



EUROPEAN PARLIAMENT

2009 - 2014

---

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

---

**2012/0192(COD)**

31.1.2013

**\*\*\*|**

## **DRAFT REPORT**

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))

Committee on the Environment, Public Health and Food Safety

Rapporteur: Glenis Willmott

### ***Symbols for procedures***

- \* Consultation procedure
- \*\*\* Consent procedure
- \*\*\*I Ordinary legislative procedure (first reading)
- \*\*\*II Ordinary legislative procedure (second reading)
- \*\*\*III Ordinary legislative procedure (third reading)

(The type of procedure depends on the legal basis proposed by the draft act.)

### ***Amendments to a draft act***

In amendments by Parliament, amendments to draft acts are highlighted in ***bold italics***. Highlighting in *normal italics* is an indication for the relevant departments showing parts of the draft act which may require correction when the final text is prepared – for instance, obvious errors or omissions in a language version. Suggested corrections of this kind are subject to the agreement of the departments concerned.

The heading for any amendment to an existing act that the draft act seeks to amend includes a third line identifying the existing act and a fourth line identifying the provision in that act that Parliament wishes to amend. Passages in an existing act that Parliament wishes to amend, but that the draft act has left unchanged, are highlighted in **bold**. Any deletions that Parliament wishes to make in such passages are indicated thus: [...].

## CONTENTS

	<b>Page</b>
DRAFT EUROPEAN PARLIAMENT LEGISLATIVE RESOLUTION.....	5
EXPLANATORY STATEMENT.....	49



## DRAFT EUROPEAN PARLIAMENT LEGISLATIVE RESOLUTION

**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))**

**(Ordinary legislative procedure: first reading)**

*The European Parliament,*

- having regard to the Commission proposal to Parliament and the Council (COM(2012)0369),
  - having regard to Article 294(2) and Article 114 and 168(4) of the Treaty on the Functioning of the European Union, pursuant to which the Commission submitted the proposal to Parliament (C7-0194/2012),
  - having regard to Article 294(3) of the Treaty on the Functioning of the European Union,
  - having regard to the opinion of the European Economic and Social Committee of 12 December 2012<sup>1</sup>,
  - having regard to Rule 55 of its Rules of Procedure,
  - having regard to the report of the Committee on the Environment, Public Health and Food Safety and the opinions of the Committee on Industry, Research and Energy and the Committee on the Internal Market and Consumer Protection (A7-0000/2013),
1. Adopts its position at first reading hereinafter set out;
  2. Calls on the Commission to refer the matter to Parliament again if it intends to amend its proposal substantially or replace it with another text;
  3. Instructs its President to forward its position to the Council, the Commission and the national parliaments.

---

<sup>1</sup> OJ C ... /Not yet published in the Official Journal.

## 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, rights **and well-being** of subjects should be protected and the data generated should be reliable and robust.

Or. en

#### *Justification*

*Pursuant to Point 6 of the World Medical Association Declaration of Helsinki, and Article 28(2) of the present proposal, the well-being of individual research subjects must take precedence over all other interests. The well-being of subjects therefore has to be emphasised more in this legislation.*

## Amendment 2

### Proposal for a regulation

#### Recital 2

*Text proposed by the Commission*

(2) In order to allow for independent control as to whether these principles are adhered to, a clinical trial should be subject to prior authorisation.

*Amendment*

(2) In order to allow for independent control as to whether these principles are adhered to, a clinical trial should be subject to prior authorisation **and prior approval by an ethics committee.**

Or. en

#### *Justification*

*Prior ethical approval is a necessary condition for any clinical trial. According to the Helsinki Declaration, research on a subject may only be undertaken if the research project has been approved by the competent body after a multidisciplinary review of its ethical acceptability.*

### Amendment 3

#### Proposal for a regulation

##### Recital 6

*Text proposed by the Commission*

(6) The Member States concerned should cooperate in assessing a request for authorisation of a clinical trial. This cooperation ***should not include*** aspects of an intrinsically national nature, ***nor ethical aspects of a clinical trial, such as informed consent.***

*Amendment*

(6) The Member States concerned should cooperate in assessing a request for authorisation of a clinical trial. This cooperation ***may exclude*** aspects of an intrinsically national nature.

Or. en

*Justification*

*Member States should be free to decide the areas on which they wish to cooperate or not. In the context of an increased mobility of people between EU member States and of cross-border health care, Member States should be encouraged to exchange views and cooperate also on ethical aspects of clinical trials, including informed consent.*

### Amendment 4

#### Proposal for a regulation

##### Recital 7

*Text proposed by the Commission*

(7) The procedure should be flexible and efficient, in order to avoid administrative delays *for* starting a clinical trial.

*Amendment*

(7) The procedure should be flexible and efficient, in order to avoid administrative delays *in* starting a clinical trial. ***The rights, safety and well-being of the individual research subject should prevail over all other interests.***

Or. en

*Justification*

*In line with Point 6 of the Declaration of Helsinki and Article 28(2) of the proposal.*

## Amendment 5

### Proposal for a regulation Recital 10

#### *Text proposed by the Commission*

(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** 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.

#### *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, **which includes ensuring that the group of subjects participating in the trial represents the population to be treated, and** 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. **In order to ensure that the clinical trial is relevant, the sponsor should, where possible, provide a systematic review of the existing data on the investigational medicinal products.**

Or. en

#### *Justification*

*Clinical trials should reflect the target population groups, including gender and age balance, to ensure that the safety and efficacy of the drugs are evaluated accurately for the population that will ultimately be treated. This is in line with point 5 of the Declaration of Helsinki. In order to further guarantee the relevance of the trial and thus to ensure that subjects have not undergone unnecessary trials, the sponsor should screen information on investigational medicinal products and should provide such information in the application.*

## Amendment 6

### Proposal for a regulation Recital 12

#### *Text proposed by the Commission*

**(12) Some aspects in a clinical trial application relate to issues of an intrinsic**

#### *Amendment*

**deleted**

***national nature or to ethical aspects of a clinical trial. Those issues should not be assessed in cooperation among all Member States concerned.***

Or. en

*Justification*

*Linked to the amendment on Recital 6. Member States should be free to decide the areas on which they wish to cooperate or not. In the context of an increased mobility of people between EU Member States and of cross-border health care, Member States should be encouraged to exchange views and cooperate also on ethical aspects of clinical trials, including informed consent.*

**Amendment 7**

**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. Member States, when determining the appropriate body or bodies, should ensure the involvement of ***an independent ethics committee which includes healthcare professionals***, lay persons and patients ***or patient representatives***. 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*

