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**A7-0208/2013**

7.6.2013

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**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: [...].

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## 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, the Committee on the Internal Market and Consumer Protection and the Committee on Civil Liberties, Justice and Home Affairs (A7-0208/2013),
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.

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<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, health and well-being** of subjects should be protected and the data generated should be **relevant**, reliable and robust **and reflect the diversity of the population in terms of age and gender balance. The interests of the participants should always take priority over other interests.**

*Justification*

*In accordance with the Declaration of Helsinki, 'well-being' applies throughout the text whenever the safety and rights of the subjects are mentioned: recital 1, recital 66, Art 49(2).*

**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 **after having been examined by the ethics committee concerned in accordance with the World Medical Associations's Declaration of Helsinki. It should be ensured that persons assessing the application do not have conflicts of interest, are independent of the sponsor, the trial site and the investigators involved, as well as free of any undue influence.**

*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 3 a (new)**

*Text proposed by the Commission*

*Amendment*

***(3a) The scope of this Regulation is essentially identical to that of Directive 2001/20/EC. Although it is limited to clinical research on medicinal products for human use, it is very wide in that it only excludes clinical studies that do not involve an ‘intervention’ i.e. surveys by medical practitioners without additional intervention. ‘Non-interventional studies’ are post-authorisation safety studies initiated, managed or financed by the marketing authorisation holder. These enable data to be ‘mined’, and are covered by Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.***

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

**Recital 4**

*Text proposed by the Commission*

*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

(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.

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 portal should reduce unnecessary red tape so that not only sponsors and academic researchers carrying out multinational research but also public authorities may benefit from its use. Given that clinical trials carried out in a single Member State are equally indispensable to European clinical research, the procedure under this Regulation should also cover such trials. The application dossier for such clinical trials should also be submitted through the single European portal.***

## Amendment 5

### 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.

### *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 6** **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 for starting a clinical trial, ***without compromising patient safety or public health.***

#### **Amendment 7** **Proposal for a regulation**

##### **Recital 8**

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

(8) The timelines for assessing an application dossier for clinical trials should be sufficiently long to assess the file, while ensuring quick access to new, innovative treatments and ensuring that the Union remains an attractive place for conducting clinical trials. Against this background, Directive 2001/20/EC introduced the concept of tacit authorisation. This concept should be maintained in order to ensure that timelines are adhered to. In the event of a public health crisis, Member States should have the possibility to assess and authorise a clinical trial application swiftly. No minimal timelines for approval should therefore be established.

##### *Amendment*

(8) The timelines for assessing an application dossier for clinical trials should be sufficiently long to assess the file, while ensuring quick access to new, innovative ***as well as, existing (e.g. generic medicinal products)*** treatments and ensuring that the Union remains an attractive place for conducting clinical trials, ***ensuring first and foremost the safety and well-being of all subjects.*** Against this background, Directive 2001/20/EC introduced the concept of tacit authorisation. This concept should be maintained in order to ensure that timelines are adhered to. ***If a Member State concerned and a reporting Member State do not produce the assessment report, assess the application or take the authorisation decision within the set deadlines, the concept of tacit authorisation should apply automatically.***

In the event of a public health crisis, Member States should have the possibility to assess and authorise a clinical trial application swiftly. No minimal timelines for approval should therefore be established.

*Justification*

*It is important that an effective Clinical Trial authorisation system (particularly vis-à-vis timelines) is guaranteed for such trials related to generic medicinal products authorisation, so that existing treatments coming off patent can be registered rapidly as generic medicines to benefit a greater number of patients while providing savings to healthcare systems*

**Amendment 8  
Proposal for a regulation**

**Recital 8 a (new)**

*Text proposed by the Commission*

*Amendment*

***(8a) The Member States should guarantee that clinical trials can be conducted in both public and private centres under equal conditions, subject to any statutory requirements.***

*Justification*

*In Member States such as Spain, where there are substantial differences between the public and private health system, this clarification is necessary to ensure that there is nothing to prevent clinical trials being carried out in a private centre.*

**Amendment 9  
Proposal for a regulation**

**Recital 9**

*Text proposed by the Commission*

*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

(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

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-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 low-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. **Less stringent rules should not compromise scientific standards and should guarantee the safety of subjects at all times. Those low-risk trials should, however, be subject to the vigilance and traceability rules governing normal clinical practice.**

## **Amendment 10**

### **Proposal for a regulation**

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

*Text proposed by the Commission*

*Amendment*

***(9a) The OECD Council adopted its Recommendation on the Governance of Clinical Trials on 10 December 2012 which has introduced different risk categories for clinical trials. Those risk categories are compatible with the ones of this Regulation as the OECD Categories A and B(1) correspond to the definition of low-risk clinical trial, and the OECD Categories B(2) and C correspond to the definition of a clinical trial under this***

**Regulation.**

**Amendment 11**

**Proposal for a regulation  
Recital 9 b (new)**

*Text proposed by the Commission*

*Amendment*

***(9 b) Clinical studies supporting the registration of generic medicinal products (e.g. bioequivalence or therapeutic equivalence studies) pose minimal risks and inconveniences for the study subjects compared to the normal clinical practice, as defined in this Regulation, since the reference medicinal product, used as comparator, is a well-characterised authorised medicinal product for which the quality safety and efficacy have already been assessed.***

**Amendment 12**

**Proposal for a regulation**

**Recital 9 c (new)**

*Text proposed by the Commission*

*Amendment*

***(9c) The concept of 'Normal Clinical Practice' is of vital importance in determining whether an application is authorised as a 'low-risk clinical trial'. The definition of 'Normal Clinical Practice' should be clarified by the Commission in guidelines.***

*Justification*

*The definition of 'Normal Clinical Practice' is vital in the first stage of the authorisation procedure when the reporting Member State makes the first assessment of a clinical trial application in Article 5. This definition should be flexible, though the Commission should provide non-legislative guidelines on this matter to assist the process.*

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

**Recital 9 d (new)**

*Text proposed by the Commission*

*Amendment*

***(9d) An ‘investigational medicinal product’ is an active ingredient in a pharmaceutical or placebo form tested or used as a reference in a clinical trial, including a medicinal product which is covered by a marketing authorisation but which is used off-label or in accordance with current clinical practice.***

**Amendment 14**  
**Proposal for a regulation**

**Recital 9 e (new)**

*Text proposed by the Commission*

*Amendment*

***(9e) An ‘auxiliary medicinal product’ is a medicinal product used in the context of a clinical trial but not as an investigational 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 15**  
**Proposal for a regulation**

**Recital 9 f (new)**

*Text proposed by the Commission*

*Amendment*

***(9f) All the deadlines set out in this Regulation should be based on calendar days. Since the Member States have different calendars of public holidays, a procedure based on working days could result in different deadlines for admissibility, assessment and decisions in one of the Member States concerned.***

*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 16  
Proposal for a regulation**

**Recital 9 g (new)**

*Text proposed by the Commission*

*Amendment*

***(9g) In the case of an emergency situation as well as for rare and ultra-rare diseases which are life-threatening and for which therapeutic options and expertise are limited and geographically spread across the world, Member-States should have the possibility to assess and authorise clinical trial applications in priority.***

**Amendment 17**

**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

(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.

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 groups of subjects participating in the trial represent the population to be treated, in particular with regard to gender, age and other specific characteristics of the subject, or if not, explanation and justification is provided, 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.

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

**Recital 10 a (new)**

*Text proposed by the Commission*

*Amendment*

***(10a) In order to improve treatments available for vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders, medicinal products which are likely to be of significant clinical value should be fully and appropriately studied for their effects in these specific groups, including requirements related to their specific characteristics and the protection of their health and well-being.***

**Amendment 19**

**Proposal for a regulation**  
**Recital 10 b (new)**

*Text proposed by the Commission*

*Amendment*

***(10b) Experience with Directive 2001/20/EC has also shown that 60% of***

*clinical trials are sponsored by the pharmaceutical industry and 40% by other stakeholders, such as academics. The value of academic contribution should be duly recognised by Member States. Academic sponsors frequently rely on funding which partly or entirely comes from the public funds or charities. In order to maximize the use of this valuable contribution and to further stimulate academic research but without any discrimination towards the quality of trials, measures should be put in place by Member States to make appropriate exemptions from fees (application fees, inspection fees etc...) for trials conducted by academic sponsors.*

*Justification*

*A waiver from fees does not have any impact on the trial quality. Public funds and support from charities should not be used to pay fees and other taxes, but to conduct research otherwise not feasible.*

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

**Recital 11 a (new)**

*Text proposed by the Commission*

*Amendment*

*(11a) In order to follow a given clinical trial from initial ethical approval to final publication, a Universal Trial Registration Number (UTRN) should be assigned to each trial to be conducted in the Union or whose results are used as part of the Common technical document for a marketing authorisation of a medicinal product.*

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

**Recital 11 b (new)**

*Text proposed by the Commission*

*Amendment*

***(11b) 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 22**

### **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.***

***deleted***

#### *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 23**

### **Proposal for a regulation**

#### **Recital 12 a (new)**

*Text proposed by the Commission*

*Amendment*

***(12a) In the case of rare diseases as defined by Union law or ultra-rare diseases, 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 Union 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 covered by 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 provided for in this Regulation for clinical trials conducted in the field of diseases other than rare and ultra-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 24**

### **Proposal for a regulation Recital 12 b (new)**

*Text proposed by the Commission*

*Amendment*

***(12b) Whereas most clinical trials are conducted for the assessment of therapies, targeted at large patient populations, and involving a large sample of patient populations, this Regulation should not discriminate against patients suffering from rare and ultra-rare diseases, and***

***should integrate the specificities of low-prevalence conditions into the assessment of a trial.***

*Justification*

*The Commission's proposal does not reflect the specificities of rare and ultra-rare diseases. The future regulation must take into account therapeutic innovations and must be in compliance with policies on rare and ultra-rare diseases which have been developed since adoption of Directive 2001/20/EC.*

**Amendment 25**

**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 consisting of health-care professionals and non-medical members including at least one well-experienced, knowledgeable patient or patient representative***. 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. ***Names, qualifications, and declaration of interest of the persons assessing the application should be made publicly available.***

**Amendment 26**  
**Proposal for a regulation**  
**Recital 14 a (new)**

*Text proposed by the Commission*

*Amendment*

***(14a) In any event, the assessment by the ethics committee should be carried out within the deadlines provided for in this Regulation and should not delay the assessment procedures.***

**Amendment 27**

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

*Text proposed by the Commission*

*Amendment*

***(14b) Currently, the ethical 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 28

### 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.***

#### *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 29

### 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 on clinical trials recorded in a publicly ***and easily*** accessible ***database without imposing any cost on the access to the*** database. ***Clinical***

***trial data based on clinical trials conducted before the date of application of this 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.***

*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 30**

**Proposal for a regulation**

**Recital 20 a (new)**

*Text proposed by the Commission*

*Amendment*

***(20a) According to the policy of European Medicines Agency on access to documents, the Agency releases documents submitted as part of applications for marketing authorisation, including clinical trial reports, on request once the decision-making process for the medicinal product in question has been completed. Furthermore, the Agency continues to extend its transparency policy to proactive publication of clinical trial data for medicinal products once the decision-making process on an application for a Union-wide marketing authorisation has been completed. Those standards on transparency and access to documents should be upheld and reinforced. For the purposes of this Regulation, in general the data included in clinical study reports should not be considered commercially confidential once a marketing authorisation has been granted or the decision-making process on an application for marketing***

*authorisation has been completed.*

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

**Recital 21**

*Text proposed by the Commission*

(21) It should be left to Member States to establish the language requirements for the application dossier. To ensure that the assessment of the application for authorisation of a clinical trial functions smoothly, Member States should *consider* accepting a commonly understood language in the medical field as the language for the documentation not destined to the subject.

*Amendment*

(21) It should be left to Member States to establish the language requirements for the application dossier. To ensure that the assessment of the application for authorisation of a clinical trial functions smoothly, Member States should *work towards* accepting a commonly understood language in the medical field as the language for the documentation not destined to the subject, *such as the Patient Information and the Informed Consent Sheet.*

**Amendment 32**  
**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

*Amendment*

(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. *Incapacitated subjects, minors, pregnant and breastfeeding women, and where the law of the Member State concerned allows, persons deprived of liberty, as well as subjects with specific*

Member States to determine the legal representative of incapacitated *persons* and minors.

***needs require additional protection measures. Existing rules and international standards, in particular the provisions of the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research of the Council of Europe should be upheld and integrated into this Regulation in order to guarantee a high level of protection for those subjects with specific needs throughout the Union.***

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.

***Therefore, this Regulation should be without prejudice to provisions of national law which may require that the consent of more than one legal representative of a minor is required.***

### **Amendment 33**

#### **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 certain circumstances, due to the unconsciousness of the patient and the absence of an immediately available legal representative, it is not possible to obtain

##### *Amendment*

(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 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.

informed consent prior to the intervention ***in a sufficiently timely manner***. The Regulation should therefore set clear rules whereby such patients may be enrolled in the clinical trial under very strict conditions ***and only when there are grounds to expect that a clinically relevant benefit can be obtained***. 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 ***or where appropriate, his or her legal representative***, must be respected, and informed consent from the subject or the legal representative should be sought as soon as possible. ***If the subject or the legal representative declines to give consent, rules should be established for the use of data obtained earlier in the trial.***

## Amendment 34

### 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) ***Prior to obtaining informed consent, the potential subject should receive information orally and in writing which is clear, relevant and understandable to the subject, and presented in a language which is easily understood by him or her. The subject should have the opportunity to ask questions at any moment. Adequate time should be provided for the subject to consider his or her decision.*** In accordance with international guidelines, the free and informed consent of the subject should be ***given*** in writing. ***In exceptional situations justified under this Regulation, the clinical trial might be conducted without obtaining informed consent.***

**Amendment 35**

**Proposal for a regulation**

**Recital 25 a (new)**

*Text proposed by the Commission*

*Amendment*

***(25a) For the sake of transparency, sponsors should submit the summary of the results of a clinical trial together with a layperson's summary, and, where applicable, the clinical study report, within the deadlines and in the format specified by this Regulation. The power to adopt delegated acts in accordance with Article 290 of the Treaty on the functioning of the European Union should be delegated to the Commission in respect of on the preparation of the layperson's summary and the communication of the clinical study report. The Commission should provide guidelines for the management of, and the facilitating of sharing of raw data from all clinical trials.***

**Amendment 36**

**Proposal for a regulation**

**Recital 25 a (new)**

*Text proposed by the Commission*

*Amendment*

***(25a) A subject should always have the option to give broad consent, to be given to the treating institution, for his or her data to be used for historical, statistical or scientific research purposes, and to withdraw his or her consent at any time.***

*Justification*

*Physicians have always gained new knowledge from data on their previous patients. Appropriately, today, it is required that each patient consents to his/her data being used for research purposes. However, while having the right to dissent, patients should also have the right to give their treating institution a 'broad' consent, if they wish, such that data can be*

used for any type of future research (unless they withdraw their original consent). In this way, patients can have the right to 'donate' their data for research purposes.

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

**Recital 27**

*Text proposed by the Commission*

(27) The sponsor should assess the information received from the investigator, and report safety information on serious adverse events which are suspected unexpected serious adverse reactions to the Agency.

*Amendment*

(27) The sponsor should assess the information received from the investigator, and ***without delay and within the time limit set by this Regulation*** report safety information on serious adverse events which are suspected unexpected serious adverse reactions to the Agency ***via the electronic database for safety reporting***.

**Amendment 38**  
**Proposal for a regulation**

**Recital 28**

*Text proposed by the Commission*

(28) The Agency should forward this information to the Member States for them to assess this information.

*Amendment*

(28) The Agency should ***as soon as possible*** forward this information to the Member States for them to assess this information.

**Amendment 39**  
**Proposal for a regulation**

**Recital 30**

*Text proposed by the Commission*

(30) The conduct of a clinical trial should be adequately monitored by the sponsor in order to ensure the reliability and robustness of the results. Monitoring may also contribute to subject safety, taking into

*Amendment*

(30) The conduct of a clinical trial should be adequately monitored by the sponsor in order to ensure the reliability and robustness of the results. Monitoring may also contribute to subject safety, taking into

account the characteristics of the clinical trial and respect for fundamental rights of subjects. ***When establishing the extent of monitoring, the characteristics of the clinical trial should be taken into account.***

account the characteristics of the clinical trial and respect for fundamental rights of subjects. ***Monitoring should be adapted to the nature of the trial and focus on mitigating the key risks.***

#### *Justification*

*Each trial application dossier should contain a risk assessment covering the whole spectrum of risk determinants, and defining its consequences on the trial management, including (but not limited to) the trial monitoring.*

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

#### **Recital 31**

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

(31) The individuals involved in conducting the clinical trial, in particular investigators and other healthcare ***staff***, should be sufficiently qualified to perform their tasks in a clinical trial and the facilities where the clinical trial is to be conducted should be suitable for the clinical trial.

