clinical trials in the European Union. However, experience shows that a harmonised approach to the regulation of clinical trials has only been partly achieved. This makes it in particular difficult to perform a clinical trial in several Member States. Scientific development however, suggests that future clinical trials will target more specific patient populations, such as subgroups identified through genomic information. In order to include a sufficient number of patients for such trials it may be necessary to involve many, or all, Member States. The new procedures for the authorisation of clinical trials should stimulate the inclusion of as many member states as possible. Therefore, in order to simplify submission procedures, the multiple submission of largely identical information should be avoided and replaced by the submission of one application dossier through a single submission portal to all the Member States concerned. ***The application dossier related to a clinical trial conducted in a single Member State***

***should also be submitted through that single submission portal.***

*Justification*

*Clarification that the single submission procedure applies to both multinational and to single-country clinical trials.*

**Amendment 3**  
**Proposal for a regulation**

**Recital 9**

*Text proposed by the Commission*

(9) The risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the intervention. Many clinical trials, however, pose only a minimal additional risk to subject safety compared to normal clinical practice. This is in particular the case where the investigational medicinal product is covered by a marketing authorisation (i.e. the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure) and where the intervention poses only very limited additional risk to the subject compared to normal clinical practice. Those ‘**low-intervention** clinical trials’ are often of crucial importance to assess standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. **They** should be subject to less stringent rules, such as shorter deadlines for approval.

*Amendment*

(9) The risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the intervention. Many clinical trials, however, pose only a minimal additional risk to subject safety compared to normal clinical practice. This is in particular the case where the investigational medicinal product is covered by a marketing authorisation (i.e. the quality, safety and efficacy has already been assessed in the course of the marketing authorisation procedure) and where the intervention poses only very limited additional risk to the subject compared to normal clinical practice. Those ‘**minimal-risk** clinical trials’ are often of crucial importance to assess standard treatments and diagnoses, thereby optimising the use of medicinal products and thus contributing to a high level of public health. **Given that minimal-risk clinical trials have only a very limited and temporary adverse effect – if any – on the subject’s health, they** should be subject to less stringent rules, such as shorter deadlines for approval. **They should, however, be subject to the vigilance and traceability rules governing normal clinical practice.**

### *Justification*

*The amendment seeking to replace the term 'low-intervention clinical trial' by the term 'minimal-risk clinical trial' applies to the whole text. If it is adopted, changes will be required throughout the text.*

#### **Amendment 4 Proposal for a regulation**

##### **Recital 9 a (new)**

*Text proposed by the Commission*

*Amendment*

***(9a) For the purpose in this Regulation, the notion of 'Auxiliary medicinal product' should be understood as any medicinal product used in the context of a clinical trial but not as an experimental medicinal product. Auxiliary medicinal products include, in particular, medicinal products used for background treatment, pharmacological agents, rescue medication or medicinal products used to assess end-points in a clinical trial. Auxiliary medicinal products do not include medicaments which are unconnected with the clinical trial and are not pertinent to the trial design.***

### *Justification*

*For the sake of clarity, examples of auxiliary medicinal products should be provided.*

#### **Amendment 5 Proposal for a regulation**

##### **Recital 10**

*Text proposed by the Commission*

*Amendment*

(10) The assessment of the application for a clinical trial should address in particular the anticipated therapeutic and public health benefits ('relevance') and the risk and inconveniences for the subject. Regarding the relevance, numerous aspects should be taken into account, ***including***

(10) The assessment of the application for a clinical trial should address in particular the anticipated therapeutic and public health benefits ('relevance') and the risk and inconveniences for the subject. Regarding the relevance, numerous aspects should be taken into account, ***such as the***

whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products.

***subpopulation groups to be studied and the potential differences in efficacy and/or safety for specific subpopulations notably gender and age differences, or*** whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products.

#### *Justification*

*Some therapeutic options are not equally effective and safe in men and women. Research shows that women have been under-represented in cardiovascular research resulting in safety and efficacy of several drugs being evaluated predominantly in male populations. Therefore, potential differences should be duly taken into account when assessing the relevance of clinical trials.*

### **Amendment 6 Proposal for a regulation**

#### **Recital 11**

##### *Text proposed by the Commission*

(11) The authorisation procedure should provide for the possibility to suspend the assessment in order to allow the sponsor to address questions or comments raised during the assessment of the application dossier. The maximum duration of the suspension should reflect whether the clinical trial ***is a low-intervention clinical trial*** or not. Moreover, it should be ensured that, following the end of the suspension, there is always sufficient time for assessing the additional information submitted.

##### *Amendment*

(11) The authorisation procedure should provide for the possibility to suspend the assessment in order to allow the sponsor to address questions or comments raised during the assessment of the application dossier. The maximum duration of the suspension should reflect whether the clinical trial ***poses only a low risk*** or not. Moreover, it should be ensured that, following the end of the suspension, there is always sufficient time for assessing the additional information submitted.

#### *Justification*

*It would be better to define the second category of research by the level of risk incurred by the subject rather than the type of intervention. This reflects the main objective of the draft regulation, which is to establish a risk-based approach. Furthermore, the regulation should be brought into line with the provisions of the Oviedo Convention. Article 17 of that convention, which has been ratified by several Member States, contains a definition of the term 'minimal risk'.*



**Amendment 7**  
**Proposal for a regulation**  
**Recital 11 a (new)**

*Text proposed by the Commission*

*Amendment*

***(11a) The role of the reporting Member State and of the Member States concerned should be clarified in order to avoid duplication of assessment. Therefore, the authorisation procedure should also include a joint assessment phase during which the Member States concerned have the possibility to submit comments on the initial assessment report communicated to them by the reporting Member State. This joint assessment should be carried out before the reporting date and allow for sufficient time for the Reporting Member State to incorporate comments from Member States concerned.***

**Amendment 8**  
**Proposal for a regulation**  
**Recital 12**

*Text proposed by the Commission*

*Amendment*

(12) Some aspects in a clinical trial application relate to issues of an intrinsic national nature or to ethical aspects of a clinical trial. Those *issues* should not be assessed in cooperation among all Member States concerned.

(12) Some aspects in a clinical trial application relate to issues of an intrinsic national nature of a clinical trial or to ethical aspects, ***such as informed consent***. Those ***aspects*** should not be assessed in cooperation among all Member States concerned.

*Justification*

*Text adapted in line with the deletion of the last paragraph in Recital 6 for consistency reasons.*

**Amendment 9**  
**Proposal for a regulation**  
**Recital 12 a (new)**

*Text proposed by the Commission*

*Amendment*

***(12a) The ethical aspects of a clinical trial application or an application of a substantial modification thereof should be assessed by the competent body or bodies of the Member State concerned prior the notification of its decision on the clinical trial. In any event, the ethical assessment should be carried out within the deadlines provided for in this Regulation and should not delay the assessment procedures.***

**Amendment 10**  
**Proposal for a regulation**

**Recital 12 b (new)**

*Text proposed by the Commission*

*Amendment*

***(12b) In the case of rare diseases as defined by EU legislation, the necessary data and expertise to perform a well-informed assessment of the application for authorisation of a clinical trial may be scarce at national level. Therefore, such expertise should be sought at European level. To this end, the reporting Member State should cooperate in the assessment process with the Scientific Advice Working Party of the European Medicines Agency which should provide an opinion on the disease or disease group concerned. Where relevant, this opinion may cover aspects related to Part II of the assessment, in which case the reporting Member State should notify it to the Member States concerned. This cooperation should be organised within the same deadlines foreseen in this Regulation for clinical trials conducted in the field of diseases other than rare diseases.***

## *Justification*

*Recital corresponding to the insertion of a new article 7b on the assessment report on clinical trials in the field of rare diseases.*

### **Amendment 11** **Proposal for a regulation**

#### **Recital 14**

##### *Text proposed by the Commission*

(14) It should be left to the Member State concerned to determine the appropriate body or bodies to be involved in this assessment. This decision is a matter of internal organisation of each Member State. *Member States, when determining the appropriate body or bodies, should ensure the involvement of lay persons and patients. They should also ensure that the necessary expertise is available. In any case, however, and in accordance with international guidelines, the assessment should be done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience. The persons assessing the application should be independent from the sponsor, the institution of the trial site, and the investigators involved, as well as free of any other undue influence.*

##### *Amendment*

(14) It should be left to the Member State concerned to determine the appropriate body or bodies to be involved in this assessment. This decision is a matter of internal organisation of each Member State. *However, irrespective of the organisation of the assessment process and the bodies involved, Member States should make sure that the assessment is entirely completed within the deadlines provided for in this Regulation and that no further assessment can prevent the sponsor from starting the clinical trial after the notification of the decision granting the authorisation.*

## *Justification*

*Amendment of this Recital aiming at clarifying the intention of Amendment 13 of the draft opinion. The second part should become a separate recital for clarity reasons.*

### **Amendment 12** **Proposal for a regulation**

#### **Recital 14 a (new)**

##### *Text proposed by the Commission*

##### *Amendment*

*(14a) Member States, when determining the appropriate body or bodies, should*

*ensure the involvement of lay persons and patients. They should also ensure that the necessary expertise is available. In any case, however, and in accordance with international guidelines, the assessment should be done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience. The persons assessing the application should be independent from the sponsor, the institution of the trial site, and the investigators involved, as well as free of any other undue influence.*

*Justification*

*Text corresponding to the last part of Recital 14 which was deleted to ensure clarity.*

**Amendment 13**  
**Proposal for a regulation**

**Recital 16**

*Text proposed by the Commission*

(16) The sponsor should be allowed to withdraw the application for authorisation of a clinical trial. To ensure the reliable functioning of the assessment procedure, however, an application for authorisation of a clinical trial should be withdrawn only for the entire clinical trial. It should be possible for the sponsor to submit a new application for authorisation of a clinical trial following the withdrawal of an application.

*Amendment*

(16) The sponsor should be allowed to withdraw the application for authorisation of a clinical trial. To ensure the reliable functioning of the assessment procedure, however, an application for authorisation of a clinical trial should be withdrawn only for the entire clinical trial. It should be possible for the sponsor to submit a new application for authorisation of a clinical trial following the withdrawal of an application, ***provided that the new application contains explanations regarding any previous withdrawals.***

**Amendment 14**  
**Proposal for a regulation**  
**Recital 17**

*Text proposed by the Commission*

(17) In practice, in order to reach

*Amendment*

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recruitment targets or for other reasons, sponsors may have an interest to extend the clinical trial to an additional Member States after the initial authorisation of the clinical trial. An authorisation mechanism should be provided to allow for this extension, while avoiding the re-assessment of the application by all the Member States concerned which were involved in the initial authorisation of the clinical trial.

recruitment targets or for other reasons, sponsors may have an interest to extend the clinical trial to an additional Member States after the initial authorisation of the clinical trial. An authorisation mechanism should be provided to allow for this extension, while avoiding the re-assessment of the application by all the Member States concerned which were involved in the initial authorisation of the clinical trial. ***To this end, clear rules should be laid down with regard to the designation of the reporting Member State for such procedures. As a general rule, the reporting Member State for the subsequent addition of a Member State concerned should be the reporting Member State for the initial procedure. Sponsors may also add a subsequent Member State concerned to single-country clinical trials where there was no reporting Member State for the initial procedure. In such cases the Member State to which the application was initially submitted should be considered the reporting Member State.***

## **Amendment 15**

### **Proposal for a regulation**

#### **Recital 20**

*Text proposed by the Commission*

(20) In order to increase transparency in the area of clinical trials, clinical trial data submitted in support of a clinical trial application should be based only on clinical trials recorded in a publicly accessible database.