*In line with Point 15 of the Helsinki Declaration, an ethics committee has to be involved in the assessment procedure. The Commission proposal is too vague in this respect.*

**Amendment 8**

**Proposal for a regulation**  
**Recital 14 a (new)**

*Text proposed by the Commission*

*Amendment*

***(14a) Currently, the ethics review procedure varies greatly between Member States, often with various bodies at national, regional and local levels, and multiple procedures leading to divergent assessments. This is a source of delays and fragmentation. In the interests of European patients and public health, the procedures and principles of ethical review should be better harmonised through the sharing of best practices between ethics committees. To this end the Commission should facilitate the cooperation of ethics committees.***

*Justification*

*In order to bring clarity and consistency into the ethical review of clinical trials, without imposing the burden of full harmonisation, the Commission should set up a platform to encourage cooperation and the sharing of best practices between ethics committees. Participation in this platform should be voluntary.*

## Amendment 9

### 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. ***The reasons for withdrawal should be communicated via the EU portal.*** 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.***

Or. en

#### *Justification*

*Sponsors should be required to provide the rationale of the decision to withdraw an application. This would ensure efficiency and transparency, would enhance the exchange of information between Member States, and would prevent sponsors from “shopping around” for the authorisation of clinical trials. This is also in line with the new Pharmacovigilance legislation (Directive 2010/84/EU and Regulation 1235/2010) that requires marketing authorisation holders to inform the authorities of the reasons for the withdrawal of a product from the market.*

## Amendment 10

### 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

*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 on clinical trials recorded in a publicly accessible

accessible database.

database. *Clinical trial data based on clinical trials conducted before the date of application of the present Regulation should be registered in a public register which is a primary or partnered registry of the international clinical trials registry platform of the World Health Organisation.*

Or. en

#### *Justification*

*Clinical trials from older trials might be still relevant; for the sake of reliability of data arising from older trials, the registration of older trials should be encouraged. Clinicaltrials.gov, which is not a primary but partnered registry of the international clinical trials registry platform of the WHO, should also be included in the data sources.*

#### **Amendment 11**

##### **Proposal for a regulation Recital 20 a (new)**

*Text proposed by the Commission*

*Amendment*

*(20a) Clinical trial data should not be considered commercially confidential once a marketing authorisation has been obtained.*

Or. en

#### *Justification*

*For the sake of transparency, once a clinical trial has led to marketing authorisation, data generated during the clinical trial should be fully accessible.*

#### **Amendment 12**

##### **Proposal for a regulation Recital 22**

*Text proposed by the Commission*

*Amendment*

(22) The human dignity and right to the

(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.

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. ***Subjects from vulnerable population groups such as incapacitated subjects, minors or other vulnerable people, require additional protection measures.*** 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 *subjects* and minors.

Or. en

#### *Justification*

*The most vulnerable trial subjects need additional protection measures.*

### **Amendment 13**

#### **Proposal for a regulation Recital 24**

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

(24) In accordance with international guidelines, the free and informed consent of the subject should be in writing, save in exceptional situations. It should be based on information which is clear, relevant and understandable to the subject.

##### *Amendment*

(24) In accordance with international guidelines, the free and informed consent of the subject should be ***given*** in writing, save in exceptional situations. It should be based on information which is clear, relevant and understandable to the subject. ***Where possible, such information should be given orally, with the opportunity for the subject to ask questions, and the subject should be provided with comprehensive written information which he or she is allowed to keep. Adequate***

***time should be provided for the subject to consider his or her decision.***

Or. en

*Justification*

*Information, or the lack of it, has implications for both patients' willingness to participate in clinical trials, as well as their commitment and adherence during trials. Information given to potential trial subjects, and how this is presented, should meet the information needs of people who are considering participating in a trial. Specific patient populations may have different needs. Information should be provided in a simple format, complemented by more comprehensive scientific information for those who wish to access it. Information should be available at any time throughout the trial.*

**Amendment 14**

**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) The database should contain all relevant information as regards the clinical trial. ***All clinical trials should be registered in the database prior to being started. The start and end dates of the recruitment of subjects should also be published in the database.*** 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.

Or. en

*Justification*

*Information on the start and end of the recruitment period for trials should be available so*

that patients can easily see what trials are available to them.

## Amendment 15

### Proposal for a regulation

#### Article 2– paragraph 2 – point 1 – introductory wording

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

(1) '**Clinical** study': any investigation in relation to humans intended

##### *Amendment*

(1) 'Study **relating to a medicinal product**': any investigation in relation to humans intended

*(Horizontal amendment applying throughout the text. Adopting it will necessitate corresponding changes.)*

Or. en

##### *Justification*

*The Commission's proposal for the definition of 'clinical study' has caused confusion amongst stakeholders, as under international guidelines the terms 'clinical study' and 'clinical trial' are used interchangeably.*

## Amendment 16

### Proposal for a regulation

#### Article 2– paragraph 2 – point 2 – point b

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

(b) according to the protocol of the clinical study, the investigational medicinal products are not used in accordance with the terms of the marketing authorisation of the Member State concerned;

##### *Amendment*

(b) according to the protocol of the clinical study, the investigational medicinal products are not used in accordance with the terms of the marketing authorisation of the Member State concerned **and their use does not fall within normal clinical practice**;

Or. en

### *Justification*

*Clarification of the text. As many standard treatment protocols use medicines outside their marketing authorisation, it has to be clarified that studies collecting data on the standard off-label use of a medicinal product are not considered as clinical trials.*

### **Amendment 17**

#### **Proposal for a regulation**

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

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

(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***;

##### *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 ***in any of the Member States concerned*** or, ***where the use of a medicinal product is outside the terms of the marketing authorisation***, their use is ***supported by sufficient published evidence and/or*** standard treatment ***guidelines***;

Or. en

### *Justification*

*In many rare diseases the medicines used in their treatment are nearly always being used as standard practice outside their marketing authorisation ('off-label use'). In order to avoid fundamental differences between Member States in applying the definition of a low-interventional trial including off-label use, the acceptable level of evidence should be stated; and if the trial treatment is only to compare standard practice treatment approaches, then, regardless of whether the drugs are being used off-label, the trial should be categorised within the low-interventional trial category.*

### **Amendment 18**

#### **Proposal for a regulation**

#### **Article 2 – paragraph 2 – point 3 – subparagraph 2 (new)**

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

##### *Amendment*

***Low intervention clinical trials may include the administration of placebos where the use of placebos does not pose***

*more than minimal additional risk to the safety or well-being of the subjects compared to normal clinical practice.*

Or. en

*Justification*

*The amendment ensures that a clinical trial can still meet the definition of low interventional where placebo is used without increasing the risk for trial subjects.*