##### *Amendment*

(31) The individuals involved in conducting the clinical trial, in particular investigators and other healthcare ***professionals***, should be sufficiently qualified to perform their tasks in a clinical trial and the facilities where the clinical trial is to be conducted should be suitable for the clinical trial.

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

#### **Recital 33**

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

(33) During a clinical trial, a sponsor may become aware of serious breaches of the 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.

##### *Amendment*

(33) During a clinical trial, a sponsor may become aware of serious breaches of the 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 42**  
**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 43**  
**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 44**  
**Proposal for a regulation**

**Recital 37**

*Text proposed by the Commission*

(37) The information generated in the clinical trial should be recorded, handled and stored adequately for the purpose of

*Amendment*

(37) The information generated in the clinical trial should be recorded, handled and stored adequately for the purpose of

ensuring subject rights **and safety**, the robustness and reliability of the data generated in the clinical trial, accurate reporting and interpretation, effective monitoring by the sponsor and effective inspection by Member States or the Commission.

ensuring subject rights, safety **and well-being**, the robustness and reliability of the data generated in the clinical trial, accurate reporting and interpretation, effective monitoring by the sponsor and effective inspection by Member States or the Commission.

#### *Justification*

*According to Article 3 of the proposed Regulation and to Article 6 of the World Medical Association of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008), priority should be given to the safety, rights and well-being of individuals. To be consistent with Article 3 of the proposed Regulation.*

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

#### **Recital 46**

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

(46) In clinical trials with non-authorised investigational medicinal products, or where the **intervention** poses more than an insignificant risk to subject safety, compensation should be ensured for damages successfully claimed in accordance with the applicable laws.

##### *Amendment*

(46) In clinical trials with non-authorised investigational medicinal products, or **with authorised investigational medicinal products used outside the terms of the marketing authorisation in a treatment regimen distinct from the standard of care, or** where the **diagnostic procedure** poses more than an insignificant risk to subject safety, compensation should be ensured for damages successfully claimed in accordance with the applicable laws.

#### *Justification*

*Compensation should also be secured when an authorised investigational medicinal product is used outside the standard of care, or when the diagnostic procedure (a better wording than intervention) poses more than an insignificant risk.*

### **Amendment 46 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 ***European Medicines Agency, on behalf of the*** Commission should set up and maintain a database, accessed through a portal. ***The Commission and the Member States should raise awareness among the general public about the existence of that portal.***

**Amendment 47**

**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. The database should be publicly accessible. 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.

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

**Recital 52 b (new)**

*Text proposed by the Commission*

*Amendment*

***(52b) Results of clinical trials, as well as clinical trial data, represent a relevant and valuable source of information for the continuation of biomedical or public health research on a medicinal product or active principle, and should be made available in order to support and foster the development of independent research related to a medicinal product and its clinical, pharmacological or other pharmacodynamic effects, or to its relative efficacy and effectiveness. The status of the marketing authorisation for a medicinal product should however be duly considered in accordance with this Regulation before releasing data from a clinical trial, in order not to disrupt the marketing authorisation process or the competition dynamics operating on the Union market while fostering attractiveness and long term viability of the Union based clinical research.***

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

**Recital 52 c (new)**

*Text proposed by the Commission*

*Amendment*

***(52c) Access to, release and processing of clinical trial data for medicinal products once a marketing authorisation has been granted, the decision-making process on an application for marketing authorisation has been completed, or the sponsor has decided not to submit an***

*application for a marketing authorisation, should be without prejudice to the protection of personal data, and should respond to specific guidelines in order to define and guarantee good analysis practice, clinical trial data formats, rules of engagement as well as other legal aspects. Such guidelines should promote an optimal level of transparency and public information, while ensuring the development of reliable scientific research and avoiding bias or misuse of information.*

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

**Recital 55**

*Text proposed by the Commission*

(55) In order to carry out the activities provided for in this Regulation, Member States should be allowed to levy fees. ***However, Member States should not require multiple payments to different bodies assessing, in a given Member State, an application for authorisation of a clinical trial.***

*Amendment*

(55) In order to carry out the activities provided for in this Regulation, Member States should be allowed to levy fees ***in accordance with their respective practices.***

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

**Recital 60**

*Text proposed by the Commission*

(60) Without prejudice to the national systems for the cost and reimbursement of medical treatments, subjects should not have to pay for investigational medicinal products.

*Amendment*

(60) Without prejudice to the national systems for the cost and reimbursement of medical treatments, subjects should not have to pay for investigational medicinal products. ***For low-risk trials and when marketing authorisation is not the initial objective of the investigator-initiated trial, the cost of the investigational medicinal product should be borne by the national***

**healthcare system.**

*Justification*

*Trials comparing authorised products within their licenced indication or in regimens corresponding to the standard of care should be facilitated. As the treatment would be prescribed anyway, this does not impact the budget of the healthcare systems.*

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

**Recital 62 a (new)**

*Text proposed by the Commission*

*Amendment*

***(62a) According to the Commission Communication on "An Integrated Industrial Policy for the Globalisation Era-Putting Competitiveness and Sustainability at Centre Stage", systematic evaluation of legislation should become an integral part of smart regulation. To ensure that this Regulation keeps pace with scientific, technological and medical progress with regard to the organization and conduct of clinical trials and that it interfaces with other legal provisions, the Commission should periodically report on the experience with and functioning of this Regulation, and present its conclusions to the European Parliament and to the Council.***

*Justification*

*Advances in technology and medical knowledge mean that Clinical Trials are rapidly evolving. A review clause will ensure that the Regulation reacts quickly to any necessary changes.*

*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 53**  
**Proposal for a regulation**

**Recital 66**

*Text proposed by the Commission*

(66) Since the objective of this Regulation, namely to ensure that, throughout the Union, clinical trial data are reliable and robust while ensuring the safety and rights of subjects, cannot sufficiently be achieved by the Member States and can, by reason of the scale of the measure, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Regulation does not go beyond what is necessary in order to achieve that objective,

*Amendment*

(66) Since the objective of this Regulation, namely to ensure that, throughout the Union, clinical trial data are reliable and robust while ensuring the safety and rights **and well-being** of subjects, cannot sufficiently be achieved by the Member States and can, by reason of the scale of the measure, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Regulation does not go beyond what is necessary in order to achieve that objective,

*Justification*

*According to Article 3 of the proposed Regulation and to Article 6 of the World Medical Association of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008), priority should be given to the safety, rights and well-being of individuals.*

**Amendment 54**  
**Proposal for a regulation**

**Article 1 – paragraph 1**

*Text proposed by the Commission*

This Regulation shall apply to clinical trials conducted in the Union.

*Amendment*

This Regulation shall apply to **all** clinical trials conducted in the Union.

**Amendment 55**  
**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 are not authorised **for marketing**;

*Justification*

*Amendment in the interests of consistency and precision.*

## **Amendment 56**

### **Proposal for a regulation**

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

*Text proposed by the Commission*

*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;

(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**;

*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 57**

### **Proposal for a regulation**

#### **Article 2 – paragraph 2 – point 2 – point e a (new)**

*Text proposed by the Commission*

*Amendment*

**(ea) the study serves as a post-marketing safety or post-marketing efficacy trial on an investigational medicinal product authorised for marketing within the last 10 years.**

*Justification*

*In some cases (rare diseases and cancer treatment) marketing authorisations are given when*

sufficient evidence about efficacy and safety is not available, requiring the conduct of post-efficacy and post-safety trials to complete the evaluation. These trials should be covered by the definition of a clinical trial and by the Regulation. Marketing authorisation (according to art. 24 of Directive 2001/83/EC) is reviewed after 5 years and only considered unlimited after a minimum of 10 years.

**Amendment 58**  
**Proposal for a regulation**

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

*Text proposed by the Commission*

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

*Amendment*

(3) ‘Low-**risk** clinical trial’: a clinical trial **which, given the nature and extent of the intervention, can be expected to have only a very small and temporary or no impact on the subject’s health and** which fulfils all of the following conditions:

*(The amendment whereby the term ‘low-intervention clinical trial’ is replaced by ‘low-risk clinical trial’ applies to the entire text. If it is adopted, the change will have to be made throughout the text.)*

*Justification*

*It is preferable to define the second category of research in terms of the level of risk to the subject rather than the type of intervention. This is in line with the main aim of the proposal for a regulation, namely to develop a risk-based approach. The provisions of the regulation should also be brought into line with those of the Oviedo Convention, ratified by a number of EU Member States, Article 17 of which establishes the concept of ‘minimal risk’.*

**Amendment 59**  
**Proposal for a regulation**

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

*Text proposed by the Commission*

(a) the investigational medicinal products are authorised;

*Amendment*

(a) the investigational medicinal products, **or the placebos, are authorised for marketing and tested in accordance with their marketing authorisation;**

### *Justification*

*This stratification is based only on the marketing authorisation status of the investigational medicinal product and the risk associated with the diagnostic procedures. It underlines a difference between two distinct situations: low-risk if the authorised investigational medicinal product is used within its licensed indication, and medium-risk if the authorised investigational medicinal product is used outside its licensed indication.*

### **Amendment 60**

#### **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***;

### *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 61**

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

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

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

##### *Amendment*

***A low intervention clinical trial 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.*

*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 62  
Proposal for a regulation**

**Article 2 – paragraph 2 – point 4**

*Text proposed by the Commission*

(4) ‘Non-interventional study’: a clinical study other than a clinical trial;

*Amendment*

(4) ‘Non-interventional study’: a clinical study other than a clinical trial, ***which which fulfils all of the following conditions:***

***(a) the medicinal product or products are prescribed in the usual way in accordance with the terms of the marketing authorisation;***

***(b) the assignment of the subject to a particular therapeutic strategy is not decided in advance by a research protocol and falls within usual practice;***

***(c) the decision to prescribe the medicinal product is clearly dissociated from the decision to include the patient in the clinical study;***

***(d) the patients are not subject to any additional diagnostic or monitoring procedures;***

***(e) epidemiological methods are used to analyse the data gathered;***

**Amendment 63  
Proposal for a regulation**

**Article 2 – paragraph 2 – point 7**

*Text proposed by the Commission*

*Amendment*

**(7) 'Advanced therapy investigational medicinal product': an investigational medicinal product which is an advanced therapy medicinal product as defined in Article 2(1) of Regulation (EC) No 1394/2007 of the European Parliament and of the Council ;**

**deleted**

*Justification*

*'Advanced therapy medicinal products' are deleted from the rest of the regulation and therefore the definition is no longer required.*

#### **Amendment 64**

##### **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, consisting of health-care professionals and non-medical members including at least one well-experienced, knowledgeable patient or patient representative. Its responsibility is to protect the rights, safety, physical and mental integrity, dignity and well-being of subjects and to provide public assurance of that protection in full transparency. In cases of clinical trials involving minors, the ethics committee shall include at least one healthcare professional with paediatric expertise.**

#### **Amendment 65**

##### **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 66**  
**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 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;

*Amendment*

(12) ‘Substantial modification’: any change to any aspect of the clinical trial, **including a change in number of subjects participating in the clinical trial**, which is made after notification of the decision referred to in Articles 8, 14, 19, 20 and 23 and which **could** have a substantial impact on the safety, rights **or well-being** of the subjects or on the reliability and robustness of the data generated in the clinical trial **or could change the interpretation of the scientific documents used to support the conduct of the clinical trial, or any other change to any aspect of the clinical trial that is otherwise significant.**

*Justification*

*Any modifications in the conduct, design, methodology, numbers of participants, investigational or auxiliary medicinal product of clinical trials after they have been authorized can impair the data reliability and robustness. Therefore the more accurate wording from Directive 2001/20/EC Article 10(a) has been reintroduced.*

*According to Article 3 of the proposed Regulation and to Article 6 of the World Medical Association of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008), priority should be given to the safety, rights and well-being of individuals. To be consistent with Article 3 of the proposed Regulation*

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

**Article 2 – paragraph 2 – point 13**

*Text proposed by the Commission*

*Amendment*

(13) ‘Sponsor’: an individual, company, institution or organisation which takes responsibility for the initiation **and management** of the clinical trial;

(13) ‘Sponsor’: an individual, company, institution or organisation which takes responsibility for the initiation, **management and/or financing** of the clinical trial;

*Justification*

*Reintroduction of the definition provided for in Directive 2001/20/EC. In order to avoid that the responsibility of the sponsor is outsourced to others the definition from Directive 2001/20/EC needs to be reintroduced which also covers the individual, company, institution or organisation that finances the clinical trial.*

**Amendment 68**  
**Proposal for a regulation**

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

*Text proposed by the Commission*

*Amendment*

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

(14) ‘Investigator’: **a physical person who is trained or has experience to a level equivalent to the requirements set out in Article 46 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 69**  
**Proposal for a regulation**

**Article 2 – paragraph 2 – point 14 a (new)**

*Text proposed by the Commission*

*Amendment*

**(14a) ‘Principal investigator’: the investigator responsible for a team of investigators conducting a clinical trial at**

*a single site;*

*Justification*

*The proposal for a regulation does not specify the different categories of investigator. However, the concept of ‘principal investigator, as defined in the International Conference on Harmonisation’s Good Clinical Practice guidelines, is relevant and is used systematically in all research protocols.*

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

**Article 2 – paragraph 2 – point 14 b (new)**

*Text proposed by the Commission*

*Amendment*

***(14b) ‘Coordinating investigator’: an investigator responsible for the coordination of a clinical trial conducted at several centres in one or more of the Member States concerned;***

*Justification*

*The proposal for a regulation does not specify the different categories of investigator. However, the concept of ‘coordinating investigator, as defined in the International Conference on Harmonisation’s Good Clinical Practice guidelines, is relevant and is used systematically in all research protocols.*

**Amendment 71**  
**Proposal for a regulation**

**Article 2 – paragraph 2 – point 15**

*Text proposed by the Commission*

*Amendment*

(15) ‘Subject’: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control;

(15) ‘Subject’: an individual who ***freely and voluntarily*** participates in a clinical trial, either as recipient of an investigational medicinal product or as a control;

**Amendment 72**  
**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 73**  
**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 **freely and** 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*

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

**Article 2 – paragraph 2 – point 20**

*Text proposed by the Commission*

(20) ‘Protocol’: a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial;

*Amendment*

(20) ‘Protocol’: a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial; ***the term protocol refers to the protocol, successive versions of the protocol and protocol amendments;***

*Justification*

*In order to ensure the subjects right to information in case of modifications to the protocol a reintroduction of the definition of protocols from Directive 2001/20/EC is needed.*

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

**Article 2 – paragraph 2 – point 29**

*Text proposed by the Commission*

(29) ‘Serious adverse event’: any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect, is life-threatening or results in death;

*Amendment*

(29) ‘Serious adverse event’: any untoward medical occurrence, ***or other event deemed serious by the investigator in the context of the clinical trial,*** that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect, is life-threatening or results in death;

**Amendment 76**

**Proposal for a regulation**

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

*Text proposed by the Commission*

*Amendment*

***(30a) 'Clinical study report': a report on***

*the clinical trial presented in an easily searchable format, prepared in accordance with Annex I, Part I, Module 5 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.*

## Amendment 77

### Proposal for a regulation

#### Article 3 – paragraph 1 – indent 1

*Text proposed by the Commission*

- the rights, safety and well-being of subjects are protected; and

*Amendment*

- the rights, safety, **physical and mental integrity, dignity** and well-being of subjects are protected, **and the ethics committee has provided assurances thereof;**

## Amendment 78

### 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 **can be expected** to be reliable, robust **and relevant.**

#### *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 79

### Proposal for a regulation

#### Article 4 a (new)

*Text proposed by the Commission*

*Amendment*

#### *Article 4 a*

##### *Ethics Committees*

***1. Authorisation for conducting a clinical trial by the concerned Member State shall be granted only after examination by the ethics committee concerned in accordance with the World Medical Association's Declaration of Helsinki.***

***The ethics committee of the reporting Member State, referred to in the second and third subparagraphs of Article 5(1), may examine any aspect addressed in Part I of the assessment report referred to in Article 6 as well as any consideration referred to in Article 6(5) which fall within the remit of the ethics committee according to the national law of the reporting Member State. The ethics committee of each Member State concerned may examine any aspect addressed in Part II of the assessment report referred to in Article 7 which fall within the remit of the ethics committee according to the national law of the Member State concerned.***

***The ethics committee shall work with such efficiency as to enable the Member State concerned to comply with the procedural deadlines set out in this Chapter.***

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

***The Commission shall develop guidelines on patient involvement in ethics committees, drawing upon existing good***

*practices.*

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

**Article 5 – paragraph 1 – subparagraph 1**

*Text proposed by the Commission*

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

*Amendment*

1. ***For any clinical trial conducted in the Union,*** in order to obtain an authorisation, the sponsor shall submit an application dossier to the intended Member States concerned through the portal referred to in Article 77 (hereinafter 'EU portal'). ***At this stage the application dossier shall not be accessible to the public on the EU portal. It shall be made public only on completion of the Part I assessment referred to in Article 6.***

*Justification*

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

**Amendment 81**

**Proposal for a regulation**

**Article 5 – paragraph 1 – subparagraphs 2 and 3**

*Text proposed by the Commission*

***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.***

*Amendment*

***deleted***

***The reporting Member State shall be appointed among the Member States concerned in a procedure which shall be based on objective criteria and set out in this Regulation.***

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

**Article 5 – paragraph 1 – subparagraph 3 a (new)**

*Text proposed by the Commission*

*Amendment*

***If the sponsor submits an application dossier to only one of the Member States concerned, that Member State shall automatically be designated as the reporting Member State.***

**Amendment 83**

**Proposal for a regulation**

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

*Text proposed by the Commission*

*Amendment*

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:

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

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

**Article 5 – paragraph 2 – point a**

*Text proposed by the Commission*

*Amendment*

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

(a) ***who*** the reporting Member State ***is***;

*Justification*

*This is a consequential amendment of the amendment of article 5(1) subparagraph 2 (that Member States shall determine which state is the reporting Member State according to objective criteria set by the Commission)*

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

**Article 5 – paragraph 2 – point d a (new)**

*Text proposed by the Commission*

*Amendment*

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

*Justification*

*The registration number i.e. a specific identifier similar to the registry in the existing EudraCT would facilitate better cooperation among Member States at Union level.*

**Amendment 86**

**Proposal for a regulation**  
**Article 5 – paragraph 3**

*Text proposed by the Commission*

*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 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.***

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, ***and*** the clinical trial shall be considered a low-***risk*** clinical trial if this is claimed by the sponsor.