*Amendment*

(20) In order to increase transparency in the area of clinical trials, clinical trial data submitted in support of a clinical trial application should be based only on clinical trials recorded in a publicly ***and easily accessible database without imposing any cost on the access to the*** database.

**Amendment 16**  
**Proposal for a regulation**  
**Recital 22**

*Text proposed by the Commission*

(22) The human dignity and right to the integrity of the person are recognized in the Charter of Fundamental Rights of the European Union. In particular, the Charter requires that any intervention in the field of biology and medicine cannot be performed without free and informed consent of the person concerned. Directive 2001/20/EC contained an extensive set of rules for the protection of subjects. These rules should be upheld. Regarding the rules concerning the determination of the legal representative of incapacitated persons and minors, those rules diverge in Member States. It should therefore be left to Member States to determine the legal representative of incapacitated persons and minors.

*Amendment*

The human dignity and right to the integrity of the person are recognized in the Charter of Fundamental Rights of the European Union. In particular, the Charter requires that any intervention in the field of biology and medicine cannot be performed without free and informed consent of the person concerned. Directive 2001/20/EC contained an extensive set of rules for the protection of subjects. These rules should be upheld. Regarding the rules concerning the determination of the legal representative of incapacitated persons and minors, those rules diverge in Member States. It should therefore be left to Member States to determine the legal representative of incapacitated persons and minors. ***Therefore, this Regulation should be without prejudice to national provisions which may require that the consent of more than one legal representative of a minor is required.***

**Amendment 17**  
**Proposal for a regulation**

**Recital 23**

*Text proposed by the Commission*

(23) This Regulation should provide for clear rules concerning informed consent in emergency situations. Such situations relate to cases where for example a patient has suffered a sudden life-threatening medical condition due to multiple traumas, strokes or heart attacks, necessitating immediate medical intervention. For such cases, intervention within an ongoing clinical trial, which has already been approved, may be pertinent. However, in

*Amendment*

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certain circumstances, due to the unconsciousness of the patient and the absence of an immediately available legal representative, it is not possible to obtain informed consent prior to the intervention. The Regulation should therefore set clear rules whereby such patients may be enrolled in the clinical trial under very strict conditions. In addition, the said clinical trial should relate directly to the medical condition which causes the impossibility of the patient to give informed consent. Any previously expressed objection by the patient must be respected, and informed consent from the subject or the legal representative should be sought as soon as possible.

certain circumstances, due to the unconsciousness of the patient and the absence of an immediately available legal representative, it is not possible to obtain informed consent prior to the intervention. The Regulation should therefore set clear rules whereby such patients may be enrolled in the clinical trial under very strict conditions. ***For example, in cases where the research needs to start without delay and there is reason to expect that the potential benefit to the subject of taking part in the clinical trial outweighs the risks or the subject's participation entails only a minimal risk, it should be possible for the clinical trial to begin without his or her prior consent.*** In addition, the said clinical trial should relate directly to the medical condition which causes the impossibility of the patient to give informed consent. Any previously expressed objection by the patient must be respected, and informed consent from the subject or the legal representative should be sought as soon as possible

#### *Justification*

*Philippe Juvin welcomes the fact that proposal for a regulation provides for possible exemption from the requirement for prior consent in the event of emergencies. However, he does not wish this possibility to be restricted to minimal-risk clinical trials, as such a provision would be too restrictive in practice and would rule out much research in the field of resuscitation and emergency medical treatment relating to innovatory products.*

### **Amendment 18** **Proposal for a regulation**

#### **Recital 25**

##### *Text proposed by the Commission*

(25) In order to allow patients to assess possibilities to participate in a clinical trial, and to allow for effective supervision of a clinical trial by the Member State concerned, the start of the clinical trial, the end of recruitment for the clinical trial and

##### *Amendment*

(25) In order to allow patients to assess possibilities to participate in a clinical trial, and to allow for effective supervision of a clinical trial by the Member State concerned, the start of the clinical trial, the end of recruitment for the clinical trial and

the end of the clinical trial should be notified. ***In accordance with international standards, the results of the clinical trial should be reported to the competent authorities within one year of the end of the clinical trial.***

the end of the clinical trial should be notified.

*Justification*

*Text moved to a new recital.*

**Amendment 19**  
**Proposal for a regulation**

**Recital 25 a (new)**

*Text proposed by the Commission*

*Amendment*

***(25a) The sponsor shall submit, in a timely manner, to the EU database a summary of the results of a clinical trial. This submission shall respect the level of development of the product and shall not include any personal data or commercially confidential information. The summary of the results of the clinical trial should be submitted either within one year of the end of the clinical trial or of the decision to discontinue the development of a medicinal product, or no later than 30 days after the marketing authorisation has been granted.***

*Justification*

*In line with changes to article 34.*

**Amendment 20**  
**Proposal for a regulation**

**Recital 33**

*Text proposed by the Commission*

*Amendment*

During a clinical trial, a sponsor may become aware of serious breaches of the

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rules for the conduct of the clinical trial. This should be reported to the Member States concerned in order for action to be taken by those Member States, where necessary.

rules for the conduct of the clinical trial. This should be reported to the Member States concerned ***without delay*** in order for action to be taken by those Member States, where necessary.

**Amendment 21**  
**Proposal for a regulation**

**Recital 34**

*Text proposed by the Commission*

(34) Apart from the reporting of suspected unexpected serious adverse reactions, there may be other events which are relevant in terms of benefit-risk balance and which should be reported in a timely manner to the Member States concerned.

*Amendment*

(34) Apart from the reporting of suspected unexpected serious adverse reactions, there may be other events which are relevant in terms of benefit-risk balance and which should be reported in a timely manner to the ***competent bodies of the*** Member States concerned, ***including those responsible for the assessment of ethical aspects.***

**Amendment 22**  
**Proposal for a regulation**

**Recital 36**

*Text proposed by the Commission*

(36) In order to ensure compliance of the conduct of the clinical trial with the protocol, and in order for investigators to be informed about the investigational medicinal products they administer, the sponsor should supply the investigators with an investigator's brochure.

*Amendment*

(36) In order to ensure compliance of the conduct of the clinical trial with the protocol, and in order for investigators to be informed about the investigational medicinal products they administer, the sponsor should supply the investigators with an investigator's brochure. ***This brochure should be updated whenever new safety information becomes available, including information about events other than suspected unexpected serious adverse reactions.***

**Amendment 23**  
**Proposal for a regulation**

**Recital 51**

*Text proposed by the Commission*

(51) In order to streamline and facilitate the flow of information between sponsors and Member States as well as between Member States, the Commission should set up and maintain a database, accessed through a portal.

*Amendment*

(51) In order to streamline and facilitate the flow of information between sponsors and Member States as well as between Member States, the Commission should set up and maintain a database, accessed through a portal. ***The Commission and Member States should raise awareness among the general public on the existence of the portal.***

**Amendment 24**  
**Proposal for a regulation**  
**Recital 52**

*Text proposed by the Commission*

(52) The database should contain all relevant information as regards the clinical trial. No personal data of data subjects participating in a clinical trial should be recorded in the database. The information in the database should be public, unless specific reasons require that a piece of information should not be published, in order to protect the right of the individual to private life and the right to the protection of personal data, recognised by Articles 7 and 8 of the Charter of Fundamental Rights of the European Union.

*Amendment*

(52) ***In order to ensure a sufficient level of transparency in clinical trials, the database should contain all relevant information as regards the clinical trial submitted through the EU portal.*** No personal data of data subjects participating in a clinical trial should be recorded in the database. The information in the database should be public, unless specific reasons require that a piece of information should not be published, in order to protect the right of the individual to private life and the right to the protection of personal data, recognised by Articles 7 and 8 of the Charter of Fundamental Rights of the European Union.

**Amendment 25**  
**Proposal for a regulation**

**Recital 64 a (new)**

*Text proposed by the Commission*

*Amendment*

***(64a) According to the Commission Communication on "An Integrated Industrial Policy for the Globalisation Era Putting Competitiveness and Sustainability at Centre Stage" systematic evaluations of legislation must become an integral part of smart regulation. In order to ensure this Regulation keeps pace with scientific and technological progress in the organization and conduct of clinical trials and interfaces with other legal provisions, the Commission should periodically report on the experience and functioning of the Regulation and present its conclusions thereof.***

*Justification*

*In accordance with the concept of smart regulation and in order to assure that the Regulation remains "fit for purpose" to support advances in science and technology in a rapidly changing environment, regular review of the Regulation has to be established.*

**Amendment 26  
Proposal for a regulation**

**Article 2 – paragraph 2 – point 2 – point a**

*Text proposed by the Commission*

*Amendment*

a) the investigational medicinal products  
***are not authorised;***

a) the investigational medicinal products  
***have not been granted a marketing authorisation;***

*Justification*

*To bring the wording of the proposal into line with terms used in relation to market authorisation.*

**Amendment 27  
Proposal for a regulation**

**Article 2 – paragraph 2 – point 2 – point c**

*Text proposed by the Commission*

*Amendment*

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

*(Does not affect English version)*

## **Amendment 28** **Proposal for a regulation**

### **Article 2 – paragraph 2 – point 2 – point d**

*Text proposed by the Commission*

*Amendment*

d) the decision to prescribe the investigational medicinal **products** is **taken together with the decision to include the subject in the clinical study**;

d) the decision to prescribe the investigational medicinal **product** is **determined by the research protocol**;

#### *Justification*

*The wording of the Commission proposal is unclear. In clinical trials, the decision to prescribe the medicinal product is dictated by the protocol, in contrast to non-interventional studies where the product is prescribed for therapeutic rather than research purposes.*

## **Amendment 29** **Proposal for a regulation**

### **Article 2 – paragraph 2 – point 3 – introductory part**

*Text proposed by the Commission*

*Amendment*

3) ‘**Low-intervention** clinical trial’: a clinical trial **which** fulfils all of the following conditions:

3) ‘**Minimal-risk** clinical trial’: a clinical trial **presents a minimal risk if, given the nature and extent of the intervention, it can be expected to have only a very small and temporary impact - if any - on the subject’s health.**

*A ‘minimal-risk clinical trial’ fulfils all of the following conditions:*

### *Justification*

*(The amendment seeking to replace the term ‘low-intervention clinical trial’ by the term ‘minimal-risk clinical trial’ applies to the whole text. If it is adopted, changes will have to be made throughout.) It would be better to define the second category of research by the level of risk incurred by the subject rather than the type of intervention. This reflects the main objective of the draft regulation, which is to establish a risk-based approach. Furthermore, the regulation should be brought into line with the provisions of the Oviedo Convention. Article 17 of that convention, which has been ratified by several Member States, contains a definition of the term ‘minimal risk’.*