**Amendment 19**

**Proposal for a regulation**

**Article 2 – paragraph 2 – point 10 a (new)**

*Text proposed by the Commission*

*Amendment*

***(10a) 'Ethics committee': an independent body in a Member State, which includes healthcare professionals, laypersons and at least one well-experienced, knowledgeable patient or patient representative whose responsibility it is to protect the rights, safety and well-being of subjects and to provide public assurance of that protection.***

Or. en

*Justification*

*In line with Point 15 of the Helsinki Declaration, an ethics committee has to be involved in the assessment procedure. The Commission proposal is too vague in this respect.*

**Amendment 20**

**Proposal for a regulation**

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

*Text proposed by the Commission*

*Amendment*

(19) 'Informed consent': a process by which a subject voluntarily confirms his or her willingness to participate in a particular

(19) 'Informed consent': a process by which a subject ***freely and*** voluntarily confirms his or her willingness to participate in a

trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate;

particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate;

Or. en

*Justification*

*In line with Point 24 of the Declaration of Helsinki, and with Article 29 of this regulation, informed consent has to be given freely.*

**Amendment 21**

**Proposal for a regulation**

**Article 2 – paragraph 2 – point 30 a (new)**

*Text proposed by the Commission*

*Amendment*

***(30a) ‘Clinical study report’: a report containing the full protocol and any subsequent modifications and dates thereof, a statistical analysis plan, summarised efficacy and safety data on all outcomes, and individual anonymised patient data in the form of tabulations or listings, in accordance with the guidelines provided by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) on the structure and content of clinical study reports (ICH E3).***

Or. en

*Justification*

*The introduction of the clinical study report is in the interest of increased transparency. These are internationally accepted guidelines on preparing a full description of a clinical trial and its results. This will help sponsors provide harmonised information, and increase transparency by greatly increasing the amount of data available to the public and independent researchers.*

## Amendment 22

### Proposal for a regulation Article 3 – indent 2

#### *Text proposed by the Commission*

– the data generated in the clinical trial are going to be reliable **and** robust.

#### *Amendment*

– the data generated in the clinical trial are going to be reliable, robust **and relevant**.

Or. en

#### *Justification*

*Clinical trials should be conducted only if the results are relevant for improving the prevention and treatment of diseases. The relevance of the trial is one of the assessment criteria pursuant to Article 6, and should therefore be included in the general principles of clinical trials.*

## Amendment 23

### Proposal for a regulation Article 6 – paragraph 1 – point a – point i – introductory wording

#### *Text proposed by the Commission*

(i) The anticipated therapeutic **and** public health benefits taking account of all of the following:

#### *Amendment*

(i) The anticipated therapeutic, public health **and quality of life** benefits taking account of all of the following:

Or. en

#### *Justification*

*In the assessment in Part I, the reporting Member State must evaluate the clinical trial application with regard to the anticipated benefits for the quality of life of patients, when weighing up various factors.*

## Amendment 24

### Proposal for a regulation

#### Article 6 – paragraph 1 – point a – point i – indent 2

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

– the relevance of the clinical trial, taking account of the current state of scientific knowledge, and of 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;

##### *Amendment*

– the relevance of the clinical trial, ***ensuring that the groups of subjects participating in the trials represent the population to be treated, and*** taking account of the current state of scientific knowledge, and of 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;

Or. en

##### *Justification*

*Clinical trials should reflect the target population groups, including gender and age balance, to ensure that the safety and efficacy of the drugs is evaluated accurately for the population that will ultimately be treated. This should be assessed when considering the relevance of the trial.*

## Amendment 25

### Proposal for a regulation

#### Article 6 – paragraph 1 – point a – point i – indent 3

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

– the reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the trial and methodology (including sample size and randomisation, comparator and endpoints);

##### *Amendment*

– the reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the trial and methodology (including sample size ***allowing for a stratified analysis by age and gender*** and randomisation, comparator and endpoints);

Or. en

*Justification*

*The data generated in clinical trials can be considered as reliable and robust only if they adequately reflect the population groups (e.g. women, the elderly) that are likely to use the product under investigation.*

**Amendment 26**

**Proposal for a regulation**

**Article 6 – paragraph 1 – point a – point ii – indent 4**

*Text proposed by the Commission*

*Amendment*

the risk to subject health posed by the medical condition for which the investigational medicinal product is being investigated;

the risk to subject health **or quality of life** posed by the medical condition for which the investigational medicinal product is being investigated;

Or. en

*Justification*

*The potential benefits to a patient's quality of life should also be taken into account.*

**Amendment 27**

**Proposal for a regulation**

**Article 6 – paragraph 1 – point d a (new)**

*Text proposed by the Commission*

*Amendment*

**(da) compliance with the requirements for informed consent as set out in Chapter V;**

Or. en

*Justification*

*Compliance with the core elements of informed consent as set out in Chapter V should be assessed by the reporting Member State in Part I. While individual Member States are best placed to decide on certain cultural aspects, the core elements set out in Chapter V should also be considered in Part I.*

## Amendment 28

### Proposal for a regulation

#### Article 6 – paragraph 5 – subparagraph 1 a (new)

*Text proposed by the Commission*

*Amendment*

***The reporting Member State shall send a preliminary version of Part I of the assessment report to the Member States concerned in due time and, where applicable, shall state the reasons why certain considerations have not been included in the assessment report.***

Or. en

*Justification*

*The obligation on the reporting Member State to take due account of the considerations expressed by the Member States concerned needs to be strengthened. To this end, it is proposed that the reporting Member State sends the preliminary version of the Part I assessment report to the Member States concerned including justification on how those concerns were evaluated.*

## Amendment 29

### Proposal for a regulation

#### Article 7 – paragraph 1 – subparagraph 2

*Text proposed by the Commission*

*Amendment*

The assessment of the aspects referred to in the first subparagraph shall constitute Part II of the assessment report.