*Justification*

*Corresponds to amended Art 5 (1).*

**Amendment 87**  
**Proposal for a regulation**

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

*Text proposed by the Commission*

*Amendment*

Where the ***proposed*** reporting Member State finds that the application is not

Where the reporting Member State finds that the application is not complete, that

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.

the clinical trial applied for does not fall within the scope of this Regulation, or that the clinical trial is not a low-**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. ***The reporting Member State shall not invoke ethical concerns as a justification for considering the application as complete or as not falling within the scope of this Regulation.***

#### *Justification*

*Ethical committees fill an important role ensuring that Member States' particular traditions and concerns are taken into account. However, an ethical concern in the reporting Member State should not be allowed to hinder other Member States concerned in proceeding with a clinical trial.*

### **Amendment 88**

#### **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 reporting Member State has not notified the sponsor according to points (a) to (d) of paragraph 2 within **five 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-**risk** clinical trial if this is claimed by the sponsor.

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

**Article 5 – paragraph 5**

*Text proposed by the Commission*

5. For the purposes of this Chapter, the date on which the sponsor is notified in accordance with paragraph 2 shall be the **validation** date of the application. Where the sponsor is not notified, the **validation** date shall be the last day of the time periods referred to in paragraphs 2 and 4.

*Amendment*

5. For the purposes of this Chapter, the date on which the sponsor is notified in accordance with paragraph 2 shall be the **admissibility** date of the application. Where the sponsor is not notified, the **admissibility** date shall be the last day of the time periods referred to in paragraphs 2 and 4.

*(The amendment substituting ‘admissibility date’ for ‘validation date’ applies to the entire text. If it is adopted, the change will have to be made throughout the text.)*

*Justification*

*Substituting ‘admissibility date’ for ‘validation date’ makes for better overall understanding of the procedure. The amendment to that effect applies to the entire text. If it is adopted, the change will have to be made throughout the text.*

**Amendment 90**

**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, **including the anticipated benefits for the subjects**, taking account of all of the following:

*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 91

### 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 clinical trial represent the population to be treated, or if not, explanation and justification is provided in accordance with Annex I, point 13, sixth indent, 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;

## Amendment 92

### 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 ***expected from*** the clinical trial, ***based on pre-determined primary outcome parameters,*** taking account of statistical approaches, design of the trial and methodology (including sample size ***and pre-determined sub-groups allowing for a stratified analysis by age and gender*** and randomisation, comparator and endpoints) ***and the prevalence of the condition, especially for rare diseases (defined as severe, debilitating and often life-threatening diseases which affect no more than five persons per 10 000), and ultra-rare diseases (defined as severe, debilitating and often life-threatening diseases which meet a prevalence threshold of no more than one affected***

*person per 50 000);*

*Justification*

*It is important that primary outcome parameters are defined in advance to avoid manipulation of the findings. 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. Sub-groups need to be defined in advance to ensure proper interpretation and use of the data. In the case of a rare disease, the difficulty of leading a clinical trial is most often associated with a low number of patients for each disease, and to their geographical dispersion.*

**Amendment 93**

**Proposal for a regulation**

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

*Text proposed by the Commission*

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

*Amendment*

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

*Justification*

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

**Amendment 94**

**Proposal for a regulation**

**Article 6 – paragraph 1 – point a – point ii – indent 4 a (new)**

*Text proposed by the Commission*

**– the life-threatening and debilitating effects of certain diseases, such as some rare and ultra-rare diseases for which there are limited existing treatment options;**

*Amendment*

*Justification*

*In the case of a rare disease, the difficulty of leading a clinical trial is most often associated with a low number of patients for each disease, and to their geographical dispersion.*

**Amendment 95**  
**Proposal for a regulation**

**Article 6 – paragraph 1 – point a – sub-paragraph 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*

*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 96**

**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.***

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

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

*Text proposed by the Commission*

*Amendment*

4. The reporting Member State shall submit

4. 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:

Part I of the assessment report, including its conclusion, to the sponsor and to the other Member States concerned, **via the EU portal**, within the following time periods:

#### **Amendment 98**

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

##### **Article 6 – paragraph 4 – point a**

*Text proposed by the Commission*

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

*Amendment*

(a) within **12 days** from the **admissibility** date for low-**risk** clinical trials;

#### **Amendment 99**

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

##### **Article 6 – paragraph 4 – 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 **27 days** from the **admissibility** date for clinical trials other than low-**risk** clinical trials;

#### **Amendment 100**

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

##### **Article 6 – paragraph 4 – subparagraph 2**

*Text proposed by the Commission*

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

*Amendment*

For the purposes of this Chapter, the assessment date shall be the date on which the assessment report is submitted to the sponsor and to the other Member States concerned. **The assessment report shall be submitted through the EU portal, and stored in the EU database. As from the assessment date, the assessment report shall be accessible to the public on the EU**

*portal.*

*Justification*

*The assessment report shall be made publicly available for allow for public confidence in the authorisation process.*

**Amendment 101**

**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.***

*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 102**

**Proposal for a regulation**

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

*Text proposed by the Commission*

*Amendment*

6. 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.

6. The reporting Member State, and only the reporting Member State, may, between the **admissibility** date and the assessment date, request additional explanations from the sponsor, taking into account considerations **that it has, as well as considerations communicated by the other Member States concerned,** as referred to in paragraph 5.

## *Justification*

*Amendment not intended to alter the substance of the provision proposed by the Commission, but made in the interests of clarity.*

### **Amendment 103**

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

##### **Article 6 – paragraph 6 – subparagraph 2**

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

For the purpose of obtaining those additional explanations, the reporting Member State may suspend the time period referred to in paragraph 4 for a maximum of **10 days** for low-*intervention* clinical trials and for a maximum of **20 days** for trials other than low-*intervention* clinical trials.

###### *Amendment*

For the purpose of obtaining those additional explanations, the reporting Member State may suspend the time period referred to in paragraph 4 for a maximum of **12 days** for low-*risk*clinical trials and for a maximum of **22 days** for trials other than low-*risk*clinical trials. ***The reporting Member State shall inform the sponsor, via the EU portal, of the suspension of the time period.***

### **Amendment 104**

#### **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 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.

###### *Amendment*

Where, upon receipt of the additional explanations, the remaining time period for submitting Part I of the assessment report is less than **five days** in the case of low-*risk*clinical trials, and less than **seven days** for **clinical trials** other than low-*risk*clinical trials, it shall be extended to **five** and **seven days** respectively.

### **Amendment 105**

#### **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 set out in paragraphs 4, 6 and 7, the aspects addressed in Part I shall be deemed to have been 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 106**  
**Proposal for a regulation**

**Article 7 – paragraph 1 – subparagraph 1 – introductory part**

*Text proposed by the Commission*

*Amendment*

1. Each Member State concerned shall assess, for its own territory, the application with respect to the following aspects:

**1. *The assessments of the aspects to be addressed in Parts I and II of the assessment report shall be conducted simultaneously.*** Each Member State concerned shall assess, for its own territory, the application with respect to the following aspects:

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

**Article 7 – paragraph 1 – subparagraph 1 – point a**

*Text proposed by the Commission*

*Amendment*

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

(a) compliance with the requirements for ***the protection of the subjects and*** informed consent as set out in Chapter V;

### *Justification*

*Limiting ethic assessment only to the verification of the informed consent procedure is not enough. The regulation proposal must take into account Member States' diversity in ethical assessment for the protection of the subjects, a principle that is respected by various international instruments eg. the Declaration of Helsinki and the Oviedo Convention on Human Rights and Biomedicine.*

### **Amendment 108**

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

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

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

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

##### *Amendment*

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.**

### *Justification*

*Clarification of the text.*

### **Amendment 109**

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

#### **Article 7 – paragraph 2**

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

2. Each Member State concerned shall complete its assessment within **ten days** from the **validation** date. It may request, with justified reasons, additional explanations from the sponsor regarding the aspects referred to in paragraph 1 only within that time period.

##### *Amendment*

2. Each Member State concerned shall complete its assessment within **12 days** from the **admissibility** date. It may request, with justified reasons, additional explanations from the sponsor regarding the aspects referred to in paragraph 1 only within that time period.

### **Amendment 110**

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

#### **Article 7 – paragraph 3 – subparagraph 1 a (new)**

*Text proposed by the Commission*

*Amendment*

***The Member State concerned shall inform the sponsor of the suspension of the period referred to in paragraph 2 via the EU portal.***

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

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

*Text proposed by the Commission*

*Amendment*

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.

Where, ***in response to a request from the Member State concerned***, the sponsor does not provide additional explanations within the time period set in accordance with the first subparagraph, the application ***for a clinical trial which is being assessed*** shall be considered as withdrawn. The withdrawal shall apply only with respect to the Member State concerned.

*Justification*

*Clarification of wording.*

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

**Article 7 – paragraph 3 a (new)**

*Text proposed by the Commission*

*Amendment*

***3a. Where the Member State concerned does not submit the assessment report within the time periods set out in paragraphs 2 and 3, the aspects to be addressed in Part II of the assessment report shall be deemed to have been accepted by the Member State concerned.***

*Justification*

*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 prompt access to innovatory treatment, but also for the safeguarding of the competitiveness of European clinical research.*

**Amendment 113**

**Proposal for a regulation**

**Article 7 – paragraph 3 – subparagraph 4**

*Text proposed by the Commission*

*Amendment*

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

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

*Justification*

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

**Amendment 114**

**Proposal for a regulation**

**Article 7 a (new)**

*Text proposed by the Commission*

*Amendment*

**Article 7a**

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

***1. In the specific case of clinical trials in the field of rare or ultra-rare diseases as defined in the third indent of point (a)(i) of Article 6(1), 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 covered by Part II of the assessment, the reporting Member State shall notify the opinion referred to in***

***paragraph 1 to the Member States concerned without undue delay.***

*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 115  
Proposal for a regulation**

**Article 8 – title**

*Text proposed by the Commission*

*Amendment*

Decision on the clinical trial

***Final*** decision on the clinical trial

**Amendment 116  
Proposal for a regulation**

**Article 8 – paragraph 1 – subparagraph 1**

*Text proposed by the Commission*

*Amendment*

1. Each Member State concerned shall notify the sponsor through the EU Portal ***as to whether*** the clinical trial ***is authorised, whether it is authorised*** subject to conditions, or ***whether*** authorisation ***is refused***.

1. Each Member State concerned shall notify the sponsor through the EU Portal ***of its final decision to authorise*** the clinical trial, ***to authorise it*** subject to conditions, or ***to refuse*** authorisation.

**Amendment 117  
Proposal for a regulation**

**Article 8 – paragraph 2 – subparagraph 2 – point a a (new)**

*Text proposed by the Commission*

*Amendment*

***(aa) safety of the subject, in particular with respect to the criteria of inclusion or non-inclusion into the clinical trial, and***

*the monitoring procedures foreseen in the proposed clinical trial;*

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

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

*Text proposed by the Commission*

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.

*Amendment*

Where the Member State concerned 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. ***The reasons for disagreement should be made publicly available.***

*Justification*

*The amendment seeks to make the wording of the proposal more precise. Disagreement from a Member State with the conclusion on the basis of point (a) of the second subparagraph should be made publicly available in order to ensure transparency and public information about decision related to clinical trial authorisation refusal at national level.*

**Amendment 119**  
**Proposal for a regulation**

**Article 8 – paragraph 2 – subparagraph 3 a (new)**

*Text proposed by the Commission*

*Amendment*

***Notwithstanding the first and second subparagraphs, in the event of disagreement on other grounds, the Member States concerned shall attempt to agree on a conclusion. If no conclusion is found, the Commission shall take a decision on the conclusion after having heard the Member States concerned, and, if appropriate, having taken advice from***

*Justification*

*The decision of the reporting member state is binding for the others. It could happen that a reporting member state supports a clinical trial while the authorities and ethic committees of the majority of the concerned member states not. Even if the authorities and ethic committees work together to find agreement, there must a solution to resolve conflicts. The Commission is accountable to scrutiny by the EP and Council, so is better authorised to take such a decision then the reporting member state. As it is foreseen only in extraordinary circumstances, the additional time needed is acceptable.*

**Amendment 120**  
**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 makes clear 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 121**  
**Proposal for a regulation**

**Article 8 – paragraph 3**

*Text proposed by the Commission*

*Amendment*

3. Where, regarding Part I of the assessment report, the clinical trial is acceptable or acceptable subject to

3. Where, regarding Part I of the assessment report, the clinical trial is acceptable or acceptable subject to

conditions, the Member State concerned shall include in its decision its conclusion on Part II of the assessment report.

conditions, the Member State concerned shall include in its decision its conclusion on Part II of the assessment report. ***The Member State concerned shall submit both Part I and Part II of the assessment report, including their conclusions, to the sponsor.***

#### *Justification*

*Submitting both parts of the assessment report will add further clarity to the assessment process.*

### **Amendment 122 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 the aspects covered by Part II, the sponsor may appeal, once only, to the Member State concerned through the EU portal. 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 fails to provide a conclusion as regards the aspects covered by Part II within the seven-day time period, the application shall be deemed to have been definitively refused and the clinical trial shall not take place in the Member State concerned.***

### *Justification*

*This amendment seeks to make it possible for sponsors to lodge an appeal in the context of the assessment procedure for Part II. 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 that the assessment procedure is not excessively prolonged, the possibility of appeal is counterbalanced by the principle of tacit approval.*

### **Amendment 123** **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 124**

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

#### **Article 9**

*Text proposed by the Commission*

*Amendment*

Article 9

Article 9

Persons assessing the application

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

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.

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

***Persons admitting and assessing Parts I***

*and II of the application shall declare any financial or personal interests or shall make a statement that they do not have any such interest. Such declarations and statements shall be made publicly available in the EU database.*

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.

2. Member States shall ensure that the assessment is done jointly by a reasonable number of persons, *of whom a significant number shall be medical doctors as defined in their national law*, who collectively have the necessary qualifications and experience, *in order to guarantee compliance with scientific and ethical quality requirements.*

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. *Ethics committees shall be involved in the assessment in accordance with Article 4a.*

**Amendment 125**  
**Proposal for a regulation**

**Article 10 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

*2a. Where the subjects belong to vulnerable population groups including pregnant and breastfeeding women, persons deprived of liberty, persons with specific needs including the elderly, frail people and people with dementia, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant disease, or the medical or social circumstances of the subject, or after taking advice on the specific clinical, ethical and psychosocial issues in the field.*

**Amendment 126**  
**Proposal for a regulation**

**Article 11 – paragraph 1**

*Text proposed by the Commission*

Where the sponsor so requests, the application for authorisation of a clinical trial, its assessment and the decision shall be limited to the aspects covered by Part I of the assessment.

*Amendment*

***The assessments of the addressed in Parts I and II shall be conducted simultaneously. However,*** where the sponsor so requests, the application for authorisation of a clinical trial, its assessment and the decision shall be limited to the aspects covered by Part I of the assessment.