### **Amendment 30** **Proposal for a regulation**

#### **Article 2 – paragraph 2 – point 3 – point a**

*Text proposed by the Commission*

*Amendment*

a) the investigational medicinal products  
*are authorised;*

a) the investigational medicinal products  
*have been granted a marketing  
authorisation;*

### *Justification*

*To bring the wording of the proposal into line with terms used in relation to market authorisation.*

### **Amendment 31** **Proposal for a regulation**

#### **Article 2 – paragraph 2 – point 3 – point b**

*Text proposed by the Commission*

*Amendment*

b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation or their use is *a standard treatment* in any of the Member States concerned;

b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation or their use is *in line with normal clinical practice* in any of the Member States concerned;

### *Justification*

*The notion of ‘standard treatment’ is imprecise and could lead to divergent interpretations. It should be replaced by the term ‘normal clinical practice’.*

**Amendment 32**  
**Proposal for a regulation**

**Article 2 – paragraph 2 – point 6**

*Text proposed by the Commission*

6) '**Normal** clinical practice': the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder;

*Amendment*

*(Does not affect English version)*

**Amendment 33**  
**Proposal for a regulation**  
**Article 2 - paragraph 2 – point 11 a (new)**

*Text proposed by the Commission*

*Amendment*

***(11a) 'Joint assessment': the procedure whereby the Member States concerned submit comments to the initial assessment by the reporting Member State;***

**Amendment 34**  
**Proposal for a regulation**  
**Article 2 – paragraph 2 – point 12**

*Text proposed by the Commission*

(12) 'Substantial modification': any change to any aspect of the clinical trial which is ***made after notification of the decision referred to in Articles 8, 14, 19, 20 and 23 and*** likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial;

*Amendment*

(12) 'Substantial modification': any change to any aspect of the clinical trial which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial, ***i.e. modifications that change the interpretation of the scientific documents used to support the conduct of the trial;***

*Justification*

*The timing of the substantial modification of a clinical trial is not relevant in the definition section. The relevant provisions are included in Articles 8, 14, 19, 20 and 23.*

**Amendment 35**  
**Proposal for a regulation**

**Article 2 – paragraph 2 – point 14**

*Text proposed by the Commission*

14) ‘Investigator’: an individual responsible for the conduct of a clinical trial at a clinical trial site;

*Amendment*

14) ‘Investigator’: an individual *whose training and experience meet the requirements laid down in Article 46 of this Regulation and who is* responsible for the conduct of a clinical trial at a clinical trial site;

*Justification*

*In the interests of consistency, a detailed definition of the term ‘investigator’ should be provided, based on the definition established by the ICH GCP (International Conference of Harmonisation Guideline for Good Clinical Practice).*

**Amendment 36**  
**Proposal for a regulation**

**Article 2 – paragraph 2 – point 17**

*Text proposed by the Commission*

17) ‘Incapacitated subject’: a subject who is, *for other reasons than the age of legal competence to give informed consent*, legally incapable of giving informed consent according to the laws of the Member State concerned;

*Amendment*

17) ‘Incapacitated subject’: a subject who is, legally *or de facto*, incapable of giving informed consent according to the laws of the Member State concerned;

*Justification*

*As this definition relates solely to legal incapacity, it excludes other forms of incapacity covered by national legislation to which specific consent rules apply. French law, for example, draws a distinction between persons lacking legal capacity (e.g. persons placed under statutory guardianship or supervision, and minors) and persons who are de facto incapable of giving informed consent (as a result of cognitive impairment). Different provisions apply to these two types of incapacity.*

**Amendment 37**  
**Proposal for a regulation**

**Article 2 – paragraph 2 – point 19**

*Text proposed by the Commission*

19) 'Informed consent': a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate;

*Amendment*

19) 'Informed consent': a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been **duly** informed, **according to the laws of the Member State concerned**, of all aspects of the trial that are relevant to the subject's decision to participate;

*Justification*

*(Translator's note: the amendment only partially affects the English version.)*

**Amendment 38**  
**Proposal for a regulation**  
**Article 5 – paragraph 1 – subparagraph 1**

*Text proposed by the Commission*

5. In order to obtain an authorization, the sponsor shall submit an application dossier to the intended Member State concerned through the portal referred to in Article 77 (hereinafter the 'EU portal').

*Amendment*

5. **For any clinical trial in the Union**, in order to obtain an authorization, the sponsor shall submit an application dossier to the intended Member State concerned through the portal referred to in Article 77 (hereinafter the 'EU portal').

*Justification*

*Clarification that the single submission procedure applies to both multinational and to single-country Clarification clinical trials.*

**Amendment 39**  
**Proposal for a regulation**  
**Article 5 – paragraph 1 – subparagraph 2**

*Text proposed by the Commission*

The sponsor shall propose one of the

*Amendment*

The sponsor shall propose one of the



Member States concerned as reporting Member State.

*Where the proposed reporting Member State does not wish to be the reporting Member State, it shall agree with another Member State concerned that the latter will be the reporting Member State. If no Member State concerned accepts to be the reporting Member State, the proposed reporting Member State shall be the reporting Member State.*

Member States concerned as reporting Member State.

*The Member States concerned may accept the proposal made by the sponsor or agree on another reporting Member State. If such an agreement is not reached within 3 calendar days, the proposed reporting Member State shall be the reporting Member State.*

## **Amendment 40** **Proposal for a regulation**

### **Article 5 – paragraph 2 – introductory part**

*Text proposed by the Commission*

2. Within *six* days following *submission of the application dossier*, the *proposed* reporting Member State shall notify the sponsor through the EU portal of the following:

*Amendment*

2. Within *three calendar* days following *its appointment*, the reporting Member State shall notify the sponsor through the EU portal of the following:

*Justification*

*The proposal for a regulation should refer to calendar days rather than working days. Compliance with time-limits, which helps ensure the competitiveness of European clinical research, requires efficient cooperation between the Member States concerned. Public holidays differ from one Member State to another. A procedure based on working days could result in different deadlines for validation, assessment and decisions in each of the Member States concerned.*

## **Amendment 41** **Proposal for a regulation**

### **Article 5 – paragraph 2 – point a to da(new)**

*Text proposed by the Commission*

(a) *whether it is the reporting Member State or* which other Member State *concerned* is the *reporting* Member State;

*Amendment*

(a) that it is the reporting Member State;

(b) whether the clinical trial falls within the scope of this Regulation;

(c) whether the application is complete in accordance with Annex I;

(d) whether the clinical trial is a low-intervention clinical trial, where claimed by the sponsor.

(b) whether the clinical trial falls within the scope of this Regulation;

(c) whether the application is complete in accordance with Annex I;

(d) whether the clinical trial is a low-intervention clinical trial, where claimed by the sponsor.

***(da) the clinical trial registration number in the EU portal.***

## **Amendment 42**

### **Proposal for a regulation**

#### **Article 5 – paragraph 3**

##### *Text proposed by the Commission*

3. Where the proposed reporting Member State has not notified the sponsor within the time period referred to in paragraph 2, the clinical trial applied for shall be considered as falling within the scope of this Regulation, the application shall be considered complete, the clinical trial shall be ***considered a low-intervention*** clinical trial if this is claimed by the sponsor, and the proposed reporting Member State shall be the reporting Member State.

##### *Amendment*

3. Where the proposed reporting Member State has not notified the sponsor within the time period referred to in paragraph 2, the clinical trial applied for shall be considered as falling within the scope of this Regulation, the application shall be considered complete, the clinical trial shall be ***regarded as posing a minimal risk*** if this is claimed by the sponsor, and the proposed reporting Member State shall be the reporting Member State.

##### *Justification*

*It would be better to define the second category of research by the level of risk incurred by the subject rather than the type of intervention. This reflects the main objective of the draft regulation, which is to establish a risk-based approach. Furthermore, the regulation should be brought into line with the provisions of the Oviedo Convention. Article 17 of that convention, which has been ratified by several Member States, contains a definition of the term 'minimal risk'.*

## **Amendment 43**

### **Proposal for a regulation**

#### **Article 5 – paragraph 4 – subparagraph 1**

*Text proposed by the Commission*

Where the proposed reporting Member State finds that the application is not complete, that the clinical trial applied for does not fall within the scope of this Regulation, or that the clinical trial is not a **low-intervention** clinical trial while this is claimed by the sponsor, it shall inform the sponsor thereof through the EU portal and shall set a maximum of six days for the sponsor to comment or to complete the application through the EU portal.

*Amendment*

Where the proposed reporting Member State finds that the application is not complete, that the clinical trial applied for does not fall within the scope of this Regulation, or that the clinical trial is not a **minimal-risk** clinical trial while this is claimed by the sponsor, it shall inform the sponsor thereof through the EU portal and shall set a maximum of six days for the sponsor to comment or to complete the application through the EU portal.

*Justification*

*It would be better to define the second category of research by the level of risk incurred by the subject rather than the type of intervention. This reflects the main objective of the draft regulation, which is to establish a risk-based approach. Furthermore, the regulation should be brought into line with the provisions of the Oviedo Convention. Article 17 of that convention, which has been ratified by several Member States, contains a definition of the term 'minimal risk'.*

**Amendment 44**  
**Proposal for a regulation**

**Article 5 – paragraph 4 – subparagraph 3**

*Text proposed by the Commission*

Where the proposed reporting Member State has not notified the sponsor according to points (a) to (d) of paragraph 2 within three days following receipt of the comments or of the completed application, the application shall be considered complete, the clinical trial shall be considered as falling within the scope of this Regulation, the clinical trial shall be **considered as a low-intervention clinical trial** if this is claimed by the sponsor, and the proposed reporting Member State shall be the reporting Member State.

*Amendment*

Where the proposed reporting Member State has not notified the sponsor according to points (a) to (d) of paragraph 2 within three days following receipt of the comments or of the completed application, the application shall be considered complete, the clinical trial shall be considered as falling within the scope of this Regulation, the clinical trial shall be **regarded as posing a minimal risk** if this is claimed by the sponsor, and the proposed reporting Member State shall be the reporting Member State.