The assessment of the aspects referred to in the first subparagraph shall constitute Part II of the assessment report ***and shall be compiled into the assessment report by the reporting Member State.***

Or. en

*Justification*

*Clarification of the text.*

## Amendment 30

### Proposal for a regulation Article 9 – title

*Text proposed by the Commission*

*Amendment*

Persons assessing the application

Persons assessing the application (**Part I  
and Part II**)

Or. en

#### *Justification*

*It is noteworthy that the same conditions apply to the persons assessing the application both in Parts I and II, and that ethics committees also take part in the Part I assessment.*

## Amendment 31

### Proposal for a regulation Article 9 – paragraph 1 – subparagraph 1 a

*Text proposed by the Commission*

*Amendment*

***Persons assessing the application should declare any financial and personal interests and this should be made available in the EU database.***

Or. en

#### *Justification*

*Guarantees with regard to the independence of the persons assessing the applications need to be reinforced.*

## Amendment 32

### Proposal for a regulation Article 9 – paragraph 2

*Text proposed by the Commission*

*Amendment*

2. Member States shall ensure that the assessment is done jointly by a reasonable

2. Member States shall ensure that the assessment is done jointly by a reasonable

number of persons who collectively have the necessary qualifications and experience.

number of persons who collectively have the necessary qualifications and experience ***in order to guarantee compliance with scientific and ethical quality requirements.***

Or. en

*Justification*

*It needs to be clarified that ethical and scientific issues are not separated into Parts I and II of the assessment report.*

**Amendment 33**

**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 ***an ethics committee*** shall be taken into account. ***The Commission shall develop guidelines on patient involvement, drawing upon existing good practices.***

Or. en

*Justification*

*In line with Point 15 of the Helsinki Declaration, an ethics committee has to be involved in the assessment procedure. The Commission proposal is too vague in this respect.*

**Amendment 34**

**Proposal for a regulation  
Article 10 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***2 a. Where the subjects are from other vulnerable population groups, specific consideration shall be given to the assessment of the application for the authorisation of a clinical trial on the***

*basis of expertise from professionals in the given field, or after taking advice on clinical, ethical and psychosocial problems in the field.*

Or. en

*Justification*

*There is a need for clinical trials involving representatives from vulnerable population groups (for example those suffering from a multitude of health conditions, elderly and frail people) to improve the treatments available to them, and these trials should be carried out under conditions affording the best possible protection for those subjects.*

**Amendment 35**

**Proposal for a regulation**

**Article 12**

*Text proposed by the Commission*

The sponsor may withdraw the application at any time until the assessment date. In such a case, the application may only be withdrawn with respect to all Member States concerned.

*Amendment*

The sponsor may withdraw the application at any time until the assessment date. In such a case, the application may only be withdrawn with respect to all Member States concerned. ***The reasons for the withdrawal shall be communicated to all Member States concerned and submitted to the EU portal.***

Or. en

*Justification*

*To increase transparency, the reasons for withdrawal should be made public. This is also in line with the new Pharmacovigilance legislation (Directive 2010/84/EU and Regulation 1235/2010) that requires marketing authorisation holders to inform the authorities of the reasons for the withdrawal of a product from the market.*

## Amendment 36

### Proposal for a regulation Article 13

#### *Text proposed by the Commission*

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.

#### *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. ***An explanation about previous applications which have been withdrawn or refused shall be included in the new application.***

Or. en

#### *Justification*

*To ensure efficiency, transparency and completeness of information, an explanation about previous withdrawals or refusals should be included in the new application.*

## Amendment 37

### Proposal for a regulation Article 25 – paragraph 2 – point b

#### *Text proposed by the Commission*

(b) a clear description of the substantial modification;

#### *Amendment*

(b) a clear description of ***the nature of, reasons for and content of the*** substantial modification;

Or. en

#### *Justification*

*If modifications are made to a trial, then for the sake of transparency, this needs to be fully explained.*

## Amendment 38

### Proposal for a regulation Article 25 – paragraph 4

*Text proposed by the Commission*

4. Where reference is made in the application dossier to data generated in a clinical trial, that clinical trial shall have been conducted in accordance with this Regulation.

*Amendment*

4. Where reference is made in the application dossier to data generated in a clinical trial, that clinical trial shall have been conducted in accordance with this Regulation ***or, if conducted prior to the date of application of this Regulation, in accordance with Directive 2001/20/EC.***

Or. en

*Justification*

*The Article does not take into account the fact that previous trials may contribute to the data in new applications which will pre-date the new Regulation.*

## Amendment 39

### Proposal for a regulation Article 25 – paragraph 5

*Text proposed by the Commission*

5. Where the clinical trial has been conducted outside the Union, it shall comply with ***principles equivalent to those of*** this Regulation as regards subject rights ***and*** safety and reliability and robustness of data generated in the clinical trial.

*Amendment*

5. Where the clinical trial ***referred to in paragraph 4*** has been conducted outside the Union, it shall comply with this Regulation ***and respect the ethical principles of the World Medical Association's Declaration of Helsinki, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects by the Council for International Organizations of Medical Sciences,*** as regards subject rights, safety ***and well-being,*** and the reliability and robustness of data generated in the clinical trial.

Or. en

### *Justification*

*Clinical trials in third countries should apply the same standards of safety and protection of patients as in the EU, so that the safety and well-being of participants always prevails over all other interests. "Equivalence" leaves too much open to interpretation. The ethical principles of the Declaration of Helsinki and the CIOMS guidelines should be respected by all studies, including those conducted outside the EU.*

### **Amendment 40**

#### **Proposal for a regulation**

#### **Article 25 – paragraph 6**

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

6. Clinical trial data submitted in an application dossier shall be based on clinical trials which have been registered prior to their start in a public register which is a primary registry of the international clinical trials registry platform of the World Health Organisation.

##### *Amendment*

6. Clinical trial data ***based on clinical trials conducted as from ... [date of application of this Regulation] and*** submitted in an application dossier shall be based on clinical trials which have been registered prior to their start in a public register which is a primary ***or partnered*** registry of the international clinical trials registry platform of the World Health Organisation.

Or. en

### *Justification*

*Clarification that this only applies to trials carried out after the entry into force of this Regulation. Clinicaltrials.gov, which is not a primary but partnered registry of the international clinical trials registry platform of the WHO, should also be included in the data sources.*

### **Amendment 41**

#### **Proposal for a regulation**

#### **Article 25 – paragraph 6 – subparagraph 1 a (new)**

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

##### *Amendment*

***Clinical trial data based on clinical trials conducted before ... [date of application of this Regulation] shall be registered in a public register which is a primary or***

*partnered registry of the international clinical trials registry platform of the World Health Organisation.*

Or. en

*Justification*

*Clinical trials from older trials might be still relevant, and for the sake of reliability of data from older trials, the registration of older trials should be encouraged. Clinicaltrials.gov, which is not a primary but partnered registry of the international clinical trials registry platform of the WHO, should also be included in the data sources.*

**Amendment 42**

**Proposal for a regulation**

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

*Text proposed by the Commission*

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

*Amendment*

(a) the anticipated therapeutic, public health **and quality of life** benefits justify the foreseeable risks and inconveniences;

Or. en

*Justification*

*The potential benefits to a patient's quality of life should also be taken into account.*

**Amendment 43**

**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

*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 **or other appropriate means of contact** with the investigator, member of the investigating team **or an appropriately qualified individual**, to understand the objectives,

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;

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. ***During the prior interview or other appropriate contact referred to above, the potential subject shall also be informed of the right to refuse to participate in the clinical trial without any resulting detriment;***

Or. en

#### *Justification*

*(i) The use of the wording “interview” is problematic as it implies a face to face interaction which in some settings may not be feasible. Recruitment for clinical trials also takes place via correspondence. (ii) It has to be emphasised that not only a subject may withdraw from a trial, but a potential subject may, any time before enrolment/recruitment, refuse to participate in a trial without any consequences.*

#### **Amendment 44**

##### **Proposal for a regulation Article 28 – paragraph 2**

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

2. The rights, safety and well-being of the subjects shall prevail over ***the*** interests ***of science and society***.