**Amendment 127**  
**Proposal for a regulation**

**Article 11 a (new)**

*Text proposed by the Commission*

*Amendment*

***Article 11a***

***Clinical trial applications shall be prioritised by Member States to improve, where possible, the defined timelines when the clinical trial is related to a condition that is a rare or ultra-rare disease, as defined in the third indent of point (a)(i) of Article 6(1), and, as such, is subject to significant administrative burden due to the extremely small patient populations.***

*Justification*

*It is appropriate to prioritise certain clinical trials applications within the agreed timelines and measures to be adopted in this Regulation, in order to improve the situation for patients suffering from severe, life-threatening rare and ultra-rare diseases.*

## Amendment 128

### 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.***

#### *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 129 Proposal for a regulation

### Article 13 – paragraph 1

#### *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*

Following the refusal to grant an authorisation or the withdrawal of an application, ***the sponsor may submit a new*** application for authorisation to any intended Member State. That application shall be considered as a ***resubmission of the*** application for authorisation of another clinical trial. ***It shall be accompanied by any previous assessment report, by the considerations of the concerned Members States, and it shall highlight the changes made to the original version of the protocol or the reasons justifying the resubmission of the application dossier. The new application shall, however, specify the grounds on which the original application was rejected or withdrawn and***

*the changes made to the original version of the protocol.*

*Justification*

*According to the proposal, this would allow sponsors to "cherry pick" the most permissive Member States, particularly when the scientific rationale for a clinical trial was considered questionable by the Members States involved in the initial application. The resubmission of the application be accompanied by its track record is key to avoid unnecessary bureaucratic burdens and avoid duplication of work.*

**Amendment 130**  
**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 ***in any Member State.***

*Justification*

*In order to improve the conduct of multinational clinical trials, sponsors should be allowed to extend to an additional Member States after authorisation decision is taken by any of the concerned Member State from the first round.*

**Amendment 131**  
**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, that Member State*** 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 132 Proposal for a regulation**

#### **Article 14 – paragraph 3 – point c**

*Text proposed by the Commission*

*Amendment*

***(c) 40 days from the date of submission of the application referred to in paragraph 1 for any clinical trial with an advanced therapy investigational medicinal product.***      ***deleted***

### *Justification*

*'Advanced therapy investigational medicinal products' vary in terms of our understanding and understanding within the medical profession, regulators and industry. Many advanced therapies medicines have been used for decades, are no longer novel and should not require extra time to assess. An additional timeline should not be required for advanced therapies medicines as a whole. Member States can request further information if they consider the advanced therapy medicines to require extra scrutiny.*

### **Amendment 133 Proposal for a regulation**

#### **Article 14 – paragraph 5**

*Text proposed by the Commission*

*Amendment*

***5. Between the date of submission of the application referred to in paragraph 1 and the expiry of the relevant time period referred to in paragraph 3, the additional Member State concerned may communicate to the reporting Member State any considerations relevant to the application.***

***5. The additional Member State concerned may communicate to the reporting Member State any considerations relevant to Part I of the assessment report within the timelines laid down in paragraph 3 starting from the date of submission referred to in paragraph 1.***

**Amendment 134**  
**Proposal for a regulation**

**Article 14 – paragraph 6 – subparagraph 1**

*Text proposed by the Commission*

6. The reporting Member State, and only the reporting Member State, may, ***between the date of submission of the application referred to in paragraph 1 and the expiry of the relevant time period referred to in paragraph 3***, request additional explanations from the sponsor concerning Part I of the assessment report, ***taking into account the considerations referred to in paragraph 5***.

*Amendment*

6. The reporting Member State, and only the reporting Member State, may, ***within the timelines specified*** in paragraph 5, request additional explanations from the sponsor concerning Part I of the assessment report.

**Amendment 135**  
**Proposal for a regulation**

**Article 14 – paragraph 6 – subparagraph 5 a (new)**

*Text proposed by the Commission*

*Amendment*

***The updated assessment report concerning Part I shall be submitted through the EU portal to the EU database and made publicly available.***

*Justification*

*Transparency fosters citizens' confidence in the authorisation process for clinical trials.*

**Amendment 136**  
**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

*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 is pending.

III as regards that clinical trial, ***and relating to an aspect addressed in 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 137**

**Proposal for a regulation**

**Article 15**

*Text proposed by the Commission*

A substantial modification may only be implemented if it has been approved in accordance with the procedure set out in this Chapter.

*Amendment*

A substantial modification may only be implemented if it has been approved in accordance with the procedure set out in this Chapter ***after being examined by the ethics committee concerned in accordance with the World Medical Association's Declaration of Helsinki***.

**Amendment 138**

**Proposal for a regulation**

**Article 17 – paragraph 2 – introductory part**

*Text proposed by the Commission*

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

*Amendment*

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

**Amendment 139**

**Proposal for a regulation**

**Article 18 – paragraph 4**

*Text proposed by the Commission*

4. 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*

4. 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 ***and shall document them in the assessment report.***

*Justification*

*The assessment of the application for a substantial modification should follow the same requirements as for the initial application.*

**Amendment 140**  
**Proposal for a regulation**

**Article 18 – paragraph 4 a (new)**

*Text proposed by the Commission*

*Amendment*

***4a. The assessment report shall be submitted through the EU Portal to the EU database and made publicly available.***

*Justification*

*The assessment report shall be shall be made publicly available for allow for public confidence in the authorisation process.*

**Amendment 141**

**Proposal for a regulation**

**Article 19 – paragraph 1 – subparagraph 2**

*Text proposed by the Commission*

*Amendment*

Notification shall be done by way of one single decision within ***ten days*** from the assessment date.

Notification shall be done by way of one single decision within ***twelve days*** from the assessment date.

## Amendment 142

### Proposal for a regulation

#### Article 20 – paragraph 5 – subparagraph 2

*Text proposed by the Commission*

Notification shall be done by way of one single decision within **ten days** from the assessment date.

*Amendment*

Notification shall be done by way of one single decision within **twelve days** from the assessment date.

## Amendment 143

### Proposal for a regulation

#### Article 20 – paragraph 5 – subparagraph 2

*Text proposed by the Commission*

Notification shall be done by way of one single decision within ten days from the **validation date**.

*Amendment*

Notification shall be done by way of one single decision within ten days from the **assessment date in accordance with Article 6(4)**.

*Justification*

*Assessment of aspects covered by Part II is inextricably linked to aspects covered by Part I. E.g. the required scope and extent of information provided to subjects and their indemnification in case of damages is dependent, in particular, on the risk-benefit ratio. If additional requirements were attached to Part I, and the assessment of Part II were performed first, a repeated assessment might be necessary after the completion of Part I. The amendment to the time period is to ensure that the assessment of aspects covered by Part II will be submitted after completion of the Part I assessment.*

## Amendment 144

### Proposal for a regulation

#### Article 22 – paragraph 1

*Text proposed by the Commission*

1. Each Member State concerned shall assess, for its territory, the aspects of the substantial modification which are covered by Part II of the assessment report within

*Amendment*

1. Each Member State concerned shall assess, for its territory, the aspects of the substantial modification which are covered by Part II of the assessment report within **twelve days from the admissibility date, in**

*ten days* from the *validation* date.

*accordance with the procedure referred to in Article 7(1).*

#### **Amendment 145**

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

##### **Article 23 – paragraph 1 – subparagraph 2**

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

Notification shall be done by way of one single decision *within ten days* from the assessment date or the last day of the assessment referred to in Article 22, whichever is later.

###### *Amendment*

Notification shall be done by way of one single decision *within twelve days* from the assessment date or the last day of the assessment referred to in Article 22, whichever is later.

#### **Amendment 146**

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

##### **Article 25 – paragraph 2 – subparagraph 1 – point a**

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

(a) a reference to the clinical trial or clinical trials which are substantially modified;

###### *Amendment*

(a) a reference to the clinical trial or clinical trials which are substantially modified; *by using the registration number in the EU portal;*

###### *Justification*

*This would make it easier to identify on which trial the modification is proposed and permits to trace protocol changes.*

#### **Amendment 147**

##### **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;

*Justification*

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

**Amendment 148**

**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.***

*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 149**

**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.

*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 150**  
**Proposal for a regulation**

**Article 25 – paragraph 5 – subparagraph 1a (new)**

*Text proposed by the Commission*

*Amendment*

***Clinical data submitted as part of the Common Technical Document to apply for a marketing authorisation shall have been obtained from registered clinical trials that duly comply with this Regulation.***

**Amendment 151**

**Proposal for a regulation**  
**Article 25 – paragraph 6**

*Text proposed by the Commission*

*Amendment*

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.

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.

*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 152**

### **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.***

*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 153**

### **Proposal for a regulation**

#### **Article 26 – subparagraph 1 a (new)**

*Text proposed by the Commission*

*Amendment*

***As regards clinical trials conducted in a single Member State, the application dossier may be drawn up in one of the official languages of the Member State concerned.***

## **Amendment 154**

### **Proposal for a regulation**

#### **Article 26 – subparagraph 1 b (new)**

*Text proposed by the Commission*

*Amendment*

***In the event of the enlargement of the Union to include another Member State, paragraph 4 shall apply.***

**Amendment 155**

**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;

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

*Justification*

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

**Amendment 156**

**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 157**

**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***

***deleted***

***legal representative has given informed consent;***

*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 drawbacks of the clinical trial before giving his/her informed consent.*

**Amendment 158**

**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 ***or other appropriate means of contact with a medical doctor who is the investigator or his/her representative, or an appropriately qualified individual***, 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. ***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;***

*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.*

(iii) *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.*

(iv) *Only a medical doctor has the necessary scientific knowledge and experience to comprehensively inform subjects about the risks and inconveniences of the clinical trial. Therefore, the informed consent process must be conducted by a member of the clinical trial team who is a qualified medical doctor.*

**Amendment 159**  
**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 freely and voluntarily 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 drawbacks of the clinical trial before giving his/her informed consent. According to the World Medical Association's Declaration of Helsinki on Ethical principles for medical research involving human subjects and to Article 29.1 of the proposed Regulation, the decision to participate in a clinical trial should be given freely and voluntarily.*

**Amendment 160**  
**Proposal for a regulation**

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

*Text proposed by the Commission*

*Amendment*

***(db) the prior interview with the investigator or a member of the investigating team in order to obtain the subject's informed consent shall include a test of full understanding on the part of the subject and/or his or her de facto representative by, for example, asking them to summarise the information which***

*they have received;*

## **Amendment 161**

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

*Text proposed by the Commission*

*Amendment*

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

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

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

### **Article 28 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

**2a. When the subject is required to give his/her consent for a clinical trial, the option of broad consent shall be available to the subject, to be given to the treating institution, for his data to be used after the end of the clinical trial for historical, statistical or scientific research purposes, and to withdraw consent at any time.**

#### *Justification*

*When a patient is enrolled in a clinical trial, he is asked to sign a form where he gives his informed consent exclusively for the duration and within the scope of the trial. After the trial is over, further follow-up data cannot be used, even for research purposes, unless the researcher acquires additional consents. Within the original consent, an option of broad consent should be made available to the patient, whereby his/her data could be allowed to be used at the behest of the treating institution for future research.*

**Amendment 163**  
**Proposal for a regulation**

**Article 28 – paragraph 3**

*Text proposed by the Commission*

3. Any subject may, without any resulting detriment, withdraw from the clinical trial at any time by revoking his or her informed consent. The withdrawal of consent shall not affect the activities carried out based on consent before its withdrawal.

*Amendment*

3. Any subject ***or his or her legal representative*** may, without any resulting ***liability or*** detriment, withdraw from the clinical trial at any time by revoking ***without any justification*** his or her informed consent. The withdrawal of consent shall not affect the activities carried out based on consent before its withdrawal. ***The data collected between the date on which the subject gave his or her informed consent and the date on which consent was withdrawn may be used in the context of the clinical trial, unless the person concerned objects.***

**Amendment 164**

**Proposal for a regulation**

**Article 29 – paragraphs 1 and 2**

*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. ***Prior to obtaining his or her informed consent, the potential subject and/or the legal representative shall be comprehensively and comprehensibly informed orally and in writing of the nature, duration, significance, implications and risks of the clinical trial, including information on possible treatment alternatives in the event that the trial has to be discontinued, and any other relevant information. The information shall also include medical and legal information together with information on damage compensation. The potential subject shall also be informed about his or her right to refuse to participate in the trial or to revoke his or her informed***

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.*

*consent without any resulting detriment.*

*Any written information shall be presented in a language which is easily understood by him or her, and shall be concise, clear, relevant, and understandable to a layperson. Special attention shall be paid to the information needs of individual subjects and specific patient populations, as well as to the methods used to give the information.*

*Adequate time shall be given for the subject to consider his or her decision to participate in the trial.*

2. *Informed consent shall be written, dated and signed and given freely by the subject or his or her legal representative after being duly informed in accordance with paragraph 1.*

*The information provided and the informed consent shall be appropriately documented. That document shall include the trial registration number in the EU portal, and information about the availability of the trial results in accordance with paragraph 4a.*

*Where the subject is unable to write, oral consent in the presence of at least one impartial witness independent of the investigator may be given in exceptional cases. The identity of the witness shall be registered on the informed consent document referred to in the previous subparagraph.*

*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 165

### Proposal for a regulation

#### Article 29 – paragraph 2 a (new)

*Text proposed by the Commission*

*Amendment*

**2a. Consent shall not prejudice the rights of subjects to the respect of their rights to human dignity, the right to physical and mental integrity, the right for respect of private and family life and the right of the child.**

*Justification*

*Consent may not be a means to waive the fundamental rights to human dignity, the right to physical and mental integrity, the right for respect of private and family life and the right of the child.*

## Amendment 166

### Proposal for a regulation

#### Article 29 – paragraph 2 b (new)

*Text proposed by the Commission*

*Amendment*

**2b. 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.**

*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 167**

**Proposal for a regulation**

**Article 29 – paragraph 3 a (new)**

*Text proposed by the Commission*

*Amendment*

***3a. Without prejudice to Article 32, and by way of derogation from Article 28, paragraph 1, points (c) and (d), and paragraphs 1 and 2 of this Article, clinical trials may be conducted without obtaining informed consent only if all of the following conditions are fulfilled:***

***(a) the methodology of the trial requires the inclusion of hospitals, health centres or clinics rather than individual subjects into the trial;***

***(b) the trial is a low-risk trial;***

***(c) the protocol states that the trial is conducted without obtaining informed consent, and describes the scope of information provided to the subjects, as well as the ways of providing information;***

***(d) the ethics committee has examined the protocol;***

***(e) prior to the start of the trial, the potential subjects have received comprehensive and comprehensible written information on the nature, duration, significance, implications and risks of the clinical trial, and any other relevant information, and have been duly informed that they can refuse to participate in the trial without any resulting detriment;***

***(f) prior to the start of the trial, the subject has been informed that he or she can withdraw from the trial any time without any resulting detriment;***

***(g) the potential subject, after being informed, does not object to participating in the trial;***

*(h) the clinical trial corresponds to a public health objective.*

**Amendment 168**

**Proposal for a regulation**

**Article 29 – paragraph 4 a (new)**

*Text proposed by the Commission*

*Amendment*

***4a. In the document referred to in the second subparagraph of paragraph 2, the subject shall be informed that within one year from the end of the clinical trial or its early termination, the summary of the results of the trial and a summary presented in terms understandable to a layperson will be made available in the EU database pursuant to Article 34, paragraph 3, irrespective of the trial outcome, or that he or she can obtain information from the investigator or its representative about the overall results of the trial.***

**Amendment 169**

**Proposal for a regulation**

**Article 30 – paragraph 1 – point a**

*Text proposed by the Commission*

*Amendment*

(a) the informed consent of the legal representative has been obtained, ***whereby*** consent ***shall*** represent the subject's presumed will;

(a) the informed consent of the legal representative has been obtained; consent ***shall*** represent the subject's presumed will ***and may be revoked at any time, without detriment to the subject;***

*Justification*

*The level of protection of incapacitated subjects should under no circumstances be reduced. Therefore we should stick to the wording in 2001/20 EC.*

**Amendment 170**  
**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 national law 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 171**  
**Proposal for a regulation**

**Article 30 – paragraph 1 – point c**

*Text proposed by the Commission*

(c) the explicit wish of an incapacitated 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 considered** by the investigator;

*Amendment*

(c) the explicit wish of an incapacitated 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 **without giving a reason and with no liability or prejudice whatsoever being incurred by the subject or their legal representative as a result shall be followed** by the investigator;

*Justification*

*The proposed amendment serves to ensure that the refusal by an incapacitated subject is followed by the investigator. Otherwise, there would be a breach of the fundamental rights of the incapacitated subject under Article 3 in conjunction with Article 8 of the European Convention of Human rights and article 1 in conjunction with article 3(1) of the Charter of fundamental Rights, each in conjunction with article 6(1) and (3) of EU Treaty.*