### *Justification*

*It would be better to define the second category of research by the level of risk incurred by the subject rather than the type of intervention. This reflects the main objective of the draft regulation, which is to establish a risk-based approach. Furthermore, the regulation should be brought into line with the provisions of the Oviedo Convention. Article 17 of that convention, which has been ratified by several Member States, contains a definition of the term 'minimal risk'.*

#### **Amendment 45** **Proposal for a regulation**

##### **Article 6 – paragraph 1 – point a – subparagraph 1 a (new)**

*Text proposed by the Commission*

*Amendment*

***In the assessment of the aspects covered in points i) and ii), the reporting Member State shall, where applicable, take into account the subpopulations to be studied.***

### *Justification*

*Amendment replacing Amendment 8 of the draft opinion. The particularities of certain subpopulations (according to gender, age etc.) may also concern aspects such as relevance or the risks and inconveniences for the subject which are referred to in point ii). It is therefore proposed to enlarge the scope of this provision and to take subpopulations into account when assessing all elements referred to in points i) and ii).*

#### **Amendment 46** **Proposal for a regulation**

##### **Article 6 – paragraph 4 – subparagraph 1 – introductory part**

*Text proposed by the Commission*

*Amendment*

The reporting Member State shall submit Part I of the assessment report, including its conclusion, to the sponsor and to the other Member States concerned within the following time periods:

***For the purposes of this Chapter, the assessment date shall be the date on which the assessment report is submitted to the other Member States concerned and the reporting date shall be the date when the final assessment report is submitted to the sponsor and to the other Member States concerned.***

The reporting Member State shall submit Part I of the assessment report, including

its conclusion, to the sponsor and to the other Member States concerned within the following time periods, ***which shall include periods for initial assessment, for joint assessment and for consolidation of the final report.***

*Justification*

*The assessment process needs to be structured allowing for an initial assessment by the Reporting Member State which is distributed to all Concerned Member States who can then comment (joint assessment) and allowing for sufficient time for the Reporting Member State to incorporate comments from Concerned Member States (consolidation). This process will avoid duplication of assessment by both Reporting and Concerned Member States and clarifies the role of the Reporting Member State.*

**Amendment 47**  
**Proposal for a regulation**

**Article 6 – paragraph 4 – subparagraph 1 – point a**

*Text proposed by the Commission*

(a) within 10 days from the validation date for low-intervention clinical trials;

*Amendment*

(a) within 10 days from the validation date for low-intervention clinical trials; ***the time for the joint assessment and for consolidation by Member States concerned and the reporting Member State shall not be shorter than 5 days;***

*Justification*

*This ensures that there is sufficient time for the Reporting Member State to do an initial assessment (maximum 5 days) and there is sufficient time for the joint assessment and consolidation (minimum 5 days).*

**Amendment 48**  
**Proposal for a regulation**

**Article 6 – paragraph 4 – subparagraph 1 – point b**

*Text proposed by the Commission*

(b) within 25 days from the validation date for clinical trials other than low-intervention clinical trials;

*Amendment*

(b) within 25 days from the validation date for clinical trials other than low-intervention clinical trials; ***the time for the***

***joint assessment and for consolidation by Member States concerned and the reporting Member State shall not be shorter than 10 days;***

*Justification*

*This ensures that there is sufficient time for the Reporting Member State to do an initial assessment (maximum 15 days) and there is sufficient time for the joint assessment and consolidation (minimum 10 days).*

**Amendment 49**  
**Proposal for a regulation**

**Article 6 – paragraph 4 – subparagraph 1 – point c**

*Text proposed by the Commission*

(c) within 30 days from the validation date for any clinical trial with an advanced therapy investigational medicinal product.

*Amendment*

(c) within 30 days from the validation date for any clinical trial with an advanced therapy investigational medicinal product; ***the time for the joint assessment and for consolidation by Member States concerned and reporting Member State shall not be shorter than 10 days.***

*Justification*

*This ensures that there is sufficient time for the Reporting Member State to do an initial assessment (maximum 20 days) and there is sufficient time for the joint assessment and consolidation (minimum 10 days).*

**Amendment 50**  
**Proposal for a regulation**

**Article 6 – paragraph 5**

*Text proposed by the Commission*

5. Until the assessment date, ***any*** Member State concerned may communicate to the reporting Member State any considerations relevant to the application. The reporting Member State shall take those considerations duly into account.

*Amendment*

5. Until the assessment date ***the reporting*** Member State ***shall develop and circulate to the Member States concerned an initial assessment report. No later than 2 days before the reporting date, the Member States*** concerned may communicate to the reporting Member State ***and all other***

**Member States concerned** any considerations relevant to the application. The reporting Member State shall take those considerations duly into account **in finalising the assessment report**.

*Justification*

*This ensures that the Reporting Member State has 2 days for consolidating comments from Concerned Member States and finalising the report. This avoids a situation in which Concerned Member States can submit comments to the Reporting Member State right up until the last day of the assessment period when the final report must be submitted to the sponsor and Concerned Member States. This leaves time to deal effectively and transparently with Concerned Member States comments and incorporate them into a final consolidated report.*

**Amendment 51**  
**Proposal for a regulation**

**Article 6 – paragraph 6 – subparagraph 1**

*Text proposed by the Commission*

The reporting Member State, and only the reporting Member State, may, between the validation date and the **assessment** date, request additional explanations from the sponsor, taking into account the considerations referred to in paragraph 5.

*Amendment*

The reporting Member State, and only the reporting Member State, may, between the validation date and the **reporting** date, request additional explanations from the sponsor, taking into account the considerations referred to in paragraph 5.

*Justification*

*A clear distinction should be made between the assessment date, the last day that Concerned Member States can comment on the initial assessment by the Reporting Member State and the reporting date, the date that the final report is submitted to the sponsor and Concerned Member States.*

**Amendment 52**  
**Proposal for a regulation**

**Article 6 – paragraph 6 – subparagraph 3**

*Text proposed by the Commission*

**Where**, upon receipt of the additional explanations, **the remaining time period for submitting Part I of the assessment**

*Amendment*

Upon receipt of the additional explanations **the Member States concerned shall communicate until two days before the**

*report is less than three days in the case of low-intervention clinical trials, and less than five days for other than low-intervention clinical trials, it shall be extended to three and five days respectively.*

*reporting date, any considerations to the reporting Member State. The reporting Member State will take these considerations into account in finalising the assessment report. The time for the joint assessment and for consolidation by Member States concerned and the reporting Member State of the additional explanations shall not be shorter than 5 days for low intervention trials and 10 days for trials other than low-intervention clinical trials.*

#### *Justification*

*The process to assess the additional explanations should mirror the process for joint assessment of the application. The Reporting Member State needs 2 days to consolidate comments and finalise the assessment report. This also ensures that there is sufficient time for the Reporting Member State to do an initial assessment (maximum 15 days for low intervention trials or 20 days for other trials) and there is sufficient time for the joint assessment and consolidation (minimum 5 days for low intervention trials or 10 days for other trials).*

### **Amendment 53** **Proposal for a regulation**

#### **Article 6 – paragraph 6 – subparagraph 1**

*Text proposed by the Commission*

The reporting Member State, and only the reporting Member State, may, between the validation date and the assessment date, request additional explanations from the sponsor, taking into account the considerations referred to in paragraph 5.

*Amendment*

*(Does not affect the English version)*

### **Amendment 54** **Proposal for a regulation** **Article 6 – paragraph 6 – subparagraph 5 a (new)**

*Text proposed by the Commission*

*Amendment*

***The Member States concerned shall not request additional explanations from the***



*sponsor after the assessment date.*

*Justification*

*Insertion of the text deleted in Article 8(5) for coherence reasons. The reference to the assessment date in Article 8 appears confusing and would, therefore, better fit in this Article.*

**Amendment 55**  
**Proposal for a regulation**

**Article 6 – paragraph 7 a (new)**

*Text proposed by the Commission*

*Amendment*

***7a. Where the reporting Member State does not submit the assessment report within the time periods stipulated in paragraphs 4, 6 and 7, Part I of the clinical trial shall be considered as accepted by the reporting Member State.***

*Justification*

*It should be noted that the proposal for a regulation is based on the principle of tacit approval introduced by Directive 2001/20/EC. This principle must be applied in order to ensure compliance with the time limits, which is a prerequisite not only for allowing rapid access to innovatory treatment but also for maintaining the competitiveness of European clinical research.*

**Amendment 56**  
**Proposal for a regulation**

**Article 7 – paragraph 1 – subparagraph 1 – point a a (new)**

*Text proposed by the Commission*

*Amendment*

***(aa) compliance with more restrictive national provisions than those laid down in this Regulation relating to subjects' protection in clinical trials involving vulnerable persons as defined by national law.***

*Justification*

*In providing for the protection of vulnerable persons the regulation must respect the*

*restrictive provisions put in place by some Member States for other categories of vulnerable persons, including pregnant and breast-feeding women, women in labour, and persons deprived of their liberty.*

**Amendment 57**  
**Proposal for a regulation**

**Article 7 – paragraph 3 – subparagraph 3**

*Text proposed by the Commission*

Where the sponsor does not provide additional explanations within the time period set by the Member State in accordance with the first subparagraph, the application shall be considered as withdrawn. The withdrawal shall apply only with respect to the Member State concerned.

*Amendment*

*(Does not affect the English version)*

**Amendment 58**  
**Proposal for a regulation**  
**Article 7 – paragraph 3 – subparagraph 4**

*Text proposed by the Commission*

The request and the additional explanations shall be submitted through the EU portal.

*Amendment*

The request *for additional explanations* and the additional explanations shall be submitted through the EU portal.

*Justification*

*Clarification of the text in line with Article 6 paragraph 6 subparagraph 5.*

**Amendment 59**  
**Proposal for a regulation**  
**Article 7 a (new)**

*Text proposed by the Commission*

*Amendment*

**Article 7a**  
***Ethical Assessment***

- 1. The decision to authorise the conduct of a clinical trial or a substantial modification thereof can be granted only if the relevant ethical aspects of Part I and Part II have been favourably assessed by the competent body or bodies of the Member State concerned.***
- 2. The conclusions thereof shall be included in the assessment report drawn up in accordance with Articles 6 and 7.***

*Justification*

*It should be clarified that the assessment needed for the purpose of the authorisation of a clinical trial also includes ethical aspects. The timelines indicated in Articles 6 and 7 include also ethical review and once a decision has been notified in accordance with Article 8, the clinical trial may start.*

**Amendment 60**  
**Proposal for a regulation**

**Article 7 b (new)**

*Text proposed by the Commission*

*Amendment*

***Article 7b***

***Assessment report on clinical trials in the field of rare diseases***

***1. In the specific case of clinical trials in rare diseases as defined in the Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products<sup>1</sup>, the reporting Member State shall seek the expert opinion of the Scientific Advice Working Party of the European Medicines Agency on the disease or group of diseases concerned by the clinical trial, including on aspects covered by Part II of the assessment.***

***2. For the purposes of assessing the aspects referred to in Article 7, the reporting Member State shall notify the opinion of the Scientific Advice Working Party to the Member States concerned***

*without undue delay.*

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<sup>1</sup>*OJ L 18, 22.1.2000, p. 1.*

*Justification*

*In the case of rare diseases, the necessary expertise to assess an application is generally scarce at national level. Therefore, it may be useful for it to be sought at European level. In order to help the reporting Member State and the Member States concerned to provide a well informed assessment of the application, the reporting Member State should consult the Scientific Advice Working Party of the EMA which is better placed to provide the necessary expertise.*

**Amendment 61**  
**Proposal for a regulation**

**Article 8 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***2a. Where the Member State concerned disagrees with the conclusion of the reporting Member State on the basis of points (a) and (b) of the second subparagraph of paragraph 2, the clinical trial shall not take place in the Member State concerned.***

*Justification*

*The text proposed by the Commission (Article 8(2)) envisages the possibility of the Member State concerned disagreeing with the reporting Member State's decision to authorise a clinical trial, but does not indicate what the consequence of such disagreement would be. The amendment clearly states that, in such cases, the Member State can opt out of the conclusions of the reporting Member State, in which event it would not be possible for the clinical trial to take place in the Member State concerned.*

**Amendment 62**  
**Proposal for a regulation**

**Article 8 – paragraph 2 – subparagraph 3**

*Text proposed by the Commission*

*Amendment*

Where the Member State concerned

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.

disagrees with the conclusion *of the reporting Member State* 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.