###### *Amendment*

2. The rights, safety and well-being of the subjects shall prevail over ***all other*** interests.

Or. en

#### *Justification*

*In line with point 6 of the Declaration of Helsinki, the interests of the subjects should take precedence over all other interests, including commercial or (personal) academic ones.*

## Amendment 45

### 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 **fully** informed of the nature, significance, implications and risks of the clinical trial. ***Where possible, information on the nature, significance, implications and risks of the clinical trial shall be given orally, with the opportunity for the subject to ask questions, and the subject shall be provided with comprehensive information which he or she is allowed to keep; otherwise that information may be given in writing.*** It shall be appropriately documented. ***Adequate time shall be given for 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.

Or. en

#### *Justification*

*Information, or the lack of it, has implications for both patients' willingness to participate in clinical trials, as well as their commitment and adherence during trials. Information given to potential trial subjects, and how this is presented, should meet the information needs of people who are considering participating in a trial. Specific patient populations may have different needs. Information should be provided in a simple format, complemented by more comprehensive scientific information for those who wish to access it. Information should be available at any time throughout the trial.*

## Amendment 46

### Proposal for a regulation Article 29 – paragraph 2

#### *Text proposed by the Commission*

2. Written information given to the subject and/or the legal representative **for the purposes of** obtaining his or her informed consent shall be **kept** concise, clear, relevant, and understandable to a *lay person*. It shall include both medical and legal information. It shall inform the subject about his or her right to revoke his or her informed consent.

#### *Amendment*

2. **Any** written information given to the subject and/or the legal representative **prior to** obtaining his or her informed consent shall be concise, clear, relevant, and understandable to a *layperson*. **Special attention should be given to the information needs of individual subjects and specific patient populations, as well as to the methods used to give the information.** It shall include both medical and legal information. It shall inform the subject about his or her right to revoke his or her informed consent **at any time**.

Or. en

#### *Justification*

*Information, or the lack of it, has implications for both patients' willingness to participate in clinical trials, as well as their commitment and adherence during trials. Information given to potential trial subjects, and how this is presented, should meet the information needs of people who are considering participating in a trial. Specific patient populations may have different needs. Information should be provided in a simple format, complemented by more comprehensive scientific information for those who wish to access it. Information should be available at any time throughout the trial.*

## Amendment 47

### Proposal for a regulation Article 29 – paragraph 2 a (new)

#### *Text proposed by the Commission*

#### *Amendment*

**2a. Following consultation with the relevant stakeholders including patient organisations, the Commission shall produce guidelines on the information to be given to subjects and potential subjects, on informed consent, and on the format**

*and presentation thereof.*

Or. en

*Justification*

*Information, or the lack of it, has implications for both patients' willingness to participate in clinical trials, as well as their commitment and adherence during trials. Information given to potential trial subjects, and how this is presented, should meet the information needs of people who are considering participating in a trial. Specific patient populations may have different needs. Information should be provided in a simple format, complemented by more comprehensive scientific information for those who wish to access it. Information should be available at any time throughout the trial.*

**Amendment 48**

**Proposal for a regulation**

**Article 29 – paragraph 4 a (new)**

*Text proposed by the Commission*

*Amendment*

***4a. The subject shall be provided with information on the results of the clinical trial that he or she has participated in, once it has come to an end.***

Or. en

*Justification*

*To increase transparency, and to ensure that subjects benefit as much as possible from clinical trials, they should receive information about the outcome of the trial.*

**Amendment 49**

**Proposal for a regulation**

**Article 31 a (new)**

*Text proposed by the Commission*

*Amendment*

***Article 31a***

***Clinical trials on subjects from other vulnerable population groups***

***1. A clinical trial on subjects from other vulnerable population groups may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:***

***(a) the subject has received all relevant information from professionals trained or experienced in working with that group regarding the trial, the risks and the benefits;***

***(b) the explicit wish of a subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time, is duly taken into consideration by the investigator;***

***(c) no incentives or financial inducements are given except compensation for participation in the clinical trial;***

***(d) such research either relates directly to a medical condition from which the subject concerned suffers or it is relevant to the vulnerable population group;***

***(e) the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and both the risk threshold and the degree of distress are specially defined and constantly observed;***

***(f) some direct benefit for the group of patients (e.g. improved quality of life) is obtained from the clinical trial.***

***2. The subject shall take part in the consent procedure in a manner adapted to his or her situation and capacity.***

Or. en

#### *Justification*

*There is a need for clinical trials involving representatives from vulnerable population groups (for example those suffering from a multitude of health conditions, elderly and frail people) to improve the treatments available to them, and these trials should be carried out under conditions affording the best possible protection for those subjects.*

## Amendment 50

### Proposal for a regulation

#### Article 32 – paragraph 1 – point (e)

*Text proposed by the Commission*

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

*Amendment*

(e) the clinical trial poses a **proportionate** risk **with reference to the underlying life threatening medical condition**, and imposes a **proportionate** burden on, the subject.

Or. en

*Justification*

*In the case of a life-threatening medical condition, the risk and burden requirements should be proportionate to the seriousness of the condition.*

## Amendment 51

### Proposal for a regulation

#### Article 34 – paragraph 3

*Text proposed by the Commission*

3. 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.

However, where, for scientific reasons, it is not possible to submit **a summary of the results** within one year, **the summary of results** shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with an explanation.

*Amendment*

3. Within one year from the end of a clinical trial, the sponsor shall submit to the EU database **the clinical study report, including a lay summary** of the clinical trial.

However, where, for scientific reasons, it is not possible to submit **the clinical study report** within one year, **it** shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with an explanation.