**Amendment 172**  
**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' and which prevents him/her from giving consent.*

**Amendment 173**  
**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 174**  
**Proposal for a regulation**

**Article 30 – paragraph 1 – point h a (new)**

*Text proposed by the Commission*

*Amendment*

***(ha) the research is necessary to promote the health of the population concerned by the trial and can not instead be performed on capacitated subject.***

*Justification*

*According to the World Medical Association's Declaration of Helsinki on Ethical principles for medical research involving human subjects, clinical trials should exclusively be performed on capacitated subjects. Only if those subjects are not available, clinical trials can be performed on incapacitated subjects.*

**Amendment 175  
Proposal for a regulation**

**Article 31 – paragraph 1 – point a**

*Text proposed by the Commission*

*Amendment*

(a) the informed consent of the legal representative has been obtained, , ***whereby consent shall represent the minor's presumed will;***

(a) the ***written*** informed consent of the legal representative ***or representatives*** has been obtained, whereby consent shall represent the minor's presumed will;

**Amendment 176  
Proposal for a regulation**

**Article 31 – paragraph 1 – point a (new)**

*Text proposed by the Commission*

*Amendment*

***(aa) the informed and express consent of the minor has been obtained, where they are 12 years old and over,***

**Amendment 177  
Proposal for a regulation**

**Article 31 – paragraph 1 – point b**

*Text proposed by the Commission*

*Amendment*

(b) the minor has received all relevant

(b) the minor has received all relevant

information in a way adapted to his or her age and maturity, from **professionals** trained or experienced in working with children, regarding the trial, the risks and the benefits;

information in a way adapted to his or her age and maturity, from **a medical doctor (either the investigator or member of the trial team)** trained or experienced in working with children, regarding the trial, the risks and the benefits;

*Justification*

*Only a medical doctor has the necessary scientific knowledge and experience to comprehensively inform subjects about the risks and inconveniences of the clinical trial. Therefore, the informed consent process must be conducted by a member of the clinical trial team who is a qualified medical doctor.*

**Amendment 178**  
**Proposal for a regulation**

**Article 31 – paragraph 1 – point c**

*Text proposed by the Commission*

(c) the explicit wish of a minor 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 **in accordance with his or her age and maturity;**

*Amendment*

(c) **without prejudice to point (aa)**, the explicit wish of a minor 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

*Justification*

*The level of protection of minors should under no circumstances be reduced. Therefore we should stick to the wording in 2001/20 EC.*

**Amendment 179**  
**Proposal for a regulation**

**Article 31 – paragraph 1 – point e**

*Text proposed by the Commission*

**(e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;**

*Amendment*

**deleted**

**Amendment 180**  
**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) **there are grounds to expect that** 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 181**

**Proposal for a regulation**  
**Article 31 – paragraph 1 – point h a (new)**

*Text proposed by the Commission*

*Amendment*

**(ha) the interest of the patient shall always prevail over those of science and society;**

*Justification*

*Current Directive 2001/20/EC expressly provides, amongst the conditions to meet to conduct a clinical trial on minors that the interest of the patient shall always prevail over those of science and society. This condition should be maintained so as to make it clear that the rights of minors are protected.*

**Amendment 182**  
**Proposal for a regulation**

**Article 31 – paragraph 1 – point h b (new)**

*Text proposed by the Commission*

*Amendment*

**(hb) the corresponding scientific guidelines of the European Medicines Agency have been followed;**

*Justification*

*The level of protection of incapacitated subjects should under no circumstances be reduced. Therefore we should stick to the wording in 2001/20 EC.*

**Amendment 183**  
**Proposal for a regulation**

**Article 31 – paragraph 1 – point h c (new)**

*Text proposed by the Commission*

*Amendment*

*(h c) the clinical trial does not replicate other trials based on the same hypothesis and age-appropriate formulations are used;*

**Amendment 184**  
**Proposal for a regulation**

**Article 31 – paragraph 1 – point h d (new)**

*Text proposed by the Commission*

*Amendment*

*(hd) a restrictive use of placebo is adopted.*

**Amendment 185**  
**Proposal for a regulation**

**Article 31 – paragraph 2**

*Text proposed by the Commission*

*Amendment*

2. The minor shall take part in the consent procedure in a manner adapted to his or her age and maturity.

2. The minor shall take part in the consent procedure in a manner adapted to his or her age and maturity. *Minors who are 12 years old and over shall also give their informed and express consent to participate in the trial.*

**Amendment 186**  
**Proposal for a regulation**

**Article 31 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***2a. If during a clinical trial the minor reaches the age of majority as defined in the the national law of the Member State concerned, his/her express informed consent shall be obtained before the trial may continue.***

**Amendment 187**

**Proposal for a regulation**

**Article 31 a (new)**

*Text proposed by the Commission*

*Amendment*

***Article 31 a***

***Clinical trials on pregnant or breastfeeding women***

***A clinical trial on pregnant or breastfeeding women may be conducted only where, in addition to conditions set out in Article 28, all of the following conditions are fulfilled:***

- (a) research on a pregnant woman which does not have the potential to produce results of direct benefit to her health, or to that of her embryo, foetus or child after birth, may only be undertaken if the research has the aim of contributing to the ultimate attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or to other embryos, foetuses or children;***
- (b) research of comparable effectiveness can not be carried out on women who are not pregnant or breastfeeding;***
- (c) the clinical trial poses a minimal risk***

*to, and imposes a minimal burden on, the subject and her embryo, foetus or child after birth;*

*(d) where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child;*

*(e) no incentives or financial inducements are given except compensation for participation in the clinical trial, which shall be strictly limited to conditions making good the expenses incurred.*

## **Amendment 188**

### **Proposal for a regulation**

#### **Article 31 b (new)**

*Text proposed by the Commission*

*Amendment*

#### **Article 31b**

##### ***Clinical trials on persons deprived of liberty***

***1. A clinical trial on persons deprived of liberty may be conducted only where, in addition to conditions set out in Article 28, all of the following conditions are fulfilled:***

***(a) the national law of the Member State concerned allows research on persons deprived of liberty;***

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

***(c) no incentives or financial inducements are given except compensation for participation in the clinical trial, which shall be strictly limited to conditions making good the expenses incurred.***

***2. Informed consent shall be sought from the subject or his or her legal representative as decided upon by the***

*national law of the Member State concerned.*

**Amendment 189**

**Proposal for a regulation**

**Article 31 c (new)**

*Text proposed by the Commission*

*Amendment*

**Article 31c**

***Clinical trials on subjects with specific needs***

***1. A clinical trial on subjects with specific needs may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are fulfilled:***

***(a) it has been assessed and duly justified whether and what specific needs the subject has;***

***(b) the subject has received all relevant information from professionals trained or experienced in working with subjects with specific needs regarding the trial, the risks and the benefits;***

***(c) no incentives or financial inducements are given except compensation for participation in the clinical trial, which shall be strictly limited to conditions making good the expenses incurred;***

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

***(e) the clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage, 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 is expected to be obtained from the clinical trial.*

*2. The subject shall take part in the consent procedure in a manner catering for, where necessary, his or her specific needs, situation and capacity.*

## **Amendment 190**

### **Proposal for a regulation**

#### **Article 32**

##### *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:

(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;

(b) *no legal representative is available;*

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

*(d) the research relates directly to a medical condition which causes the*

##### *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 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:

(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;

*(b) due to the urgency of the situation, it is impossible to obtain prior informed consent from the legal representative in a sufficiently timely manner;*

(c) the subject *or the legal representative of an incapacitated subject or a minor* has not previously expressed objections known to the investigator;

***impossibility to obtain prior informed consent and to supply prior information;***

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

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

***(ea) where there are grounds to expect that the research would result in a clinically relevant benefit but where the direct benefit for the subject can not be ensured, that research shall have the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to subject or to other persons afflicted with the same disease or disorder or having the same condition;***

***(eb) the protocol has been approved specifically for the emergency situation.***

2. The informed consent referred to in paragraph 1 shall be obtained, and information on the clinical trial shall be given, in accordance with the following requirements:

(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;

(b) regarding other subjects, the informed consent referred to in paragraph 1 shall be obtained as soon as possible from the legal representative or the subject, whichever is sooner and the information referred to in paragraph 1 shall be given as soon as possible to the legal representative or the subject, whichever is sooner.

2. The informed consent referred to in paragraph 1 shall be obtained, and information on the clinical trial shall be given, in accordance with the following requirements:

(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 ***and the legal representative by the investigator or a member of the investigating team;***

(b) regarding other subjects, the informed consent referred to in paragraph 1 shall be obtained as soon as possible from the legal representative or the subject, whichever is sooner and the information referred to in paragraph 1 shall be given as soon as possible to the legal representative or the subject, whichever is sooner ***by the investigator or a member of the***

For the purposes of point (b), where informed consent has been obtained from the legal representative, informed consent to continue the trial shall be obtained from the subject as soon as it is capable of giving informed consent.

*investigating team.*

For the purposes of point (b), where informed consent has been obtained from the legal representative, informed consent to continue the trial shall be obtained from the subject as soon as it is capable of giving informed consent.

***2a. If the subject or, where applicable, the legal representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the trial.***

**Amendment 191  
Proposal for a regulation**

**Article 33 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***2a. Prior to the start, all clinical trials shall be registered in the EU database. Information provided shall include the start date and the end date of the recruitments of subjects.***

**Amendment 192  
Proposal for a regulation**

**Article 34 – title**

*Text proposed by the Commission*

*Amendment*

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

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

*Justification*

*Clarification of the title to align it to the content of the Article.*

## Amendment 193

### Proposal for a regulation

#### Article 34 – paragraphs 3 and 3 a

*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. Irrespective of the outcome of the clinical trial**, within one year from the end of a clinical trial **or from its early termination**, the sponsor shall submit to the EU database a summary of the results of the clinical trial **in accordance with Annex IIIa. It shall be accompanied by a summary presented in terms that are easily understandable to a layperson.**

However, where, for **justified** 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 **a justification**.

***In addition to the summary of the results, where the trial was intended to be used for obtaining a marketing authorisation for the investigational medicinal product, the sponsor shall submit to the EU database the clinical study report 30 days after the marketing authorisation has been granted, the decision-making process on an application for a marketing authorisation has been completed, or the sponsor has decided not to submit an application for marketing authorisation.***

***In the event of non-compliance by the sponsor with the obligations referred to in this paragraph, financial penalties shall be imposed on the sponsor by the Member States concerned. The penalties shall be effective, proportionate and dissuasive.***

***3a. The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to define the content***

*and structure of the layperson's summary.*

*The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to establish rules for the communication of the clinical study report.*

*For cases where the sponsor decides to share raw data on a voluntary basis, the Commission shall produce guidelines for the formatting and sharing of those data.*

## Amendment 194

### 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, ***extended to include the period during which the subjects are subject to monitoring under the terms of the protocol***, 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.***

***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*

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

**Amendment 195**  
**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 196**  
**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, 39 and 41**.

**Amendment 197**  
**Proposal for a regulation**

**Article 36 – paragraph 1**

*Text proposed by the Commission*

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.

*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. ***That electronic database shall be a module of the database referred to in Article 24 of Regulation (EC) No 726/2004.***

*Justification*

*Clarification that the database referred to is EUdraVigilance and that this is not a new database. This Regulation has to build on existing tools.*

**Amendment 198**  
**Proposal for a regulation**

**Article 37 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***2a. In the case of low-risk clinical trials the protocol may stipulate that the normal rules on pharmacovigilance shall apply.***

**Amendment 199**  
**Proposal for a regulation**

**Article 38 – paragraph 1**

*Text proposed by the Commission*

*Amendment*

1. The sponsor shall report electronically and without delay to the electronic database referred to in Article 36 all relevant information about suspected unexpected serious adverse reactions to investigational medicinal products insofar as the suspected unexpected serious adverse reaction occurred in a clinical trial conducted by the sponsor, or occurred in a clinical trial related to the sponsor.

1. The sponsor shall report electronically and without delay to the electronic database referred to in Article 36 all relevant information about suspected unexpected serious adverse reactions to investigational ***and auxiliary*** medicinal products insofar as the suspected unexpected serious adverse reaction occurred in a clinical trial conducted by the sponsor, or occurred in a clinical trial

related to the sponsor, *in accordance with the time limits set out in Annex III, points 2.4 and 2.5.*

**Amendment 200**  
**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.

**Amendment 201**  
**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. *The sponsor shall submit annually by electronic means to the Agency a report on the safety of each investigational medicinal product - or of all the investigational medicinal products – used in a clinical trial for which it is the sponsor if the clinical trial involves authorised investigational medicinal products being tested in accordance with treatment strategies which were not envisaged under the terms of their marketing authorisation and which are not supported by data or recommendations and if the clinical trial involves a high level of risk.***

**Amendment 202**  
**Proposal for a regulation**

**Article 39 – paragraph 1 a (new)**

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

### **Amendment 203**

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

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

*Text proposed by the Commission*

*Amendment*

***1b. The annual report referred to in paragraph 1 shall only contain aggregate and anonymous data.***

#### *Justification*

*An annual report must only contain aggregate information and does not need to contain personal details of patients. This amendment takes into consideration the opinion of the European Data Protection Supervisor (EDPS).*

### **Amendment 204**

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

#### **Article 39 a (new)**

*Text proposed by the Commission*

*Amendment*

#### ***Article 39a***

***Reporting on efficacy defects of authorised investigational medicinal products***

***Regarding authorised investigational medicinal product which, according to the protocol, are used in accordance with the***

*terms of the marketing authorisation, the investigator shall inform the sponsor and the Agency of any observed efficacy defect related to the authorised investigational medicinal product.*

*Justification*

*Efficacy defect on an authorised medicinal product could represent a serious risk for patient safety and should therefore be added as a reporting obligation under Chapter VII of this regulation.*

**Amendment 205**  
**Proposal for a regulation**

**Article 40 – paragraph 1**

*Text proposed by the Commission*

1. The Agency shall, by electronic means, forward to the relevant Member States the information reported in accordance with Article 38 and 39.

*Amendment*

1. The Agency shall, by electronic means, forward to the relevant Member States the information reported in accordance with Article 38, 39, **39a and 41**.

**Amendment 206**  
**Proposal for a regulation**

**Article 40 – paragraph 2**

*Text proposed by the Commission*

2. Member States shall cooperate in assessing the information reported in accordance with Articles 38 and 39.

*Amendment*

2. Member States shall cooperate in assessing the information reported in accordance with Articles 38, 39 **and 41**.

**Amendment 207**  
**Proposal for a regulation**

**Article 40 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

**2 a. The responsible Ethics Committee shall be involved in the assessment of the information referred in paragraphs 1 and**

2.

**Amendment 208**  
**Proposal for a regulation**

**Article 41 – title**

*Text proposed by the Commission*

Annual reporting by the sponsor to the **marketing authorisation holder**

*Amendment*

Annual reporting by the sponsor to the **Agency regarding authorised investigational medicinal products**

**Amendment 209**  
**Proposal for a regulation**

**Article 41 – paragraph 1**

*Text proposed by the Commission*

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.

*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 **Agency** 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 210**  
**Proposal for a regulation**

**Article 43**

*Text proposed by the Commission*

Safety reporting with regard to auxiliary medicinal products shall be made **in accordance with Chapter 3 of** Directive

*Amendment*

Safety reporting with regard to auxiliary medicinal products shall be made **by the investigator in accordance with** Directive

*Justification*

*The reporting of suspected serious adverse reactions should be streamlined with requirements already in place for marketed products under the pharmacovigilance legislation.*

**Amendment 211**  
**Proposal for a regulation**

**Article 45 – title**

*Text proposed by the Commission*

*Amendment*

Monitoring

***Risk assessment, quality management and monitoring***

**Amendment 212**  
**Proposal for a regulation**

**Article 45 – paragraph 1 – introductory part**

*Text proposed by the Commission*

*Amendment*

The sponsor shall adequately monitor the conduct of a clinical trial. The extent and nature of the monitoring shall be determined by the sponsor on the basis of ***all characteristics*** of the clinical trial, ***including*** the following characteristics:

The sponsor shall adequately monitor the conduct of a clinical trial. The extent and nature of the monitoring shall be determined by the sponsor on the basis of ***a risk assessment covering all the risk determinants*** of the clinical trial (***risk to subject rights, risk to subject safety and integrity, risk to data quality and robustness of results***). ***The risk assessment shall determine the quality management and trial monitoring, taking into account*** the following characteristics:

*Justification*

*A trial-specific risk assessment, covering the whole spectrum of risk determinants (including the risk associated with diagnostic procedures) should determine the quality management of the trial, including the monitoring strategy.*

**Amendment 213**  
**Proposal for a regulation**

**Article 46 – paragraph 2**

*Text proposed by the Commission*

Other individuals involved in conducting a clinical trial shall be suitably qualified by education, training and experience to perform their tasks.