#### *Justification*

*The amendment seeks to make the wording of the proposal more precise.*

### **Amendment 63 Proposal for a regulation**

#### **Article 8 – paragraph 3 a (new)**

*Text proposed by the Commission*

*Amendment*

***3a. In the event of a Member State refusing authorisation on the basis of Part II, the sponsor may appeal, once only, to the Member State concerned through the European Union portal referred to in Article 77. The sponsor may send additional explanations within seven days. The Member State concerned shall assess for a second time, for its own territory, the aspects referred to in Article 7(1), and shall take account of the additional explanations provided by the sponsor.***

***The Member State concerned shall complete its assessment within seven days from the date on which the additional explanations are received. Where the Member State concerned refuses authorisation or does not provide a conclusion as regards Part II within the seven-day time period, the application shall be considered as definitively refused and the clinical trial shall not take place in the Member State concerned.***

*Justification*

*This amendment seeks to enable sponsors to submit an appeal in relation to Part II of the assessment procedure. This would give the sponsor a final opportunity to justify and explain to the Member State concerned the aspects of the clinical trial covered by Part II. To ensure the assessment procedure is not excessively prolonged, the possibility of appeal is offset by the principle of tacit approval.*

**Amendment 64**  
**Proposal for a regulation**  
**Article 8 – paragraph 5**

*Text proposed by the Commission*

*Amendment*

**5. The Member States concerned shall not request additional explanations from the sponsor after the assessment date.** *deleted*

*Justification*

*Text moved to Article 6 paragraph 5a (new) as a matter of clarity.*

**Amendment 65**  
**Proposal for a regulation**  
**Article 8 – paragraph 6 a (new)**

*Text proposed by the Commission*

*Amendment*

**6a. After the notification date, unless the authorisation is refused by the Member State concerned, no further assessment or decision shall prevent the sponsor from starting the clinical trial.**

*Justification*

*It should be clarified that once the single decision is notified by the Member State concerned, the sponsor can start the clinical trial.*

**Amendment 66**  
**Proposal for a regulation**  
**Article 9 – paragraph 1**

*Text proposed by the Commission*

1. Member States shall ensure that the persons validating and assessing the application do not have conflicts of interest, are independent of the sponsor, ***the institution of the trial site*** and the investigators involved, as well as free of any other undue influence.

*Amendment*

1. Member States shall ensure that the persons validating and assessing ***Parts I and II of*** the application do not have conflicts of interest, are independent of the sponsor and the investigators involved, as well as free of any other undue influence.

**Amendment 67**  
**Proposal for a regulation**

**Article 9 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***2a. Member State shall ensure that the assessment of Part II is done by a group of people at least half of whom respect the same suitability criteria as those meet the conditions laid down for investigators in Article 46 of this Regulation.***

**Amendment 68**  
**Proposal for a regulation**  
**Article 9 – paragraph 3**

*Text proposed by the Commission*

*Amendment*

3. In the assessment, the view of at least one person whose primary area of interest is non-scientific shall be taken into account. The view of at least one patient shall be taken into account.

3. In the assessment, the view of at least one person whose primary area of interest is non-scientific shall be taken into account. The view of at least one patient shall be taken into account. ***Where possible, that patient shall be a representative of a patients' organization in the disease area for which the investigational medicinal product is intended.***

*Justification*

*It is appropriate to take into account the view of a relevant patient. Ideally the patient should represent a patients' organisation for the disease that the IMP is intended to treat.*

**Amendment 69**  
**Proposal for a regulation**

**Article 10 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***2a. Where the clinical trial concerns other categories of subjects who are considered vulnerable under national law, the application to conduct the clinical trial shall be assessed on the basis of the national law of the Member States concerned.***

*Justification*

*Where the protection of vulnerable persons is concerned, this regulation must comply with the provisions (in the Member States concerned) relating to other categories of vulnerable persons, such as women who are pregnant, are about to or have just given birth, women who are breastfeeding, and people in detention.*

**Amendment 70**  
**Proposal for a regulation**

**Article 13 – paragraph 1**

*Text proposed by the Commission*

*Amendment*

This Chapter is without prejudice to the possibility for the sponsor to submit, following the refusal to grant an authorisation or the withdrawal of an application, an application for authorisation to any intended Member State concerned. That application shall be considered as a new application for authorisation of another clinical trial.

This Chapter is without prejudice to the possibility for the sponsor to submit, following the refusal to grant an authorisation or the withdrawal of an application, an application for authorisation to any intended Member State concerned. That application shall be considered as a new application for authorisation of another clinical trial. ***The new application shall specify the grounds on which the initial application was rejected or withdrawn together with the changes made to the original version of the protocol.***



**Amendment 71**  
**Proposal for a regulation**  
**Article 14 – paragraph 1 – subparagraph 2**

*Text proposed by the Commission*

The application may be submitted only after the notification date of the initial authorisation decision.

*Amendment*

The application may be submitted only after the notification date of the initial authorisation decision **by all Member States concerned**.

*Justification*

*There will be more than one notification date of the initial authorisation because these are notified by each Member State concerned individually. The decisions will probably be notified almost at the same time or with a difference of just a few days. Given the short timelines for the initial authorisation, it is preferable to keep the process simple, clear and ordered by not starting to add new Member States before the initial procedure has been closed.*

**Amendment 72**  
**Proposal for a regulation**

**Article 14 – paragraph 2**

*Text proposed by the Commission*

2. **The** reporting Member State for the **application referred to in paragraph 1** shall be the reporting Member State for the **initial authorisation procedure**.

*Amendment*

2. **Where there was a** reporting Member State for the **initial authorisation procedure it** shall be the reporting Member State for the **application referred to in paragraph 1. Where the initial application was submitted to one Member State only, that Member State shall be the reporting Member State.**

*Justification*

*This ensures that a Reporting Member State for the initial authorisation is the Reporting Member State for the procedure to extend a clinical trial. A Reporting Member State should only be appointed if there are three or more Member States involved in an application. A clinical trial should not be extended on the basis of a trial authorised by only 1 or 2 Member States. An EU decision should always be based on a majority decision of member states, which would mean that the minimum number of Member States involved to achieve this would be three.*

**Amendment 73**  
**Proposal for a regulation**  
**Article 14 – paragraph 11**

*Text proposed by the Commission*

11. A sponsor shall not submit an application in accordance with this Article where a procedure referred to in Chapter III as regards that clinical trial is pending.

*Amendment*

11. A sponsor shall not submit an application in accordance with this Article where a procedure referred to in Chapter III as regards that clinical trial **and relating to an aspect covered by Part I of the assessment report** is pending.

*Justification*

*The assessment of Part II is national, so the submission of a request to add a new Member State should not be prevented by an ongoing substantial modification procedure related to Part II.*

**Amendment 74**  
**Proposal for a regulation**

**Article 17 – paragraph 4 – subparagraph 3**

*Text proposed by the Commission*

Where the reporting Member State has not notified the sponsor according to points (a) to (c) of paragraph 2 within three days following receipt of the comments or of the completed application, the application shall be considered complete and, where the clinical trial **is a low-intervention clinical trial**, that it will remain a **low-intervention** clinical trial after its substantial modification.

*Amendment*

Where the reporting Member State has not notified the sponsor according to points (a) to (c) of paragraph 2 within three days following receipt of the comments or of the completed application, the application shall be considered complete and, where the clinical trial **poses a minimal risk**, that it will remain a **minimal-risk** clinical trial after its substantial modification.

*Justification*

*It would be better to define the second category of research by the level of risk incurred by the subject rather than the type of intervention. This reflects the main objective of the draft regulation, which is to establish a risk-based approach. Furthermore, the regulation should be brought into line with the provisions of the Oviedo Convention. Article 17 of that convention, which has been ratified by several Member States, contains a definition of the term 'minimal risk'.*

**Amendment 75**  
**Proposal for a regulation**

**Article 28 – paragraph 1 – point a**

*Text proposed by the Commission*

*Amendment*

(a) the anticipated therapeutic and public health benefits justify the foreseeable risks and inconveniences;

*Does not affect English version.*

**Amendment 76**  
**Proposal for a regulation**

**Article 28 – paragraph 1 – point b**

*Text proposed by the Commission*

*Amendment*

(b) *compliance with* point (a) is *permanently* observed;

(b) *the principles referred to in* point (a) *are* observed *throughout the study*;

*Justification*

*Clarification of the Commission text.*

**Amendment 77**  
**Proposal for a regulation**

**Article 28 – paragraph 1 – point c**

*Text proposed by the Commission*

*Amendment*

(c) *the subject or, where the subject is not able to give informed consent, his or her legal representative has given informed consent*;

*deleted*

*Justification*

*It makes more sense for this condition to be moved so that it follows on from point (d) of Article 28(1). In practice, the subject or his/her legal representative should have been duly informed of the objectives, risks and inconveniences of the clinical trial before giving his/her informed consent.*

**Amendment 78**  
**Proposal for a regulation**

**Article 28 – paragraph 1 – point d**

*Text proposed by the Commission*

(d) the subject or, where the subject is not able to give informed consent, his or her legal representative has had the opportunity, in a prior interview with the investigator or ***a member of the investigating team***, to understand the objectives, risks and inconveniences of the clinical trial, and the conditions under which it is to be conducted and has also been informed of the right to withdraw from the clinical trial at any time without any resulting detriment;

*Amendment*

(d) the subject or, where the subject is not able to give informed consent, his or her legal representative has had the opportunity, in a prior interview with the investigator or ***his/her representative***, to understand the objectives, risks and inconveniences of the clinical trial, and the conditions under which it is to be conducted and has also been informed of the right to withdraw from the clinical trial at any time without any resulting detriment;

*Justification*

*In practice, an investigator can entrust a doctor or another person with the task of informing and obtaining the consent of the person who will be the research subject or of his/her legal representative. In France for example, this approach is authorised by law.*

**Amendment 79**  
**Proposal for a regulation**

**Article 28 – paragraph 1 – point d a (new)**

*Text proposed by the Commission*

*Amendment*

***(da) the subject or, where the subject is not able to give informed consent, his or her legal representative has given informed consent;***

*Justification*

*It makes more sense for point (c) of Article 28(1) to be moved to the position indicated here. In practice, the subject or his/her legal representative should have been duly informed of the objectives, risks and inconveniences of the clinical trial before giving his/her informed consent.*

**Amendment 80**  
**Proposal for a regulation**

**Article 29 – paragraph 1**

*Text proposed by the Commission*

1. Informed consent shall be written, dated and signed and given freely by the subject or his or her legal representative after having been duly informed of the nature, significance, implications and risks of the clinical trial. It shall be appropriately documented. Where the subject is unable to write, oral consent in the presence of at least one impartial witness may be given in exceptional cases. The subject or his or her legal representative shall be provided with a copy of the document by which informed consent has been given.