Or. en

### *Justification*

*The introduction of the clinical study report is in the interest of increased transparency. A simple summary has the potential to be biased and misleading. A clinical study report provides a full account of the trial and a harmonised way of presenting full results. Public access to this information will increase public trust in trial results and enable better peer-review of studies.*

### **Amendment 52**

#### **Proposal for a regulation**

#### **Article 34 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***2a. In the event of sponsor non-compliance with the obligation referred to in paragraph 3, financial penalties shall be imposed by the Member States concerned.***

Or. en

### *Justification*

*To ensure compliance with the provision to submit the summary of the results and the clinical study report within 12 months, the Member States should be entitled to enforce a penalty.*

### **Amendment 53**

#### **Proposal for a regulation**

#### **Article 34 – paragraph 4**

*Text proposed by the Commission*

*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.

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. ***After 12 months of temporary halt, the data from the clinical trial shall be submitted to the***

***EU database, even if incomplete. The reasons for early termination of a clinical trial shall be published in the EU database.***

Or. en

*Justification*

*It is important that the reasons for an early termination of a clinical trial are published in the EU database. Reasons could include that the drug did not appear to be effective, or that there were too many side effects, any of which could be vital information for patient safety as well as for future researchers in order to avoid duplication of research.*

**Amendment 54**

**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 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.

*Amendment*

1. Regarding non-authorised investigational medicinal products other than placebo, and authorised investigational medicinal products which, according to the protocol, are not used in accordance with the terms of the marketing authorisation ***and their use falls outside normal clinical practice***, 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.

Or. en

*Justification*

*For trials using an IMP off-label, the proposal makes annual safety reporting mandatory even in case of low-interventional trials. Safety data collected in Annual Safety Reports from products used in accordance with normal clinical practice would not provide any additional information in comparison to what is already known about the safety profile of the products, and would result in an unnecessary administrative burden without any benefit to patients. The provisions for safety reporting therefore need to be revised accordingly.*

## Amendment 55

### Proposal for a regulation

#### Article 39 – paragraph 1 a (new)

*Text proposed by the Commission*

*Amendment*

***1a. 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 shall provide the reasons for this decision in the report.***

Or. en

*Justification*

*Where more than one investigational medicinal product is used in a single clinical trial, sponsors should be allowed to submit one report relating to the clinical trial rather than one report for each investigational medicinal product. This is necessary to ensure that more accurate information about safety issues relating to the combined use of drugs may be reported.*

## Amendment 56

### 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. ***Where a sponsor, due to lack of resources, is not able to inform the marketing authorisation holder, it may instead inform the Agency.***

Or. en

### *Justification*

*Direct reporting of suspected serious adverse reactions to the marketing authorisation holder is extremely challenging, if not impossible, for non-commercial sponsors where generic drugs are used in the trial, and where the subjects are supplied the drug by a number of different sources. In many trials ‘off the shelf’ IMPs are used in combination with the IMP under investigation. In such cases these IMPs may be available as a generic product which is independently ordered by the individual hospital or GP, and therefore there is no direct link between the sponsor and the marketing authorisation holder.*

### **Amendment 57**

#### **Proposal for a regulation Article 49 – paragraph 1**

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

1. Where the sponsor is aware, with respect to a clinical trial for which it is a sponsor, of a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach, it shall notify the Member States concerned, through the EU portal, of that breach **within** seven days of becoming aware of that breach.

##### *Amendment*

1. Where the sponsor is aware, with respect to a clinical trial for which it is a sponsor, of a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach, it shall notify the Member States concerned, through the EU portal, of that breach **as early as possible and no later than** seven days **after** becoming aware of that breach.

Or. en

### *Justification*

*To emphasise further that any serious breach should be reported as quickly as possible, and that the seven-day period is the absolute deadline for notifying that there has been a serious breach.*

### **Amendment 58**

#### **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

##### *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 well-being** of the subjects or the

robustness of the data generated in the clinical trial.

reliability and robustness of the data generated in the clinical trial.

Or. en

*Justification*

*In line with Article 3 of the proposal, the well-being of subjects also has to be underlined.*

**Amendment 59**

**Proposal for a regulation**  
**Article 53 – paragraph 1**

*Text proposed by the Commission*

1. All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable legislation on personal data protection.

*Amendment*

1. All clinical trial information shall be recorded, processed, handled, and stored in ***the format of a clinical study report, in*** such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable legislation on personal data protection.

Or. en

*Justification*

*The introduction of the clinical study report is in the interest of increased transparency.*

**Amendment 60**

**Proposal for a regulation**  
**Article 55 – subparagraph 1**

*Text proposed by the Commission*

***Unless other Union legislation requires archiving for a longer period, the*** sponsor and the investigator shall archive the content of the clinical trial master file ***for at least five years after the end of*** the clinical trial. However, the medical files of

*Amendment*

***The*** sponsor and the investigator shall archive the content of the clinical trial master file ***for an indefinite period of time*** after ***concluding*** the clinical trial. However, the medical files of subjects shall be archived in accordance with national

subjects shall be archived in accordance with national legislation.

legislation. ***If the sponsor is unable to archive the master file, it may be archived in the EU database.***

Or. en

*Justification*

*Should a sponsor come under investigation for misconduct, the clinical trial master file would be vital. Therefore the master file should be archived indefinitely unless national legislation states otherwise. The master file can be stored in the EU database if necessary.*

**Amendment 61**

**Proposal for a regulation**

**Article 69 – paragraph 2 – introductory wording**

*Text proposed by the Commission*

2. By way of derogation from paragraph 1, all sponsors shall be responsible for establishing one ***sponsor*** responsible for each of the following:

*Amendment*

2. By way of derogation from paragraph 1, all sponsors shall be responsible for establishing one ***or more sponsors*** responsible for each of the following:

Or. en

*Justification*

*Ensure more flexibility on how responsibilities are shared between sponsors.*

**Amendment 62**

**Proposal for a regulation**

**Article 69 – paragraph 2 – point b**

*Text proposed by the Commission*

(b) providing responses to all questions from subjects, investigators or any Member State concerned regarding the clinical trial;

*Amendment*

(b) providing responses to all questions from subjects, investigators or any Member State concerned regarding the clinical trial. ***In meeting this obligation the sponsor may delegate tasks as required, in accordance with the second paragraph of Article 68;***

*Justification*

*Clarification that sponsors are able to delegate tasks.*

**Amendment 63**

**Proposal for a regulation**  
**Article 78 – paragraph 1 – subparagraph 1**

*Text proposed by the Commission*

The Commission shall set up and maintain a database at Union level (hereinafter, the ‘EU database’). The Commission shall be considered controller of the database.