*Amendment*

Other individuals involved in conducting **and monitoring** a clinical trial shall be suitably qualified by education, training and experience to perform their tasks.

**Amendment 214**  
**Proposal for a regulation**

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

*Text proposed by the Commission*

1. 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*

1. Investigational medicinal products shall be **received**, traceable, stored, **administered**, 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 clinical trial is a **low-risk** clinical trial.

**Amendment 215**  
**Proposal for a regulation**

**Article 48 – paragraph 1 – subparagraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***These operations shall be carried out by persons legally authorised in the Member State to carry out the operations in question and, particularly where they are carried out in hospitals, medical centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out the operations in question.***

**Amendment 216**  
**Proposal for a regulation**

**Article 48 – paragraph 2**

*Text proposed by the Commission*

2. The relevant information regarding the traceability, storage, destruction and return of medicinal products referred to in paragraph 1 shall be contained in the application dossier.

*Amendment*

2. The relevant information regarding the **reception**, traceability, storage, **administration**, destruction and return of medicinal products referred to in paragraph 1 shall be contained in the application dossier.

**Amendment 217**

**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.

*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 218

### 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, **health and well-being** of the subjects or the reliability and robustness of the data generated in the clinical trial.

*Justification*

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

## Amendment 219 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 220 Proposal for a regulation

### Article 52 – paragraph 3

*Text proposed by the Commission*

3. The investigator’s brochure shall be

*Amendment*

3. The investigator’s brochure shall be

updated where new safety information becomes available, **and at least once per year**.

updated whenever new **and relevant** safety information becomes available.

**Amendment 221**  
**Proposal for a regulation**

**Article 52 – paragraph 3 a (new)**

*Text proposed by the Commission*

*Amendment*

**3a. The content of the investigator brochure shall be adapted for low-risk trials in accordance with Annex I, part 5, point 20 in the event that the investigational medicinal product is authorised and used in accordance with the terms of the marketing authorisation..**

**3b. For authorised investigational medicinal products which, according to the protocol, are used in accordance with the terms of the marketing authorisation, the approved summary of product characteristics may be the reference document.**

*Justification*

*As stated in Annex I, Part 5, point 20, the investigator’s brochure may be replaced by SmPC for low risk trials, and by the SmPC plus additional documents for medium-risk trials.*

*For the sake of clarity with respect to the lighter regulatory regime applying to trials which pose no additional risk to participants compared to normal clinical practice, it is helpful to specify in the substantive legal text the requirements for the Investigator Brochure for trials with authorised IMPs, in addition to providing this information in Annex I (point 5.20).*

**Amendment 222**  
**Proposal for a regulation**

**Article 54 – paragraph 1**

*Text proposed by the Commission*

*Amendment*

The sponsor **and** the investigator shall

The sponsor **or** the investigator shall keep a

keep a clinical trial master file.

clinical trial master file.

## **Amendment 223**

### **Proposal for a regulation Article 55 – paragraph 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 subjects shall be archived in accordance with national legislation.

*Amendment*

***The*** sponsor and the investigator shall archive the content of the clinical trial master file ***in electronic format for an indefinite period of time*** after ***concluding*** the clinical trial. However, the medical files of subjects shall be archived in accordance with national legislation. ***If the sponsor is unable to archive the master file, it may be archived in the EU database. The electronic master file shall be archived in a readable and easily searchable format.***

*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 224**

### **Proposal for a regulation**

#### **Article 58 – paragraph 5 – point a**

*Text proposed by the Commission*

(a) re-labelling, re-packaging or reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State to carry out such processes, and if the investigational medicinal products are intended to be used exclusively by those institutions;

*Amendment*

(a) ***labelling***, re-labelling, ***packaging***, re-packaging or reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State to carry out such processes, and if the investigational medicinal products are intended to be used exclusively by those institutions;

### *Justification*

*This amendment is a clarification and ensures that e.g. pharmacies in hospitals who have to prepare certain mixtures of medicines for use in a clinical trial according to the approved study plan of the sponsor and need to package and label the mixture will still be able to do so without needing a manufacturing authorisation.*

#### **Amendment 225** **Proposal for a regulation**

##### **Article 58 – paragraph 5 – point c**

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

(c) the preparation of medicinal products referred to in Article 3(1) and (2) of Directive 2001/83/EC.

###### *Amendment*

(c) the preparation of medicinal products referred to in Article 3(1) and (2) of Directive 2001/83/EC **or in accordance with the research protocol provided by the sponsor.**

#### **Amendment 226** **Proposal for a regulation**

##### **Article 64 – paragraph 1 – introductory part**

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

1. Authorised investigational medicinal products and authorised auxiliary medicinal products shall **be labelled**

###### *Amendment*

1. Authorised investigational medicinal products and authorised auxiliary medicinal products shall **not carry any additional labelling.**

#### **Amendment 227** **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 EU.** The medicinal product may be labelled in several languages.

### *Justification*

*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 228** **Proposal for a regulation**

##### **Article 68 – paragraph 2**

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

Any sponsor may delegate any or all of its tasks to an individual, a company, an institution or an organisation. Such delegation shall be without prejudice to the responsibility of the sponsor.

###### *Amendment*

Any sponsor may delegate any or all of its **logistic** tasks to an individual, a company, an institution or an organisation. Such delegation shall be without prejudice to the **scientific and ethical** responsibility of the sponsor.

#### **Amendment 229** **Proposal for a regulation**

##### **Article 68 – paragraph 3**

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

***The investigator and the sponsor may be the same person.***

###### *Amendment*

***deleted***

#### **Amendment 230**

##### **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:

*Justification*

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

**Amendment 231**

**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 232**

**Proposal for a regulation**

**Article 69 – paragraph 2 – point c a (new)**

*Text proposed by the Commission*

*Amendment*

***(ca) implementing measures taken in accordance with Article 78;***

**Amendment 233**

**Proposal for a regulation**

**Article 69 – paragraph 2 – point c b (new)**

*Text proposed by the Commission*

*Amendment*

***(cb) implementing measures , if the sponsors so wish, taken in accordance with Article 37;***

**Amendment 234**  
**Proposal for a regulation**

**Article 69 – paragraph 2 – point c c (new)**

*Text proposed by the Commission*

*Amendment*

***(cc) centralising pharmacovigilance data and complying with the obligations laid down in Chapter VII.***

**Amendment 235**

**Proposal for a regulation**

**Article 72**

*Text proposed by the Commission*

*Amendment*

***For low-risk clinical trials, Member States shall ensure that damage compensation is covered by the general compensation system established under the national social security or health care system.***

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.

For clinical trials other than ***low-risk*** 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.

***Adequate and comprehensive information shall be provided to the subject on the limits and conditions of damage compensation, and the conditions of use of the national indemnification mechanism referred to in Article 73.***

## Amendment 236

### Proposal for a regulation

#### Article 73 – paragraph 3

*Text proposed by the Commission*

3. The use of the national indemnification mechanism shall be free of charge where, for objective reasons, ***the clinical trial was not intended, at the time of submission of the application for authorisation of that clinical trial, to be used for obtaining a marketing authorisation for a medicinal product.***

For all other clinical trials, the use of the national indemnification mechanism ***may*** be subject to a fee. Member States shall establish that fee on a not-for-profit basis, taking into account the risk of the clinical trial, the potential damage, and the likelihood of the damage.

*Amendment*

3. ***For clinical trials which, for objective reasons, were not intended to be used for obtaining a marketing authorisation for a medicinal product at the point of submitting the application for the authorisation of that trial,*** the use of the national indemnification mechanism shall be free of charge.

***Member States shall be able to charge sponsors appropriate fees retrospectively in the event that the sponsor decides to use the clinical trial to obtain a marketing authorisation.***

For all other clinical trials, the use of the national indemnification mechanism ***shall*** be subject to a fee. Member States shall establish that fee on a not-for-profit basis, taking into account the risk of the clinical trial, the potential damage, and the likelihood of the damage.

## Amendment 237

### Proposal for a regulation

#### Article 75 – paragraph 3 a (new)

*Text proposed by the Commission*

*Amendment*

***3a. Inspections fees, if any, shall be waived for non-commercial sponsors..***

*Justification*

*Non-commercial sponsors should not be in the obligation to pay these fees which may easily represent 10% of a budget of an academic clinical trial.*

**Amendment 238**  
**Proposal for a regulation**

**Article 75 – paragraph 5 – subparagraph 1**

*Text proposed by the Commission*

5. Following an inspection, the Member State under whose responsibility the inspection has been conducted shall draw up an inspection report. That Member State shall make the inspection report available to the sponsor of the relevant clinical trial and shall submit the inspection report through the EU portal to the EU database.

*Amendment*

5. Following an inspection, the Member State under whose responsibility the inspection has been conducted shall draw up an inspection report. That Member State shall make the inspection report available to the sponsor of the relevant clinical trial and shall submit the inspection report through the EU portal to the EU database, ***where it shall be publicly available.***

*Justification*

*Subjects taking part in the clinical trial have the right to know whether the trial has been conducted in accordance with the regulation for them to be able to withdraw their consent should they wish to do so. Moreover these inspections are carried out in the public interest and the inspections are often paid with public money which is why the report should be made publicly accessible.*

**Amendment 239**  
**Proposal for a regulation**

**Article 75 – paragraph 5 – subparagraph 2**

*Text proposed by the Commission*

***When making the inspection report available to the sponsor, the Member State referred to in the first subparagraph shall ensure that confidentiality is protected.***

*Amendment*

***deleted***

*Justification*

*Subjects taking part in the clinical trial have the right to know whether the trial has been conducted in accordance with the regulation for them to be able to withdraw their consent should they wish to do so. Moreover these inspection are carried out in the public interest and the inspections are often paid with public money which is why the report should be made publicly accessible.*

**Amendment 240**  
**Proposal for a regulation**

**Article 76 – paragraph 1 – point c**

*Text proposed by the Commission*

(c) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that Article 25(3) of this Regulation is complied with.

*Amendment*

(c) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that Article 25(5) of this Regulation is complied with.

*Justification*

*This reference to Article 25 needs to be corrected. It is paragraph 5, not paragraph 3, that refers to clinical trials conducted outside the Union.*

**Amendment 241**  
**Proposal for a regulation**

**Article 76 – paragraph 2**

*Text proposed by the Commission*

2. The Commission may conduct inspections where it considers necessary.

*Amendment*

2. The Commission may conduct inspections where it considers necessary. *A summary of the Commission's inspection report shall be made publicly available in the EU database.*

*Justification*

*These inspection would be carried out in the public interest which is why the report should be made publicly accessible.*

**Amendment 242**  
**Proposal for a regulation**

**Article 76 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

*2a. Inspections fees, if any, shall be waived for non-commercial sponsors.*

*Justification*

*Non-commercial sponsors should not be in the obligation to pay these fees which may easily represent 10% of a budget of an academic clinical trial.*

**Amendment 243**  
**Proposal for a regulation**

**Article 76 – paragraph 2 b (new)**

*Text proposed by the Commission*

*Amendment*

***2b. The Commission shall report to the European Parliament annually on the controls and inspections conducted pursuant to this Article.***

**Amendment 244**  
**Proposal for a regulation**

**Article 77 – paragraph 1**

*Text proposed by the Commission*

*Amendment*

The Commission shall set up and maintain a portal at Union level as a single entry point for the submission of data and information relating to clinical trials in accordance with this Regulation.

The ***European Medicines Agency, on behalf of the*** Commission, shall set up and maintain a portal at Union level as a single entry point for the submission of data and information relating to clinical trials in accordance with this Regulation. ***The portal shall be technically advanced and user-friendly so as to avoid unnecessary work.***

**Amendment 245**  
**Proposal for a regulation**

**Article 77 – paragraph 2**

*Text proposed by the Commission*

*Amendment*

Data and information submitted through the EU portal shall be stored in the EU database referred to in Article 78.

Data and information submitted through the EU portal shall be stored in the EU database referred to in Article 78. ***It shall also be possible to use the EU portal in***

*only one national language in cases of research which does not extend to more than one Member State.*

## Amendment 246

### Proposal for a regulation

#### Article 78 – paragraph 1 – subparagraph 1

*Text proposed by the Commission*

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

*Amendment*

1. The **Agency** shall set up and maintain a database at Union level (hereinafter, the ‘EU database’), **on behalf of the Commission**. The **Agency** 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.**

*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 247

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

*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. **It shall also enable citizens of the Union to have access to clinical information, in easily searchable form, about medicinal products in order to enable them to make**

*informed decisions about their health. Publicly available information contained in the database shall contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors.*

*Justification*

*Clinical trials data are scientific data and therefore belong to the public. Patients accept to participate in clinical trials because their participation will benefit the public through the advancement of science. Science is hampered when the data are never made public. Moreover, industry-funded research benefits from publicly funded research bodies - access to investigators and research teams at publicly research sites; public funding for basic research.*

**Amendment 248**

**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:

*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 249**

**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 status of the marketing***

***authorisation for the medicinal product in accordance with the third sub-paragraph of Article 34(3);***

*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 250  
Proposal for a regulation**

**Article 78 – paragraph 3 – sub-paragraph 1 a (new)**

*Text proposed by the Commission*

*Amendment*

***The definition of what is considered as commercially confidential shall be in accordance with Agency guidelines and shall not be allowed to override the interest of public health research.***

**Amendment 251  
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 252  
Proposal for a regulation**

**Article 78 – paragraph 7**

*Text proposed by the Commission*

7. The Commission and Member States shall ensure that the data subject may effectively exercise his or her rights to information, to access, to rectify and to object in accordance with Regulation (EC) No 45/2001 and national data protection legislation implementing Directive 95/46/EC respectively. They shall ensure that the data subject may effectively exercise the right of access to data relating to him or her, and the right to have inaccurate or incomplete data corrected and erased. Within their respective responsibilities, the Commission and Member States shall ensure that inaccurate and unlawfully processed data is deleted, in accordance with the applicable legislation. Corrections and deletions shall be carried out as soon as possible, but no later than within 60 days after a request is made by a data subject.

*Amendment*

7. The Commission, **the Agency** and Member States shall ensure that the data subject may effectively exercise his or her rights to information, to access, to rectify, **to block** and to object in accordance with Regulation (EC) No 45/2001 and national data protection legislation implementing Directive 95/46/EC respectively. They shall ensure that the data subject may effectively exercise the right of access to data relating to him or her, and the right to have inaccurate or incomplete data corrected, **blocked** and erased. Within their respective responsibilities, the Commission, **the Agency** and Member States shall ensure that inaccurate and unlawfully processed data is deleted, in accordance with the applicable legislation. Corrections, **blocking** and deletions shall be carried out as soon as possible, but no later than within 60 days after a request is made by a data subject.

*Justification*

*The right to block personal data, which is also recognised by EU data protection law along with the rights referred to in this Article needs to be included in the proposal. This amendment takes account of the EDPS opinion.*

**Amendment 253**  
**Proposal for a regulation**

**Article 78 – paragraph 7 a (new)**

*Text proposed by the Commission*

*Amendment*

***7a. Free and convenient access to clinical data held in the Agency's database, particularly to clinical study reports, shall be granted to the public. To this end, a hyperlink shall be included to the clinical study reports of the clinical trials.***

**Amendment 254**  
**Proposal for a regulation**

**Article 82 – paragraph 1**

*Text proposed by the Commission*

This Regulation shall be without prejudice to the possibility for Member States to levy a fee for the activities set out in this Regulation, provided that the level of the fee is set in a transparent manner and on the basis of cost recovery principles.

*Amendment*

This Regulation shall be without prejudice to the possibility for Member States to levy a fee for the activities set out in this Regulation, provided that the level of the fee is set in a transparent manner and on the basis of cost recovery principles.

***Member States may establish reduced fees for non-profit clinical trials.***

*Justification*

*Non-profit clinical trials should be advantaged from financial obligation.*

**Amendment 255**  
**Proposal for a regulation**

**Article 83 – title**

*Text proposed by the Commission*

***One fee per activity per Member State***

*Amendment*

Fees ***by*** Member ***States***

*Justification*

*Establishing fees is a purely national issue.*

**Amendment 256**  
**Proposal for a regulation**

**Article 83**

*Text proposed by the Commission*

A Member State shall ***not*** require, for an assessment as referred to in Chapters II and III, ***multiple*** payments to different bodies involved in this assessment.

*Amendment*

A Member State shall require, for an assessment as referred to in Chapters II and III, payments to different bodies involved in this assessment ***in accordance with its national practices.***

*Justification*

*Establishing fees is a purely national issue.*

**Amendment 257**  
**Proposal for a regulation**

**Article 86 – paragraph 1**

*Text proposed by the Commission*

This Regulation shall not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from those cells, on grounds not dealt with in this Regulation. The Member States shall communicate the national legislation concerned to the Commission.