*Amendment*

1. Informed consent shall be written, dated and signed and given freely by the subject or his or her legal representative after having been duly informed of the nature, significance, implications and risks of the clinical trial. It shall be appropriately documented. Where ***possible, sufficient time shall be given to the subject to consider the decision.*** Where the subject is unable to write, oral consent in the presence of at least one impartial witness may be given in exceptional cases. The subject or his or her legal representative shall be provided with a copy of the document by which informed consent has been given.

*Justification*

*Sufficient time should be left to the subject to take a decision. This should not apply to emergency situations where a decision should be taken promptly.*

**Amendment 81**  
**Proposal for a regulation**

**Article 30 – paragraph 1 – point b**

*Text proposed by the Commission*

(b) the incapacitated subject has received adequate information in relation to his or her capacity for understanding regarding the trial, the risks and the benefits;

*Amendment*

(b) the incapacitated subject has received adequate information in relation to his or her capacity for understanding regarding the trial, the risks and the benefits ***from the investigator or his/her representative, in accordance with the legislation of the Member State concerned;***

*Justification*

*In practice, an investigator can entrust a doctor representing him/her with the task of*

*informing and obtaining the consent of the person who will be the research subject or of his/her legal representative. In France for example, this approach is authorised by law.*

**Amendment 82**  
**Proposal for a regulation**

**Article 30 – paragraph 1 – point f**

*Text proposed by the Commission*

*Amendment*

(f) such research relates directly to a **life-threatening or debilitating** medical condition from which the **subject** suffers;

(f) such research relates directly to a medical condition from which the **person concerned** suffers;

*Justification*

*Article 30 concerns patients who are unable to give their consent because they suffer from a condition which affects their cognitive functions. Conditions of this kind are not the same as the emergency situations covered under Article 32 and should not be referred to in this article. The adjective ‘debilitating’ (in the sense of ‘weakening’) is rarely used in France nowadays. The article should refer only to the medical condition ‘from which the person concerned suffers’*

**Amendment 83**  
**Proposal for a regulation**

**Article 30 – paragraph 1 – point h**

*Text proposed by the Commission*

*Amendment*

(h) there are grounds for expecting that participation in the clinical trial will produce a benefit to the incapacitated subject outweighing the risks or will produce **no risk at all**.

(h) there are grounds for expecting that participation in the clinical trial will produce a benefit to the incapacitated subject outweighing the risks or will produce **only a minimal risk**.

*Justification*

*The proposal for a regulation applies only to clinical trials which involve risks (whether minimal or greater than minimal). It does not apply to non-interventional research, which by its very nature poses no risk.*

**Amendment 84**  
**Proposal for a regulation**

**Article 31 – paragraph 1 a (new)**

*Text proposed by the Commission*

*Amendment*

***(1a) Without prejudice to Article 31(1), where the clinical trial poses a minimal risk and the consent of the second person with parental authority cannot be given within a period consistent with the methodological requirements of the research, and provided that a favourable ethical opinion has been issued, the clinical trial on the minor may proceed on the basis of the consent of the only person present with parental authority.***

*Justification*

*The proposal for a regulation does not lay down different arrangements for obtaining consent to take account of the specific level of risk and burden posed by the research. Member States should be able to simplify the arrangements for obtaining consent for clinical trials which pose a minimal risk to minors when it is not possible (given the timing imperative) to wait for the second person with parental authority to arrive. A favourable ethical opinion must also be issued.*

**Amendment 85**  
**Proposal for a regulation**

**Article 31 – paragraph 1 – point h**

*Text proposed by the Commission*

*Amendment*

(h) some direct benefit for the **group** of patients **is** obtained from the clinical trial.

(h) some direct benefit for the **category** of patients **concerned by the trial may be** obtained from the clinical trial.

*Justification*

*'Category' is a more appropriate term.*

**Amendment 86**  
**Proposal for a regulation**

**Article 32 – paragraph 1 – introductory part**

*Text proposed by the Commission*

1. By way of derogation from points (c) and (d) of Article 28(1), from points (a) and (b) of Article 30(1) and from points (a) and (b) of Article 31(1), informed consent **may** be obtained after the start of the clinical trial **to continue the clinical trial** and information on the clinical trial **may** be given after the start of the clinical trial provided that all of the following conditions are fulfilled:

*Amendment*

1. By way of derogation from points (c) and (d) of Article 28(1), from points (a) and (b) of Article 30(1) and from points (a) and (b) of Article 31(1), informed consent, **referred to in Article 29(1), shall** be obtained **as soon as possible** after the start of the clinical trial and information on the clinical trial **shall** be given after the start of the clinical trial provided that all of the following conditions are fulfilled:

*Justification*

*Consent for continuing the trial should preferably be sought as soon as the participant is once again in a position to give consent and, ideally, before the trial comes to an end.*

**Amendment 87**

**Proposal for a regulation**

**Article 32 – paragraph 1 – point a**

*Text proposed by the Commission*

(a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, it is impossible to obtain prior informed consent from the subject and it is impossible to supply prior information to the subject;

*Amendment*

(a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, it is impossible to obtain prior informed consent from the subject **or its legal representative (parent or guardian)** and it is impossible to supply prior information to the subject **or its legal representative (parent or guardian)**;

**Amendment 88**

**Proposal for a regulation**

**Article 32 – paragraph 1 – point b**

*Text proposed by the Commission*

(b) **no** legal representative **is available**;

*Amendment*

(b) **the consent of the** legal representative **cannot be given within a period consistent with the methodological requirements of**



***the research;***

*Justification*

*With regard to consent for clinical trials in emergency situations, the condition relating to the unavailability of a legal representative should be deleted. Anything else would represent a backward step in some Member States. For example, French law provides for a trial to go ahead without the prior consent of family members, even if the latter are actually present when a life-threatening situation arises (heart attack).*

**Amendment 89**  
**Proposal for a regulation**

**Article 32 – paragraph 1 – point c**

*Text proposed by the Commission*

*Amendment*

(c) the subject has not previously expressed objections known to the investigator;

(c) the subject ***or legal representative*** has not previously expressed objections known to the investigator;

**Amendment 90**  
**Proposal for a regulation**

**Article 32 – paragraph 1 – point d**

*Text proposed by the Commission*

*Amendment*

***(d) the research relates directly to a medical condition which causes the impossibility to obtain prior informed consent and to supply prior information;***

***deleted***

*Justification*

*An emergency situation is not always the reason why consent cannot be obtained. For example, research into states of shock might usefully involve patients who are in intensive care and who, for this reason, are unable to give consent (because they are in a coma or are sedated). A literal reading of this article could prevent this kind of research from going ahead.*

**Amendment 91**  
**Proposal for a regulation**

**Article 32 – paragraph 1 – point e**

*Text proposed by the Commission*

*Amendment*

(e) the clinical trial poses **a minimal risk to, and imposes a minimal burden on, the subject.**

(e) **there are grounds for expecting that the benefits of participating in the clinical trial are proportional to the risks for the subject or that it involves a minimal risk only and it doesn't impose a disproportionate burden on the subject.**

*Justification*

*Philippe Juvin welcomes the fact that, under the proposal for a regulation, a derogation from the prior patient consent requirement may be granted for clinical trials in emergency situations. However, applying this derogation to trials which pose only a minimal risk is too restrictive and would be a backward step for some Member States. In practice, this would rule out many forms of research relating to resuscitation and innovative products.*

**Amendment 92**  
**Proposal for a regulation**

**Article 32 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

**2a. If the subject or, where applicable, his/her legal representative does not give his/her consent for the research to continue, he/she shall be informed that he/she may object to the use of data obtained prior to the denial of consent.**

*Justification*

*In the interests of subject safety and data reliability, Philippe Juvin proposes to include an additional provision obliging the investigator, or his/her representative, to ask the subject or, where applicable, his/her representative, if he/she objects to the data being used.*

**Amendment 93**  
**Proposal for a regulation**

**Article 32 – paragraph 2 – subparagraph 1 – point a**

*Text proposed by the Commission*

*Amendment*

(a) regarding incapacitated subjects and

(a) regarding incapacitated subjects and

minors, the informed consent referred to in paragraph 1 shall be obtained as soon as possible from the legal representative and the information referred to in paragraph 1 shall be given as soon as possible to the subject;

minors, the informed consent referred to in paragraph 1 shall be obtained as soon as possible from the legal representative and the information referred to in paragraph 1 shall be given as soon as possible to the subject ***by the investigator or his/her representative***;

#### *Justification*

*In practice, an investigator can entrust a doctor representing him/her with the task of informing and obtaining the consent of the person who will be the research subject or of his/her legal representative. In France for example, this approach is authorised by law.*

### **Amendment 94 Proposal for a regulation**

#### **Article 34 – title**

##### *Text proposed by the Commission*

End of the clinical trial, early termination of the clinical trial

##### *Amendment*

End of the clinical trial, early termination of the clinical trial ***and submission of results***

#### *Justification*

*Adjustment of title to reflect the content of the article.*

### **Amendment 95 Proposal for a regulation Article 34 – paragraph 3 – subparagraph 1**

##### *Text proposed by the Commission*

Within ***one year*** from the end of a clinical trial, the sponsor shall submit to the EU database a summary of the results of the clinical trial.

##### *Amendment*

Within ***two*** years from the end of a clinical trial, the sponsor shall submit to the EU database a summary of the results of the clinical trial ***containing the elements laid down in Annex IIIa of this Regulation. Additionally, the sponsor shall also submit a summary with the same content which shall be understandable to a layperson.***

***Where the clinical trial is intended, at the time of submission of the application for authorisation, to be used for obtaining a***

***marketing authorisation for a medicinal product, the summary of the results referred to in subparagraph 1 shall be made public within 30 days after the marketing authorisation date or, where applicable, within one year from the decision to discontinue the development of a medicinal product.***

*Justification*

*Whereas the summary of the results of clinical trials needs to be disclosed, the competitiveness of the sponsor should not be affected by such disclosure. It is therefore proposed that, for commercial trials only, the results are disclosed 30 days after the marketing authorisation is granted. In case the development of the medicinal product is stopped, the results should be published within one year from the decision to discontinue the development process.*

**Amendment 96  
Proposal for a regulation**

**Article 34 – paragraph 4**

*Text proposed by the Commission*

4. For the purpose of this Regulation, if a suspended or temporarily halted clinical trial is not restarted, the date of the decision of the sponsor not to restart the clinical trial shall be considered as the end of the clinical trial. In the case of early termination, the date of the early termination shall be considered as the date of the end of the clinical trial.