*Amendment*

The Commission shall set up and maintain a database at Union level (hereinafter, the ‘EU database’). The Commission shall be considered controller of the *EU* database **and shall be responsible for avoiding unnecessary duplication between that database and the EudraCT and EudraVigilance databases.**

Or. en

*Justification*

*In order to avoid an additional administrative burden on the applicants, the Commission, as the creator of the new EU database, should make sure that there is no duplication with databases run by the Agency.*

**Amendment 64**

**Proposal for a regulation**  
**Article 78 – paragraph 2**

*Text proposed by the Commission*

2. The EU database shall be established to enable the co-operation between the competent authorities of the Member States to the extent that it is necessary for the application of this Regulation and to search for specific clinical trials. It shall also enable sponsors to refer to previous

*Amendment*

2. The EU database shall be established to enable the co-operation between the competent authorities of the Member States to the extent that it is necessary for the application of this Regulation and to search for specific clinical trials. It shall also enable sponsors to refer to previous

submissions of an application for authorisation of a clinical trial or a substantial modification.

submissions of an application for authorisation of a clinical trial or a substantial modification. ***It shall also enable the public and independent researchers to analyse the results of clinical trials.***

Or. en

#### *Justification*

*To emphasise that a key aim of the EU database is to increase transparency of trial results for patients and researchers.*

### **Amendment 65**

#### **Proposal for a regulation**

##### **Article 78 – paragraph 3 – introductory wording**

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

3. The EU database shall be publicly accessible unless, for all or parts of the data and information contained therein, confidentiality is justified on any of the following grounds:

###### *Amendment*

3. The EU database shall be publicly accessible ***in accordance with Regulation (EC) No 1049/2001*** unless, for all or parts of the data and information contained therein, confidentiality is justified on any of the following grounds:

Or. en

#### *Justification*

*Given that the Commission will set up and maintain the database, it should be accessible to the public pursuant to the provisions of Regulation (EC) No 1049/2001 regarding public access to European Parliament, Council and Commission documents.*

### **Amendment 66**

#### **Proposal for a regulation**

##### **Article -86 (new)**

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

###### *Amendment*

###### ***Article -86***

*Cooperation of ethics committees*

*The Commission shall facilitate cooperation of ethics committees and the sharing of best practices on ethical issues including the procedures and principles of ethical review.*

*(If adopted, this text is to be inserted in Chapter XVIII.)*

Or. en

*Justification*

*In order to bring clarity and consistency into the ethical review of clinical trials, without imposing the burden of full harmonisation, the Commission should set up a platform to encourage cooperation and the sharing of best practices amongst ethics committees. Participation in this platform should be voluntary.*

**Amendment 67**

**Proposal for a regulation  
Annex I – point 13 – indent 1 a (new)**

*Text proposed by the Commission*

*Amendment*

*a statement of the ethical considerations involved and how the principles of the Declaration of Helsinki have been addressed;*

Or. en

*Justification*

*As stated in Point 14 of the Declaration of Helsinki, the protocol should contain a statement on the ethical considerations and indicate how the principles of the Declaration of Helsinki have been addressed.*

## Amendment 68

### Proposal for a regulation Annex I – point 13 – indent 2

*Text proposed by the Commission*

a discussion of the relevance of the clinical trial and its design to allow assessment in accordance with Article 6;

*Amendment*

a discussion of the relevance of the clinical trial and its design to allow assessment in accordance with Article 6, ***referencing all existing evidence, including systematic reviews and meta-analysis;***

Or. en

*Justification*

*When a systematic review or meta-analysis is available this should be included in the application.*

## Amendment 69

### Proposal for a regulation Annex I – point 13 – indent 3 a (new)

*Text proposed by the Commission*

*Amendment*

***a description of patients' involvement in the trial, including identifying the research topic/questions and trial design;***

Or. en

*Justification*

*The level of patient involvement should be specified.*

## Amendment 70

### 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***

*Amendment*

***if the trial subjects do not reflect a balanced distribution in age and/or***

*justification for these exclusion criteria;*

*gender, this must be justified and explained;*

Or. en

*Justification*

*Clarification of the text: including a single female or a single elderly subject into the trial group might not remedy the problem of disproportionate representation. The trial population should be balanced in terms of age and gender, unless otherwise justified.*

**Amendment 71**

**Proposal for a regulation**

**Annex I – point 13 – indent 8 a new**

*Text proposed by the Commission*

*Amendment*

*a full statistical analysis plan;*

Or. en

*Justification*

*For the reliability of data arising from a clinical trial, sponsors should give information in advance about how they would use the data.*

**Amendment 72**

**Proposal for a regulation**

**Annex I – point 16 a (new)**

*Text proposed by the Commission*

*Amendment*

*16a. The protocol shall contain information regarding funding, sponsors, institutional affiliations, and any other potential conflicts of interest.*

Or. en

*Justification*

*In line with Point 14 of the Declaration of Helsinki, information about financial relationships*

*and other affiliations or potential conflicts of interest should be included in all research protocols.*

### **Amendment 73**

#### **Proposal for a regulation Annex I – point 53 a (new)**

*Text proposed by the Commission*

*Amendment*

***53a. All information given to the subjects or legal representatives should adhere to the core quality principles: it should be objective and unbiased; patient-oriented; evidence-based; up-to-date; reliable; understandable; accessible; transparent; relevant; and consistent with statutory information where applicable.***

Or. en

#### *Justification*

*Information, or the lack of it, has implications for both patients' willingness to participate in clinical trials, as well as their commitment and adherence during trials. Information given to potential trial subjects, and how this is presented, should meet the information needs of people who are considering participating in a trial. Specific patient populations may have different needs. Information should be provided in a simple format, complemented by more comprehensive scientific information for those who wish to access it. Information should be available at any time throughout the trial.*

### **Amendment 74**

#### **Proposal for a regulation Annex I – point 53 b (new)**

*Text proposed by the Commission*

*Amendment*

***53b. Applicants should be encouraged to have the information and the informed consent documents and procedures reviewed by patients prior to submission, to ensure they are relevant to patients and understandable.***

*Justification*

*Information, or the lack of it, has implications for both patients' willingness to participate in clinical trials, as well as their commitment and adherence during trials. Information given to potential trial subjects, and how this is presented, should meet the information needs of people who are considering participating in a trial. Specific patient populations may have different needs. Information should be provided in a simple format, complemented by more comprehensive scientific information for those who wish to access it. Information should be available at any time throughout the trial.*

## **EXPLANATORY STATEMENT**

There is broad agreement among all stakeholders that the current legislation on clinical trials urgently needs to be revised. There has been a severe decline in the number of clinical trials carried out in Europe over the last few years, which is due, at least in part, to some of the measures in the Clinical Trials Directive. Between 2007-2011, the number of trials carried out in the EU dropped by 25%, with many trials moving to emerging markets. Not only does this have dire economic consequences, but it hinders the advance of medicine to the detriment of patients. Europe must be competitive, and an attractive place for pharmaceutical companies to carry out research, whilst also fostering academic research and encouraging the development of medicines for rare diseases. At the same time Europe should be a world leader in both patient safety and transparency, in the interest of public trust and good science.