*Amendment*

This Regulation shall not affect the application of national legislation prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from those cells, on grounds not dealt with in this Regulation. The Member States shall communicate the national legislation concerned to the Commission.  
***No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.***

*Justification*

*The regulation may not fall behind the existing directive. Therefore, we should adopt the formulation of the present directive.*

**Amendment 258**  
**Proposal for a regulation**

**Article 91 a (new)**

*Text proposed by the Commission*

*Amendment*

***Article 91a***

***Review***

***Five years after the entry into force of this Regulation, and every five years thereafter, the Commission shall present a report to the European Parliament and the Council, on the application of this Regulation. The report shall include an assessment of the impact that the Regulation has had on scientific and***

*technological progress, comprehensive information on the different types of clinical trials authorised pursuant to this Regulation, and the measures required in order to maintain the competitiveness of European clinical research. The Commission shall, if appropriate, present a legislative proposal based on the report in order to update the provisions set out in this Regulation.*

#### *Justification*

*Advances in technology and medical knowledge mean that clinical trials are rapidly evolving. A review clause will ensure that the Regulation reacts quickly to any necessary changes.*

*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 259 Proposal for a regulation**

##### **Annex I – part 1 – point 1**

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

1. The sponsor shall, where appropriate, refer to previous applications. If these applications have been submitted by another sponsor, a written agreement from that sponsor shall be submitted.

###### *Amendment*

1. The sponsor shall, where appropriate, refer to previous applications ***using its Universal Trial Registration Number (UTRN) or registration number in the EU portal***. If these applications have been submitted by another sponsor, a written agreement from that sponsor shall be submitted.

#### **Amendment 260 Proposal for a regulation**

##### **Annex I – part 1 – point 2 a (new)**

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

###### *Amendment*

***2a. The EU portal shall enable sponsors to sign electronically by providing***

***sufficient guarantees about the signatory without any additional paperwork.***

*Justification*

*Some member states currently require a lot of documents with ink signatures and certified by notaries to prove that the signatory of the document is authorized to sign on behalf of the sponsor – this should not be the case anymore.*

**Amendment 261  
Proposal for a regulation**

**Annex I – part 2 – point 6 – indent 1**

*Text proposed by the Commission*

specific features of the trial population, such as subjects not able to give informed consent or minors;

*Amendment*

specific features of the trial population, such as subjects not able to give informed consent or minors, ***or other vulnerable populations (i.e. incapacitated persons, pregnant and breastfeeding women, persons deprived of liberty, and subjects with specific needs);***

**Amendment 262  
Proposal for a regulation**

**Annex I – part 2 – point 6 – indent 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***whether the trial is designed to test the therapeutic and public health benefits of a medicinal product for a target population.***

*Justification*

*Trial participants should as closely as possible reflect the target audience for the medicinal product tested. This is particularly important for phase III and phase IV trials, wherein the safety and efficacy of the medicinal product should be assessed via trials on those who are likely to be using the product when it is on the market. Earlier phases test for more basic safety concerns where it is not as crucial to assemble a representative pool of trial participants.*

**Amendment 263**  
**Proposal for a regulation**

**Annex I – part 2 – point 6 – indent 6 a (new)**

*Text proposed by the Commission*

*Amendment*

***whether the clinical trial significantly contributes to bringing a greater understanding of the physiology and pathology of a condition for which data is lacking, specifically for rare and ultra-rare diseases.***

*Justification*

*Many rare and ultra-rare diseases are not yet correctly identified or remain partially understood. In clinical trials associating patients affected by such conditions, the knowledge of these illnesses may be significantly improved by the resulting assessment of data. The reporting Member-State must have knowledge of this added value.*

**Amendment 264**  
**Proposal for a regulation**

**Annex I – part 2 – point 9**

*Text proposed by the Commission*

*Amendment*

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

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 265**  
**Proposal for a regulation**

**Annex I – part 4 – point 12 a (new)**

*Text proposed by the Commission*

*Amendment*

***12a. The protocol shall, when possible, be written in an easily accessible format, such as a searchable pdf, rather than scanned images.***

*Justification*

*It is important to ensure that it is easy to search for relevant information in the protocols.*

## **Amendment 266**

### **Proposal for a regulation**

#### **Annex I – part 4 – 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;***

*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 267**

### **Proposal for a regulation**

#### **Annex I – part 4 – point 13 – indent 2**

*Text proposed by the Commission*

*Amendment*

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

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;***

*Justification*

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

*application.*

**Amendment 268**  
**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 accordance with Article 6;

*Amendment*

· an evaluation of the anticipated benefits and risks, ***including for specific 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 269**  
**Proposal for a regulation**

**Annex I – part 4 – point 13 – indent 3 a (new)**

*Text proposed by the Commission*

*Amendment*

***primary outcome parameters***

*Justification*

*It is important that primary outcome parameters are defined in the protocol to avoid manipulation of the findings.*

**Amendment 270**

**Proposal for a regulation**  
**Annex I – part 4 – point 13 – indent 3 b (new)**

*Text proposed by the Commission*

*Amendment*

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

*Justification*

*The level of patient involvement should be specified.*

**Amendment 271**  
**Proposal for a regulation**

**Annex I – part 4 – point 13 – indent 3 c (new)**

*Text proposed by the Commission*

*Amendment*

***where possible, the full statistical analysis plan, and whether it is changed during the trial, as well as a justification for any such changes;***

*Justification*

*It is important that the statistical analyses plan cannot be changed significantly during a trial without justifying it.*

**Amendment 272**  
**Proposal for a regulation**

**Annex I – part 4 – point 13 – indent 5 a (new)**

*Text proposed by the Commission*

*Amendment*

***- a description of the groups and sub-groups of the subjects participating in the clinical trial (age, gender, and whether the subjects are healthy volunteers or patients)***

*Justification*

*This complements Amendment 25 of the rapporteur. 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. The groups and sub-groups participating in the clinical trial, their age and gender, and whether subjects are healthy volunteers or patients needs to be clearly described in the protocol.*

## **Amendment 273**

### **Proposal for a regulation**

#### **Annex I – part 4 – 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 a specific gender or age group is excluded from, or underrepresented in the trial, an explanation of the reasons and justification for these exclusion criteria;***

## **Amendment 274**

### **Proposal for a regulation**

#### **Annex I – part 4 – point 13 – indent 7 a (new)**

*Text proposed by the Commission*

*Amendment*

***a risk assessment covering all the risk determinants for a clinical trial, namely:***

***I. Risk to subjects' rights:***

- 1. information and informed consent***
- 2. personal data protection***

***II. Risk to subjects' physical integrity and safety:***

- 1. safety of the treatment intervention***
- 2. risk of diagnostic intervention***
- 3. vulnerability of the patient population***

***III. Risk to data integrity and public health:***

- 1. data quality, data management and analysis, data access and publication***
- 2. credibility of results***
- 3. impact on public health***

*Justification*

*A risk assessment should be part of the application dossier, and should drive the quality management and the monitoring plan.*

**Amendment 275**  
**Proposal for a regulation**

**Annex I – part 4 – point 13 – indent 9**

*Text proposed by the Commission*

a description of the publication policy;

*Amendment*

a description of the publication policy,  
***even in case of negative results, 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 276**

**Proposal for a regulation**  
**Annex I – part 4 – point 13 – indent 16 a (new)**

*Text proposed by the Commission*

*Amendment*

***a description of the assessment of the  
impact on the rights of the subjects to  
human dignity, the right to physical and  
mental integrity, the right for respect of  
private and family life and the right of the  
child and measures taken to safeguard  
them.***

*Justification*

*In order to assess that the clinical trial respects fundamental rights the Application dossier for initial application should include the description of the assessment conducted on the impact of fundamental rights and measures taken to safeguard them. This amendment is consistent with Amendment 1.*

**Amendment 277**  
**Proposal for a regulation**

**Annex I – part 4 – point 13 – indent 16 b (new)**

*Text proposed by the Commission*

*Amendment*

***a detailed description for measures adopted to ensure a restrictive use of placebos in paediatric trials;***

*Justification*

*In accordance with the ICH-GCP, the EU Ethical recommendations for paediatric research (Eudralex Vol.10/2008), and the Oviedo Convention and its additional protocol on biomedical research.*

**Amendment 278**  
**Proposal for a regulation**

**Annex I – part 4 – point 13 – indent 16 c (new)**

*Text proposed by the Commission*

*Amendment*

***a detailed description of procedures adopted by sponsor to regularly monitor and re-examine the risk determinants of the clinical trial;***

**Amendment 279**  
**Proposal for a regulation**

**Annex I – part 4 – point 13 – indent 16 d (new)**

*Text proposed by the Commission*

*Amendment*

***a description whether the trial replicates similar trials based on an identical hypothesis (which should be avoided);***

**Amendment 280**  
**Proposal for a regulation**

**Annex I – part 4 – point 13 – indent 16 e (new)**

*Text proposed by the Commission*

*Amendment*

***description of paediatric expertise to be available at all trial sites;***

*Justification*

*In accordance with the ICH-GCP, the EU Ethical recommendations for paediatric research (Eudralex Vol.10/2008), and the Oviedo Convention and its additional protocol on biomedical research.*

**()Amendment 281**

**Proposal for a regulation**

**Annex I – part 4 – 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.***

*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 282**

**Proposal for a regulation**

**Annex I – part 4 – point 17**

*Text proposed by the Commission*

*Amendment*

17. The protocol shall be accompanied by a synopsis of the protocol.

17. The protocol shall be accompanied by a synopsis of the protocol, ***and shall be updated with any modifications of the protocol, including the dates of each modification.***

**Amendment 283**

**Proposal for a regulation**

**Annex I – part 7 – point 45 – introductory part**

*Text proposed by the Commission*

*Amendment*

45. The applicant may submit the current version of the SmPC as the IMPD if the

45. The applicant may submit the current version of the SmPC as the IMPD if the

IMP *is authorised*. The exact requirements are detailed in Table 1.

*clinical trial is low-risk and concerns an IMP for which the treatment strategies are based on published data and/or standard treatment recommendations issued by learned societies or official bodies.* The exact requirements are detailed in Table 1.

## **Amendment 284**

### **Proposal for a regulation**

#### **Annex I – part 12 – 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.***

#### *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 285**

### **Proposal for a regulation**

#### **Annex I – part 12 – 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.*

#### **Amendment 286** **Proposal for a regulation**

##### **Annex I – part 16 – point 61 a (new)**

*Text proposed by the Commission*

*Amendment*

***61a. Information on the financing of the clinical trial shall be submitted.***

#### **Amendment 287**

##### **Proposal for a regulation** **Annex II – part 4 – point 4 – indent 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***– a description of the assessment of the impact on the rights of the subjects to human dignity, the right to physical and mental integrity, the right for respect of private and family life and the right of the child and measures taken to safeguard them.***

### *Justification*

*In order to assess whether the clinical trial respects fundamental rights the Application dossier for initial application should include the description of the assessment conducted on the impact of fundamental rights and measures taken to safeguard them. This amendment is consistent with Amendment 1.*

#### **Amendment 288** **Proposal for a regulation**

##### **Annex III – part 1 – point 4**

*Text proposed by the Commission*

4. Serious adverse **events** occurring to a subject after the end of the trial with regard to the subjects treated by him shall be reported to the sponsor if the investigator becomes aware of them.

*Amendment*

4. Serious adverse **reactions** occurring to a subject after the end of the trial with regard to the subjects treated by him **and which may be related to the medicinal product used in the clinical trial** shall be reported to the sponsor if the investigator becomes aware of them.

**Amendment 289**  
**Proposal for a regulation**

**Annex III – part 2 – point 7**

*Text proposed by the Commission*

7. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

*Amendment*

7. The definition implies a reasonable possibility of a causal relationship between the event and the IMP **and/or the auxiliary medicinal product**. This means that there are facts (evidence) or arguments to suggest a causal relationship.

**Amendment 290**

**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(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 including: a structured summary of trial design, methods, results, and conclusions; scientific background and explanation of rationale; specific objectives or hypotheses*

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

*2. Subject disposition with sufficient details to allow for replication, including:*

*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, addressing sources of potential bias and imprecisions, & Caveats**

**7. The protocol and its subsequent modifications.**

## **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.

### **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.

## **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.

21.3.2013

**OPINION OF THE COMMITTEE ON INDUSTRY, RESEARCH AND ENERGY**

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

PE504.236v02-00

148/263

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Rapporteur: Amalia Sartori

## SHORT JUSTIFICATION

The adoption of the Directive 2001/20/EC marked an important milestone in the development of the standards for the conduct of clinical trials, both within the Union and on the international level.

It is understood, however, that this Directive created difficulties for the facilitating of clinical trials in several Member States and there is a need for harmonisation, as well as a thorough assessment of the existing legal framework. It is of the utmost importance that the high standards set out in the previous Directive are adhered to and not lost in efforts to simplify procedures across Member States.

Your rapporteur introduces a number of amendments in her opinion to ensure that high standards of care and treatment of patients are upheld in the Union; while stimulating scientific research and innovation through public access to data in the form of a full clinical trial report. Given the current economic crisis, money must not be wasted on medicines that are not effective and the public must be able to make informed decisions about their health.

Your rapporteur is of the view that the new definitions, including the new definitions of a clinical trial, a clinical study, and 'low intervention trials' as set out in Article 2 are unnecessarily complicated and open to misinterpretation. Instead, they should follow a simple principle: 'observations' fall into the 'study' category and 'interventions' fall into the 'trial' category. Without such an amendment the existing text, taken together with the definition by default of a 'non-interventional study', would allow for 'clinical studies' (which do not fall under the definition of a clinical trial) to be conducted without asking patients for prior consent. Further reintroductions of definitions from the present Directive are also proposed following the same reasoning.

Your rapporteur fears that the current proposal weakens the present role of Ethics Committees without providing a proper legal base for an equivalent independent assessment body. The Union should show due respect for human rights, patient safety, and high standards of ethical scrutiny, by reintroducing independent ethics committees in the Regulation.

Article 28(2) stipulates that “the rights, safety and well-being of the subjects shall prevail over the interests of science and society”. To achieve these objectives, it is necessary to make authorisation by the Member States contingent on the decision of the interdisciplinary and independent Ethics Committee which is responsible according to their national law.

Clinical trials data are scientific data, which are gained from the inclusion of the public and which have significant impacts on the public. They therefore belong first and foremost to the

public. It needs to also be reminded that swift and well-monitored access to the results of clinical trials has its ethical aspect, since it enables patients to gain direct and rapid access to the latest pharmacological accomplishments.

Science is hampered and the social value of research is diminished if the data are never made public. That is why your rapporteur calls for a clear statement in the Regulation that enables Union citizens to have access to clinical information about medicinal products, in order to enable them to make informed decisions about their health.

Your rapporteur calls for the clinical information stored in the EU database to be in clinical study report form. Experience gained so far show that submission of a summary is not sufficient to protect patient's rights and interests. The non-disclosure of the detailed results of clinical trials impairs scientific knowledge and leads to publication bias (where negative findings are not published), which in turns paints an inaccurate picture of a medicine's effectiveness. For example, publication bias led to the wide use of the antidepressant paroxetine in children and teenagers, despite a lack of effectiveness and - more worrying - despite an increased risk of suicide in this population.

For further transparency, your rapporteur calls for the clinical trial master file to be archived indefinitely, as opposed to the suggested five years. Some long-term adverse drug reactions such as cancer or teratogenicity only appear after decades of use, sometimes even going beyond one generation of patients, i.e. Diethylstilbestrol (DES) disaster between the 1950s and 1970s, therefore it is important to guarantee the conservation of the master file for an indefinite time.

## AMENDMENTS

The Committee on Industry, Research and Energy 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, **rights and well-being** of subjects should be protected and the data generated should be **relevant**, reliable and robust.