*Amendment*

4. For the purpose of this Regulation, if a suspended or temporarily halted clinical trial is not restarted, the date of the decision of the sponsor not to restart the clinical trial shall be considered as the end of the clinical trial. In the case of early termination, the date of the early termination shall be considered as the date of the end of the clinical trial.

***If a clinical trial is discontinued, the sponsor shall notify the reasons thereof to the Member State concerned through the EU portal within 15 days from the decision to discontinue the clinical trial.***

*Justification*

*Amendment aiming at ensuring transparency about the reasons for discontinuing a clinical trial.*

**Amendment 97**  
**Proposal for a regulation**

**Article 34 – paragraph 5 a (new)**

*Text proposed by the Commission*

*Amendment*

***5a. The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to amend Annex IIIa with the objective to adapt them to scientific or global regulatory developments.***

*Justification*

*Flexibility is needed in order to adjust the contents of the summary of the results in the event of scientific or global regulatory developments.*

**Amendment 98**  
**Proposal for a regulation**

**Article 36 – paragraph 1**

*Text proposed by the Commission*

*Amendment*

The European Medicines Agency established by Regulation (EC) No 726/2004 (hereinafter, the ‘Agency’) shall set up and maintain an electronic database for the reporting provided for in Articles 38 and 39.

The European Medicines Agency established by Regulation (EC) No 726/2004 (hereinafter, the ‘Agency’) shall set up and maintain an electronic database for the reporting provided for in Articles 38 and 39. ***That electronic database shall be a module of the database referred to in Article 24 paragraph 1 of Regulation (EC) No 726/2004.***

*Justification*

*Correction of the legal basis of the EUdraVigilence database. This amendment replaces AM 17 of the draft opinion.*

**Amendment 99**  
**Proposal for a regulation**  
**Article 38 – paragraph 2**

*Text proposed by the Commission*

2. The time period for reporting shall take account of the **severity** of the reaction. Where necessary to ensure timely reporting, the sponsor may submit an initial incomplete report followed up by a complete report.

*Amendment*

2. The time period for reporting shall take account of the **seriousness** of the reaction. Where necessary to ensure timely reporting, the sponsor may submit an initial incomplete report followed up by a complete report.

*Justification*

*Amendment aiming at bringing this text in line with the pharmacovigilence legislation which refers to "seriousness", not "severity".*

**Amendment 100**  
**Proposal for a regulation**  
**Article 38 – paragraph 3**

*Text proposed by the Commission*

3. Where a sponsor, **due to a lack of resources, does not have the possibility** to report to the electronic database referred to in Article 36, it may report to the Member State where the suspected unexpected serious adverse reaction occurred. That Member State shall report the suspected unexpected serious adverse reaction in accordance with paragraph 1.

*Amendment*

3. Where a sponsor **is unable** to report **directly** to the electronic database referred to in Article 36, it may report to the Member State where the suspected unexpected serious adverse reaction occurred. That Member State shall report the suspected unexpected serious adverse reaction in accordance with paragraph 1.

*Justification*

*The reason why the sponsor is unable to directly report the SUSAR directly is irrelevant. In order to make sure that SUSARs are always reported, reporting via the Member State should be possible irrespective of the reason therefore.*

**Amendment 101**  
**Proposal for a regulation**  
**Article 39 – paragraph 1**

*Text proposed by the Commission*

1. Regarding non-authorised investigational medicinal products other than placebo, and authorised

*Amendment*

1 Regarding non-authorised investigational medicinal products other than placebo, and authorised investigational medicinal

investigational medicinal products which, according to the protocol, are not used in accordance with the terms of the marketing authorisation, the sponsor shall submit annually by electronic means to the Agency a report on the safety of each investigational medicinal product used in *a* clinical trial for which it is the sponsor.

products which, according to the protocol, are not used in accordance with the terms of the marketing authorisation, the sponsor shall submit annually by electronic means to the Agency a report on the safety of each investigational medicinal product used in *one or more* clinical trials for which it is the sponsor. ***Where relevant, that report shall clearly identify any safety aspects concerning a specific gender or age group.***

#### *Justification*

*If the investigational medical product is the object of more than one clinical trial, it should be possible, in order to avoid duplication of reporting and, hence, reduce the administrative burdens, to submit a single report on the safety of that investigational medicinal product. Moreover the safety report should contain data about differences between gender and age groups as regards safety.*

### **Amendment 102 Proposal for a regulation**

#### **Article 39 – paragraph 1 a (new)**

*Text proposed by the Commission*

*Amendment*

***1a. Where the sponsor does not have access to certain information, and therefore, is not able to submit a complete report, this should be stated in the report.***

***In the case of a clinical trial involving the use of more than one investigational medicinal product, the sponsor may submit a single safety report on all investigational medicinal products used in the trial. The sponsor should provide the reasons for this decision in the report.***

### **Amendment 103 Proposal for a regulation Article 41 – paragraph 1**

*Text proposed by the Commission*

*Amendment*

1. Regarding authorised medicinal products which, according to the protocol, are used in accordance with the terms of the marketing authorisation, the sponsor shall inform annually the marketing authorisation holder of all suspected serious adverse reactions.

1. Regarding authorised medicinal products which, according to the protocol, are used in accordance with the terms of the marketing authorisation, the sponsor shall inform annually the marketing authorisation holder of all suspected serious adverse reactions, ***including, where relevant, those reactions concerning a specific gender or age group.***

*Justification*

*Where relevant, safety aspects that are specific to a gender or age group should be identified and duly reported to the marketing authorisation holder.*

**Amendment 104**  
**Proposal for a regulation**

**Article 43 – paragraph 1**

*Text proposed by the Commission*

*Amendment*

Safety reporting with regard to auxiliary medicinal products shall be made in accordance with ***Chapter 3 of*** Directive 2001/83/EC.

Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Directive ***2010/84/EU***.

*Justification*

*The reference to the directive needs to be changed. Directive 2010/84/EU, which entered into force in January 2011, amended, as regards pharmacovigilance, Directive 2001/83/EC.*

**Amendment 105**  
**Proposal for a regulation**

**Article 45 – paragraph 1 – point a**

*Text proposed by the Commission*

*Amendment*

(a) whether the clinical trial is a ***low-intervention*** clinical trial;

(a) whether the clinical trial is a ***minimal-risk*** clinical trial;



### *Justification*

*The proposal for a regulation should preferably be based on an approach which takes account of the additional risks entailed by the research and should bring monitoring into line with the degree of risk incurred by the subject in the clinical trial.*

## **Amendment 106** **Proposal for a regulation**

### **Article 48 – paragraph 1 – subparagraph 1**

#### *Text proposed by the Commission*

Investigational medicinal products shall be traceable, stored, destroyed and returned as appropriate and proportionate to ensure subject safety and the reliability and robustness of the data generated in the clinical trial, taking into account whether the investigational medicinal product is authorised, and whether the clinical trial is a ***low-intervention*** clinical trial.

#### *Amendment*

Investigational medicinal products shall be traceable, stored, destroyed and returned as appropriate and proportionate to ensure subject safety and the reliability and robustness of the data generated in the clinical trial, taking into account whether the investigational medicinal product is authorised, and whether the clinical trial is a ***minimal-risk*** clinical trial.

### *Justification*

*The proposal for a regulation should preferably be based on an approach which takes account of the additional risks entailed by the research and should bring the provisions concerning traceability, storage, disposal and returns into line with the degree of risk incurred by the subject in the clinical trial.*

## **Amendment 107** **Proposal for a regulation**

### **Article 49 – paragraph 2**

#### *Text proposed by the Commission*

2. For the purposes of this Article, a 'serious breach' means a breach likely to affect to a significant degree the safety ***and*** rights of the subjects or the reliability and robustness of the data generated in the clinical trial.

#### *Amendment*

2. For the purposes of this Article, a 'serious breach' means a breach likely to affect to a significant degree the safety, rights ***and health*** of the subjects or the reliability and robustness of the data generated in the clinical trial.

**Amendment 108**  
**Proposal for a regulation**

**Article 50 – paragraph 1**

*Text proposed by the Commission*

1. The sponsor shall notify the Member States concerned through the EU portal and without undue delay, of all unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 38.

*Amendment*

1. The sponsor shall notify the **competent bodies of the** Member States concerned through the EU portal and without undue delay, of all unexpected events which affect the benefit-risk balance of the clinical trial, but are not suspected unexpected serious adverse reactions as referred to in Article 38.

*Justification*

*Information about risk-benefit profile should also be provided to ethical committees. The notion of "competent bodies" encompasses both national authorities and ethical committees.*

**Amendment 109**  
**Proposal for a regulation**  
**Article 52 – paragraph 3**

*Text proposed by the Commission*

3. The investigator's brochure shall be updated **where** new safety information becomes available, **and at least once per year**.

*Amendment*

3. The investigator's brochure shall be updated **whenever** new safety information becomes available.

*Justification*

*This Regulation should not impose unnecessary administrative burdens. The investigator's brochure should be updated every time new safety information becomes available, which may take more than 1 year.*

**Amendment 110**  
**Proposal for a regulation**

**Article 66 – paragraph 1**

*Text proposed by the Commission*

The language of the information on the label shall be determined by the Member State concerned. The medicinal product may be labelled in several languages.

*Amendment*

The language of the information on the label shall be determined by the Member State concerned ***and shall be one of the official languages of the Union.*** The medicinal product may be labelled in several languages.

*Justification*

*Clarification of the wording of Amendment 25. In order not to impose unnecessary burdens, the information on the label should appear in EU official languages only. This should not prevent Member States concerned from imposing the use of a language which is not an official language of that Member State, but which is relevant to the localisation of the clinical trials site. The latter should be taken into account also by Member States having more than one official language of the EU.*

**Amendment 111**  
**Proposal for a regulation**

**Article 72 – paragraph 1**

*Text proposed by the Commission*

For clinical trials other than low-intervention clinical trials, the sponsor shall ensure that compensation in accordance with the applicable laws on liability of the sponsor and the investigator is provided for any damage suffered by the subject. This damage compensation shall be provided independently of the financial capacity of the sponsor and the investigator.

*Amendment*

For clinical trials other than low-intervention clinical trials, the sponsor shall ensure that compensation in accordance with the applicable laws on liability of the sponsor and the investigator, ***including by means of insurance,*** is provided for any damage suffered by the subject. This damage compensation shall be provided independently of the financial capacity of the sponsor and the investigator.

***Where damage compensation is provided by means of insurance, a sponsor may use a single insurance policy to cover one or more clinical trials within the same Member State.***

*Justification*

*It should be clarified that commercial insurance remains an option alongside with the national indemnification system. Moreover, allowing sponsors to cover more than one*

*clinical trial within the same Member State by the same insurance policy will drive down insurance costs.*

## **Amendment 112** **Proposal for a regulation**

### **Article 73 – paragraph 1**

*Text proposed by the Commission*

1. Member States shall provide for a national indemnification mechanism for compensating damage as referred to in Article 72.