### **Regulation vs. Directive**

One of the main problems with the current Directive is precisely its legal form, i.e. that it is a directive. The patchwork of differently-implemented legislation across the EU has made cross-border trials difficult and expensive to carry out. For that reason your Rapporteur strongly supports the Commission's proposal for a regulation, which will ensure that there is consistency in application across the EU. This will be especially beneficial for those working with rare diseases, where small patient populations make it imperative to work across borders.

### **Approval times**

The Commission has been ambitious and is demanding a lot from regulatory authorities, ethics committees and sponsors. One of the major problems with the current Directive is the long approval times, which make carrying out trials in Europe more expensive. The timelines are ambitious but achievable, and are based on current best practice in the EU. The concept of tacit approval will provide a real incentive for those authorising trials to do so on time. Many Member States will want to revise this approach, therefore your Rapporteur advises the Parliament to support the Commission proposal on approval times.

### **Reduce bureaucracy**

There are a number of good measures in the Commission's proposal to reduce bureaucracy, and one of the most positive ideas is the EU Portal. This means that sponsors will only need to submit one, uniform application for approval, regardless of where in the EU the trial will be carried out, or whether the trial will be single or multi-state. Another new measure that your Rapporteur welcomes is the concept of a 'low intervention trial', which will greatly reduce bureaucracy for simpler, less-risky trials. While these reductions in bureaucracy are important, patient safety and well-being should always be the main priority in all aspects of the clinical trial.

## **Definitions**

The Commission has proposed the over-arching definition 'clinical studies', of which 'clinical trials' form a more narrowly defined sub-group. While the idea behind these definitions is understandable, giving the two terms different meanings has caused confusion amongst stakeholders, as the terms are used interchangeably in international guidelines. Therefore, your Rapporteur proposes changing the definition 'clinical study' to a 'study relating to a medicinal product'.

## **Ethics Committees**

The Commission tried to avoid the issue of ethics committees, because of their diversity across Europe. Whilst your Rapporteur agrees that the provisions should not be too prescriptive at EU level about exactly how ethics committees operate, she is of the view that it is vital to clarify that ethics committees have an important role to play in authorising trials and guaranteeing patient safety and well-being. She is also proposing that the Commission sets up a platform where ethics committees from across Europe can discuss how they authorise clinical trials and learn to work together and exchange best practice. If ethics committees can together find a more harmonised way of working, both sponsors and patients will be better informed of what to expect.

## **National Indemnification System**

Your Rapporteur fully supports the Commission's proposal for national indemnification systems to be set up. Currently insurance costs for some trials are astronomical and this can deter many sponsors from carrying them out at all. Often it is academic trials, especially into rare diseases, which are simply priced out of the market by high insurance costs. These kinds of trials need to be encouraged and supported, and that is why an indemnification system would be so important. Presently much of the public money that is invested into medical research is then spent on insurance fees. The running costs of an indemnification system would be relatively small for Member States, and there are good examples from Denmark and other countries which show how it can work.

## **Trial relevance**

Currently many trials are carried out in patient populations which do not necessarily reflect the diversity of the population group on which the drug will be used. For example, women are often under-represented in trials, which means less data is available about how drugs affect women specifically. A further example would be trials which exclude older people, who tend to have more co-morbidities and complications. Your Rapporteur has made a number of suggestions to try and make clinical trials more relevant to the patient population.

## **Patient involvement**

The Commission has proposed patient involvement in the assessment of clinical trials, which your Rapporteur fully supports. After all, it is patients who will bear the potential risks of the trial, and who will enjoy the potential benefits. Your Rapporteur wishes to emphasise that these patients should be experienced and knowledgeable, and their involvement should not be seen as tokenism.

### **Trials in developing countries**

Increasingly clinical trials are carried out in developing countries, which poses a number of ethical questions. There are several measures in the Commission proposal that address this, which your Rapporteur endorses. Firstly, the provision that if a sponsor wants to use data from a trial conducted outside the EU, then the trial must have adhered to standards equivalent to those in EU legislation, although this should be extended to include international guidelines on ethics. Alongside this is the provision for Commission officials to inspect the regulatory systems in third countries, and ensure that they have the measures in place to guarantee the same level of patient safety and well-being.

### **Transparency**

One of the major problems at the moment is the lack of transparency of clinical trial results. This has reduced public trust in trials and their findings. Independent academics often find it difficult to get the data they need to verify the results of trials and carry out systematic reviews, and a lot of data is withheld. It is also known that when trials are unsuccessful the results are often never published or made available at all. Trials can be carried out repeatedly before it becomes public knowledge that they are ineffective or even dangerous. The Commission is proposing some big steps forward in terms of transparency, by proposing that a publicly accessible, EU database on clinical trials is set up, holding information on all trials, successful or not. However, your Rapporteur is of the opinion that a simple summary of the results from the sponsor does not go far enough, as it could be biased and misleading.

#### **- Clinical Study Report**

Your Rapporteur is therefore recommending requiring sponsors to publish a full clinical study report on the EU database. The clinical study report is already a generally accepted international guideline and a comprehensive account of how the trial was carried out, and what the findings were. Many sponsors already prepare these reports, which are submitted to the regulatory bodies when applying for marketing authorisation. It includes a simplified summary, but also the much fuller results which can be analysed and checked by independent researchers. Clearly patients decide to take part in a trial to help advance medicine for themselves and other patients in their situation, not to help a particular company. Sharing more knowledge about trial results will not only increase trust in medicines, but accelerate the development of live-saving treatments. It will not compromise data protection, as all personal patient data will be anonymised. Truly commercially confidential information will be treated in line with existing legislation on access to documents.

**- Penalties for late submission**

Your Rapporteur is further proposing that Member States impose fines on sponsors that do not meet their responsibilities in terms of transparency. She is supporting the Commission's proposal to give sponsors one year to submit all the information to the database, which is more than adequate to prepare the necessary data. Sponsors that do not fulfil this requirement should be penalised.

**- Master file**

The Commission has proposed that sponsors archive the clinical trial master file for at least five years. Your Rapporteur is of the view that this is insufficient. Should a sponsor come under investigation for misconduct, the clinical trial master file would be vital. Therefore she has suggested that the master file should be archived indefinitely unless national legislation states otherwise. The master file can be stored in the EU database if necessary.