*Amendment*

**1. *For clinical trials which, for objective reasons, were not intended, at the time of submission of the application for authorisation, to be used for obtaining a marketing authorisation for a medicinal product,*** Member States shall provide for a national indemnification mechanism for compensating damage as referred to in Article 72.

***The use of the national indemnification system shall be free of charge or subject to a nominal fee.***

*Justification*

*There are uncertainties about the way in which such a system would work and be financed. In any case, the access to the national indemnification system should be limited to non-commercial clinical trials. In order to have real added value, the use of this system should be either for free or at a moderate cost (nominal fee). The commercial insurance system should not be put in competition with a public system operating on a not-for-profit basis, as this may drive insurers out of this market.*

## **Amendment 113** **Proposal for a regulation**

### **Article 74 – paragraph 2**

*Text proposed by the Commission*

2. The measures referred to in paragraph 1 shall be communicated to all Member States concerned through the EU portal.

*Amendment*

2. The measures referred to in paragraph 1 shall be ***made publicly available on and*** communicated to all Member States concerned through the EU portal.

**Amendment 114**  
**Proposal for a regulation**

**Article 78 – paragraph 3 – indent 2**

*Text proposed by the Commission*

– protecting commercially confidential information;

*Amendment*

– Protecting commercially confidential information ***in particular through taking into account the authorization status of the product;***

*Justification*

*The status of commercially confidential information is dependent on the authorization status of a medicinal product and as such should be considered when defining disclosure requirements in accordance with applicable EU legislation.*

**Amendment 115**  
**Proposal for a regulation**  
**Article 78 – paragraph 5 a (new)**

*Text proposed by the Commission*

*Amendment*

***5a The user interface of the EU database shall be available in all Union official languages.***

*Justification*

*Navigation through the EU database should be available in all EU official languages. This doesn't involve any obligation to translate the protocol of the clinical trial and other related information contained in the database, as this would generate significant costs.*

**Amendment 116**  
**Proposal for a regulation**

**Article 90 a (new)**

*Text proposed by the Commission*

*Amendment*

***Article 90a***

***Review of the Regulation***

***As from the entry into force of this Regulation, every five years the***

*Commission shall submit to the European Parliament and to the Council a report on the implementation of the Regulation. The report shall include an assessment of the impact that the Regulation has had on scientific and technological progress, and the measures required in order to maintain the competitiveness of European clinical research.*

*Justification*

*The Commission should be required to assess regularly and in detail the impact of the regulation on European clinical research. The purpose is to ascertain that the regulation does in fact support scientific and technological progress in what is a rapidly-changing environment (the European ‘smart law’ approach).*

**Amendment 117**  
**Proposal for a regulation**

**Annex I – part 2 – point 9**

*Text proposed by the Commission*

9. In the case of a resubmission, the cover letter shall highlight the changes as compared to the *previous submission*.

*Amendment*

9. In the case of a resubmission, the cover letter shall highlight the **grounds on which the original application was rejected and the changes as compared to the original version of the protocol**.

*Justification*

*The purpose of this amendment is to prevent a sponsor from submitting a proposal to another Member State without that State having first been informed that the application had previously been rejected or withdrawn and on what grounds, and without the sponsor having made the required improvements.*

**Amendment 118**  
**Proposal for a regulation**

**Annex I – part 4 – point 13 – point 3**

*Text proposed by the Commission*

· an evaluation of the anticipated benefits and risks to allow assessment in

*Amendment*

· an evaluation of the anticipated benefits and risks, **including for specific**

accordance with Article 6;

**subpopulations**, to allow assessment in accordance with Article 6;

*Justification*

*Amendment replacing Amendment 27 of the draft opinion. The term "subpopulations" is more appropriate than patient groups, as it is broader.*

**Amendment 119**  
**Proposal for a regulation**  
**Annex I – point 13 – indent 6**

*Text proposed by the Commission*

if **elderly persons or women** are excluded from the clinical trial, an explanation and justification for these exclusion criteria;

*Amendment*

if **patients from a specific gender or age group** are excluded from the clinical trial, an explanation and justification for these exclusion criteria;

*Justification*

*Some therapies may have different outcomes in different patient groups (differences according to gender, age group etc.).*

**Amendment 120**  
**Proposal for a regulation**  
**Annex I – point 13 – indent 9**

*Text proposed by the Commission*

a description of the publication policy;

*Amendment*

a description of the publication policy, **clearly indicating any information that may be available from a source other than the EU database**;

*Justification*

*For transparency reasons, if more extensive results or any other further information is to be published by the sponsor somewhere else than the EU database, this should also be specified in the description of the publication policy.*

**Amendment 121**  
**Proposal for a regulation**  
**Annex I – part 16 – point 61**

*Text proposed by the Commission*

*Amendment*

**61. Description of any agreement between the sponsor and the site shall be submitted.** *deleted*

*Justification*

*The drafting and signing of a contract by a sponsor and a hospital is a very lengthy process. The requirement to include these contracts in the initial application dossier serves no purpose. The contracts do not include any scientific details relating to the protocol or the protection of research subjects. In order to ensure that a Member States is not excluded from a clinical trial on contractual grounds, this provision should be deleted and it should be possible for contracts to be forwarded at a later date.*

**Amendment 122  
Proposal for a regulation**

**Annex III a (new)**

*Text proposed by the Commission*

*Amendment*

***Annex IIIa***

***Content of the summary of the results of clinical trials***

***The summary of the results of the clinical trials referred to in Article 34 paragraph 3 shall contain information on the following elements:***

***1. Trial information:***

***a) Study identification***

***b) Identifiers***

***c) Sponsor details***

***d) Paediatric regulatory details***

***e) Result analysis stage***

***f) General Information about the trial***

***g) Population of trial subjects with actual number of subjects included in the trial***

***2. Subject disposition:***

***a) Recruitment***

***b) Pre-assignment Period***



- c) Post Assignment Periods*
  - 3. Baseline Characteristics:**
    - a) Baseline Characteristics (Required)*
      - Age*
      - b) Baseline Characteristics (Required)*
        - Gender*
        - c) Baseline Characteristics (Optional)*
          - Study Specific Characteristic*
  - 4. End Points:**
    - a) Endpoint definitions*
    - b) End Point #1\**
      - Statistical Analyses*
    - c) End Point #2,*
      - Statistical Analyses*
- \*Information shall be provided for as many end points as defined in the protocol.*
- 5. Adverse Events:**
  - a) Adverse events information*
  - b) Adverse event reporting group*
  - c) Serious Adverse Events*
  - d) Non-serious adverse event*
- 6. More Information:**
  - a) Global Substantial Modifications*
  - b) Global Interruptions and re-starts*
  - c) Limitations & Caveats*

#### *Justification*

*Clarification on what information should be included in the summary of the results of the clinical trial. This information will also be the one that will be publicly available for transparency reasons. This proposed annex builds on the Commission's Technical Guidance on the data fields of result-related information on clinical trials of 22nd of January 2013. To provide for flexibility, the Commission should be able to adjust this annex by way of delegated acts.*

**Amendment 123**  
**Proposal for a regulation**  
**Annex IV – paragraph 1 – section 1.1. – point 1 – point e**

*Text proposed by the Commission*

*Amendment*

(e) the subject identification number/treatment number and, where relevant, the visit number;

(e) ***either*** the subject identification number ***or*** treatment number and, where relevant, the visit number;

*Justification*

*Previous experience has shown that the current formulation is not clear enough and that in some cases both the identification number and the treatment number have been requested. In practice, for reasons of space, it can be difficult to have both, which is why it should be clarified that one of the two is enough.*

**Amendment 124**  
**Proposal for a regulation**  
**Annex IV – paragraph 1 – section 1.1. – point 1 – point g**

*Text proposed by the Commission*

*Amendment*

(g) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product);

(g) directions for use (reference may be made to a leaflet or other explanatory document intended for the subject or person administering the product ***or to other indications provided by the investigator***);

*Justification*

*Investigators may also orally give indications to the subject. Therefore, such indications should also be referred to. This could be done simply by adding on the outer package a message such as "please use as indicated by your investigator".*

**Amendment 125**  
**Proposal for a regulation**  
**Annex IV – paragraph 4 – point 8**

*Text proposed by the Commission*

*Amendment*

Any of the particulars listed in sections 1, 2, and 3 may be omitted and replaced by other means (e.g. use of a centralised electronic randomisation system, use of a

Any of the particulars listed in sections 1, 2, and 3 may be omitted and replaced by other means (e.g. use of a centralised electronic randomisation system, use of a

centralised information system) provided that subject safety and the reliability and robustness of data are not compromised. This shall be justified in the protocol.

centralised information system) provided that subject safety and the reliability and robustness of data are not compromised. This shall be justified in the protocol ***or in a separate document.***

#### *Justification*

*The global dimension of clinical trials needs to be taken into account. It should be possible for sponsors to use the same protocol for all clinical trials related to the same IMP wherever this trial takes place. If these justifications are to be included in the protocol, the latter will need to be adapted for a clinical trial where this exception doesn't apply, which would be an unnecessary administrative burden.*

## PROCEDURE

|   |   |           |           |
|---|---|-----------|-----------|
| <b>Title</b>  | Clinical trials on medicinal products for human use, and repeal of Directive 2001/20/EC   |           |           |
| <b>References</b>   | COM(2012)0369 – C7-0194/2012 – 2012/0192(COD)   |           |           |
| <b>Committee responsible</b><br>Date announced in plenary | ENVI<br>11.9.2012   |           |           |
| <b>Opinion by</b><br>Date announced in plenary            | IMCO<br>11.9.2012   |           |           |
| <b>Rapporteur</b><br>Date appointed                       | Cristian Silviu Buşoi<br>18.9.2012  |           |           |
| <b>Discussed in committee</b>                             | 24.1.2013   | 21.2.2013 | 20.3.2013 |
| <b>Date adopted</b>                                       | 21.3.2013   |           |           |
| <b>Result of final vote</b>                               | +: 19   | –: 14     | 0: 0      |
| <b>Members present for the final vote</b>                 | Pablo Arias Echeverría, Adam Bielan, Preslav Borissov, Cristian Silviu Buşoi, Jorgo Chatzimarkakis, Birgit Collin-Langen, Lara Comi, António Fernando Correia de Campos, Christian Engström, Vicente Miguel Garcés Ramón, Evelyne Gebhardt, Małgorzata Handzlik, Malcolm Harbour, Philippe Juvin, Sandra Kalniete, Edvard Kožušník, Toine Manders, Hans-Peter Mayer, Phil Prendergast, Robert Rochefort, Heide Rühle, Christel Schaldemose, Andreas Schwab, Catherine Stihler, Róza Gräfin von Thun und Hohenstein, Bernadette Vergnaud |           |           |
| <b>Substitute(s) present for the final vote</b>           | Raffaele Baldassarre, María Irigoyen Pérez, Constance Le Grip, Marc Tarabella, Rafał Trzaskowski, Patricia van der Kammen, Sabine Verheyen  |           |           |