*(This amendment applies throughout the text. Adopting it will necessitate corresponding changes throughout.)*

## *Justification*

*In accordance with the Declaration of Helsinki, 'well-being' applies throughout the text whenever the safety and rights of the subjects are mentioned: recital 1, recital 66, Art 49(2).*

### **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. ***The conduct of a clinical trial should be conditioned to prior approval by an Ethics Committee.***

### **Amendment 3 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 for starting a clinical trial, ***without compromising patient safety or public health.***

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

#### **Recital 8 a (new)**

*Text proposed by the Commission*

*Amendment*

***(8a) The fact that clinical trials are conducted in both public and private centres makes it necessary to recognise them and adopt monitoring, authorisation and assessment measures that apply to both types of centre.***

**Amendment 5**  
**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 "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, ***without compromising scientific excellence, and guaranteeing patient safety at all times.***

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

**Recital 9 a (new)**

*Text proposed by the Commission*

*Amendment*

***(9a) In case of an urgent situation as well as for rare and ultra-rare diseases which are life-threatening and for which therapeutic options and expertise are limited and geographically spread across the world, Member States should have the possibility to assess and authorise clinical***

*trial applications in priority.*

**Amendment 7**  
**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 national nature or to ethical aspects of a clinical trial. ***Those issues should not be assessed in cooperation among all Member States concerned.***

*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. ***Although Member States' cooperation should be encouraged, it should be limited to exchange of views and best practices on these matters.***

*Justification*

*The more Member States cooperate on a voluntary basis the better. Cooperation between Member States is important yet such cooperation should be limited on ethical matters since these are intrinsically linked to national traditions and competences.*

**Amendment 8**  
**Proposal for a regulation**

**Recital 22 a (new)**

*Text proposed by the Commission*

*Amendment*

***(22a) Whereas most clinical trials are implemented for the assessment of therapies consisting of large samples of patient populations, this Regulation should not discriminate patients suffering from rare and ultra-rare diseases and should integrate the specificities of low-prevalence conditions when assessing a trial.***

*Justification*

*The Commission's proposal does not reflect the specificities of rare and ultra-rare diseases. The future regulation must take into account therapeutic innovations and must be in compliance with policies on rare and ultra-rare diseases which have been developed since adoption of Directive 2001/20/EC.*

**Amendment 9**  
**Proposal for a regulation**

**Recital 25 a (new)**

*Text proposed by the Commission*

*Amendment*

***(25a) A data subject should always have the option to give broad consent, to be given to the treating institution, for his or her data to be used for historical, statistical or scientific research purposes, and to withdraw his or her consent at any time.***

*Justification*

*Physicians have always gained new knowledge from data on their previous patients. Appropriately, today, it is required that each patient consents to his/her data being used for research purposes. However, while having the right to dissent, patients should also have the right to give their treating institution a 'broad' consent, if they wish, such that data can be used for any type of future research (unless they withdraw their original consent). In this way, patients can have the right to 'donate' their data for research purposes.*

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

**Recital 26**

*Text proposed by the Commission*

*Amendment*

(26) In order for the sponsor to assess all potentially relevant safety information, the investigator should ***report to him*** all serious adverse events.

(26) In order for the sponsor to assess all potentially relevant safety information, the investigator should ***record and register in the electronic database*** all serious adverse events.

**Amendment 11**  
**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 ***and allow public dissemination of objective information in order to support European research and to increase knowledge in the field of public health. It should not undermine innovation or competitiveness of European industries.*** No personal data of data subjects participating in a clinical trial should be recorded in the database, ***and the protection of commercial interests, including intellectual property, as foreseen by Article 4 of Regulation 1049/2001, should not be hampered.*** 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 commercially confidential information, as foreseen by Article 4 of Regulation 1049/2001.***

*Justification*

*The database should allow public dissemination of reliable information on the latest advances of medical research, all the while respecting the competitiveness imperatives of the pharmaceutical industry, which finances in itself approximately 60% of European clinical trials. Public disclosure should protect personal data and commercially confidential information, in order to avoid any stigmatisation of patients taking part in a clinical trial and in order to avoid stimulating unfair competition which would threaten the competitiveness of European medical research.*

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

**Recital 52 a (new)**

*Text proposed by the Commission*

*Amendment*

**(52a) Commercially confidential information should be identified and protected in order to avoid harming the interests of patients and/or the competitive position of the sponsors.**

*Justification*

*Public disclosure of information should guard protected personal data and commercially confidential information, in order to avoid any stigmatisation of patients taking part in a clinical trial and to avoid stimulating unfair competition which would threaten the competitiveness of European medical research.*

**Amendment 13**  
**Proposal for a regulation**  
**Recital 63**

*Text proposed by the Commission*

*Amendment*

(63) This Regulation is in line with the major international guidance documents on clinical trials, such as the most recent (2008) version of the World Medical Association's Declaration of Helsinki and good clinical practice, which has its origins in the Declaration of Helsinki.

(63) This Regulation is in line with the major international guidance documents on clinical trials, such as the most recent (2008) version of the World Medical Association's Declaration of Helsinki, **in particular ethical principles for medical research involving human subjects, including research on identifiable human material and data**, and good clinical practice, which has its origins in the Declaration of Helsinki.

**Amendment 14**  
**Proposal for a regulation**  
**Article 2 – paragraph 2 – point 12**

*Text proposed by the Commission*

*Amendment*

(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 which **is likely to** have a substantial impact on the safety or rights of the

(12) 'Substantial modification': any change to any aspect of the clinical trial, **including early termination of the trial and change in number of subjects participating in the trial**, which is made after notification of the decision referred to in Articles 8, 14,

subjects or on the reliability and robustness of the data generated in the clinical trial;

19, 20 and 23 and which **could** 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, ***e.g. change the interpretation of the scientific documents used to support the conduct of the trial, or if the modifications are otherwise significant.***

#### *Justification*

*Early termination allows the sponsor to avoid the risk that such difference could lose statistical significance during the end of the trial if it was due to the hazard. Any modifications in the conduct, design, methodology, investigational or auxiliary medicinal product of clinical trials after they have been authorized can impair the data reliability and robustness. Therefore the more accurate wording from Directive 2001/20/EC Article 10(a) has been reintroduced.*

### **Amendment 15 Proposal for a regulation**

#### **Article 2 – paragraph 2 – point 13**

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

(13) ‘Sponsor’: an individual, company, institution or organisation which takes responsibility for the initiation ***and management*** of the clinical trial;

##### *Amendment*

(13) ‘Sponsor’: an individual, company, institution or organisation which takes responsibility for the initiation, ***management and/or financing*** of the clinical trial;

#### *Justification*

*Reintroduction of the definition provided for in Directive 2001/20/EC.*

### **Amendment 16 Proposal for a regulation Article 2 – paragraph 2 – point 14 a (new)**

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

##### *Amendment*

***(14a) ‘Ethics Committee’: an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of***

*subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent;*

*Justification*

*Re-introduction of the definition from Directive 2001/20/EC.*

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

**Article 2 – paragraph 2 – point 15**

*Text proposed by the Commission*

(15) ‘Subject’: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control;

*Amendment*

(15) ‘Subject’: an individual who ***freely and voluntarily*** participates in a clinical trial, either as recipient of an investigational medicinal product or as a control;

**Amendment 18**  
**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 ***freely and 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**  
**Proposal for a regulation**

**Article 2 – paragraph 2 – point 28 a (new)**

*Text proposed by the Commission*

*Amendment*

**(28a) 'Adverse reaction': all untoward and unintended responses to an investigational medicinal product related to any dose administered;**

*Justification*

*Re-introduction of the definition from the previous Directive 2001/20/EC.*

**Amendment 20**  
**Proposal for a regulation**  
**Article 3**

*Text proposed by the Commission*

*Amendment*

A clinical trial may be conducted only if

- the rights, safety and well-being of subjects are protected; and

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

A clinical trial may be conducted only if

- the rights, **physical and mental integrity**, safety and well-being of subjects are protected;

**- the evaluation of the ethical acceptability of the clinical trial is positive; and**

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

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

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

*Text proposed by the Commission*

*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

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.

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. ***The reporting Member State may not infer ethical concerns as a justification for considering the application not complete or not falling within the scope of this Regulation.***

*Justification*

*Ethical committees fill an important role ensuring that Member States' particular traditions and concerns are taken into account. However, an ethical concern in the reporting Member State should not be allowed to hinder other Member States concerned in proceeding with a clinical trial.*

**Amendment 22**

**Proposal for a regulation**

**Article 6 – paragraph 1 – point a – point i – indent 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***- the similarity of the subjects to the intended recipients of the medicinal products in terms of age, gender, and whether the subjects are healthy volunteers or patients;***

*Justification*

*In order for medicinal products to be most effective they should be tested on similar populations to those that they will be used on, for example certain drugs are metabolised differently by women and men.*

**Amendment 23**

**Proposal for a regulation**

**Article 6 – paragraph 5 a (new)**

*Text proposed by the Commission*

*Amendment*

***5a. The assessment report shall be submitted through the EU portal, stored in the EU database, and made publicly***

*available.*

*Justification*

*The assessment report shall be made publicly available for allow for public confidence in the authorisation process.*

**Amendment 24**  
**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, methodology (including sample size and randomisation, comparator and endpoints) **and the prevalence of the condition, especially for rare diseases (which affect no more than five persons per 10 000), and ultra-rare diseases (which meet a prevalence threshold of no more than one affected person per 50 000).**

*Justification*

*In the case of a rare disease, the difficulty of leading a clinical trial is most often associated with a low number of patients for each disease, and to their geographical dispersion.*

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

**Article 6 – paragraph 1 – point a – point ii – indent 4 a (new)**

*Text proposed by the Commission*

*Amendment*

**- the life-threatening and debilitating effects of certain diseases, such as some rare and ultra-rare diseases for which there are limited existing treatment options**

*Justification*

*In the case of a rare disease, the difficulty of leading a clinical trial is most often associated with a low number of patients for each disease, and to their geographical dispersion.*

**Amendment 26**  
**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, 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 **and shall document them in the assessment report. If the assessment report of the reporting Member State deviates from the considerations of the Member States concerned, the reasons for such deviation shall be stated in the assessment report.**

*Justification*

*As Part I of the assessment report addresses major ethical aspects that, according to Recitals 6 and 12, are to be regulated by the concerned Member States themselves, consensus decision-making by all Member States concerned in Part I of the assessment report would be preferable. If the reporting Member State deviates in its assessment report from the considerations of the Member States concerned, the reasons for such deviation should be explained.*

**Amendment 27**  
**Proposal for a regulation**

**Article 7 – paragraph 1 – subparagraph 1 – point a**

*Text proposed by the Commission*

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

*Amendment*

(a) compliance with the requirements for **the protection of subjects and** informed consent as set out in Chapter V;

*Justification*

*According to Recitals 6 and 12, ethical aspects are to be regulated by the Member States concerned. Limiting ethic assessment only to the verification of the informed consent procedure impairs Member States' subsidiarity and hinders subject protection.*

**Amendment 28**

**Proposal for a regulation**

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

*Text proposed by the Commission*

*Amendment*

***(aa) compliance with national law related to ethics.***

*Justification*

*The role of ethics committees does not seem to be very clearly defined in the Commission's proposal. It is necessary to clarify that the assessment necessary for the authorisation of a clinical trial also involves ethical aspects.*

**Amendment 29**

**Proposal for a regulation**

**Article 8 – paragraph 1 – subparagraph 2**

*Text proposed by the Commission*

*Amendment*

Notification shall be done by way of one single decision within ten days from the assessment date or the last day of the assessment referred to in Article 7, whichever is later.

Notification shall be done by way of one single decision, ***already comprising the views of the concerned Ethics Committee,*** within ten days from the assessment date or the last day of the assessment referred to in Article 7, whichever is later.

**Amendment 30**

**Proposal for a regulation**

**Article 8 – paragraph 2 – subparagraph 2 – point b a (new)**

*Text proposed by the Commission*

*Amendment*

***(ba) refusal of the Ethics Committee to approve the conduct of the clinical trial in the Member State concerned.***

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

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

*Text proposed by the Commission*

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.

*Amendment*

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. ***The Member State concerned may not infer ethical concerns as a justification.***

*Justification*

*Ethical committees fill an important role ensuring that Member States' particular traditions and concerns are taken into account. However, an ethical concern in one Member State should not be allowed to hinder other Member States concerned in proceeding with a clinical trial.*

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

**Article 9 – paragraph 3**

*Text proposed by the Commission*

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.

*Amendment*

3. In the assessment, the view of ***an independent Ethics Committee*** shall be taken into account.

**Amendment 33**  
**Proposal for a regulation**

**Article 11 – paragraph 1**

*Text proposed by the Commission*

Where the sponsor so requests, the application for authorisation of a clinical trial, **its assessment and the decision** shall be limited to the aspects covered by Part I of the assessment report.

*Amendment*

Where the sponsor so requests, the application for authorisation of a clinical trial shall be limited to the aspects covered by Part I of the assessment report.

**Amendment 34**  
**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. ***A record of withdrawn applications shall remain in the EU database and reasons for each withdrawal shall be given.***

*Justification*

*This amendment is an effort to gain some insight into why clinical trials applications are withdrawn. There are a number of genuine reasons to withdraw an application or stop a clinical trial, related to safety of patients and efficacy of the product. Commercial reasons are also commonly cited as motivators to halt trials. Withdrawing an application for a clinical trial for commercial reasons only is unethical as it deprives patients and society of a potentially effective medical innovation.*

**Amendment 35**  
**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**.

*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. That

That application shall be considered as a ***new application for authorisation of another clinical trial.***

application shall be considered as a ***resubmission of the application. It must be accompanied by any previous assessment report, by the considerations of concerned Members States, and it must highlight the changes or the reasons justifying the resubmission of the application file.***

*Justification*

*According to the proposal, this would allow sponsors to ‘cherry pick’ the most permissive Member States, particularly when the scientific rationale for a clinical trial was considered questionable by the Members States involved in the initial application. That the resubmission of the application be accompanied by its track record is the key to avoid unnecessary bureaucratic burdens and avoid duplication of work.*

**Amendment 36  
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 ***in any Member State*** only after the notification date of the initial authorisation decision.

*Justification*

*Sponsors should have the right to extend the a multinational clinical trial to an additional Member state after the authorisation decision is taken by any of the concerned Member State in the first round. This would improve the conduct of such clinical trials.*

**Amendment 37  
Proposal for a regulation**

**Article 14 – paragraph 3 – point a**

*Text proposed by the Commission*

(a) **25** days from the date of submission of the application referred to in paragraph 1 for low-intervention clinical trials;

*Amendment*

(a) **10** days from the date of submission of the application referred to in paragraph 1 for low-intervention clinical trials;

*Justification*

*The time for additional member states to raise questions should be aligned with the initial procedure in order to guarantee an efficient addition of a new member state. The timing between submission and decision must be competitive.*

**Amendment 38**

**Proposal for a regulation**

**Article 14 – paragraph 3 – point b**

*Text proposed by the Commission*

*Amendment*

(b) **35** days from the date of submission of the application referred to in paragraph 1 for clinical trials other than low-intervention clinical trials;

(b) **25** days from the date of submission of the application referred to in paragraph 1 for clinical trials other than low-intervention clinical trials;

**Amendment 39**

**Proposal for a regulation**

**Article 14 – paragraph 3 – point c**

*Text proposed by the Commission*

*Amendment*

(c) **40** days from the date of submission of the application referred to in paragraph 1 for any clinical trial with an advanced therapy investigational medicinal product.

(c) **30** days from the date of submission of the application referred to in paragraph 1 for any clinical trial with an advanced therapy investigational medicinal product.

*Justification*

*The time for additional member states to raise questions should be aligned with the initial procedure in order to guarantee an efficient addition of a new member state. The timing between submission and decision must be competitive.*

**Amendment 40**

**Proposal for a regulation**

**Article 14 – paragraph 4 – subparagraph 2 – point b a (new)**

*Text proposed by the Commission*

*Amendment*

***(ba) refusal of the Ethics Committee to approve the conduct of the clinical trial.***

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

**Article 14 – paragraph 5**

*Text proposed by the Commission*

**5. Between the date of submission of the application referred to in paragraph 1 and the expiry of the relevant time period referred to in paragraph 3, the additional Member State concerned may communicate to the reporting Member State any considerations relevant to the application.**

*Amendment*

**5. The additional Member State concerned may communicate to the reporting Member State any considerations relevant to Part 1 of the application within the timelines laid down in paragraph 3 starting from the date of submission referred to in paragraph 1.**

**Amendment 42**  
**Proposal for a regulation**

**Article 14 – paragraph 6 – subparagraph 1**

*Text proposed by the Commission*

The reporting Member State, and only the reporting Member State, may, ***between the date of submission of the application referred to in paragraph 1 and the expiry of the relevant time period referred to in paragraph 3***, request additional explanations from the sponsor concerning Part I of the assessment report, ***taking into account the considerations referred to in paragraph 5***.

*Amendment*

The reporting Member State, and only the reporting Member State, may, ***within the timelines specified*** in paragraph 5, request additional explanations from the sponsor concerning Part I of the assessment report.

**Amendment 43**  
**Proposal for a regulation**  
**Article 15**

*Text proposed by the Commission*

A substantial modification may only be implemented if it has been approved in accordance with the procedure set out in this Chapter.

*Amendment*

A substantial modification may only be implemented if it has been approved in accordance with the procedure set out in this Chapter ***and if it has previously been***

*approved by an Ethics Committee.*

*Justification*

*Since a substantial modification is defined as a “change (...) 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”, the same procedure as for the authorisation of a clinical trial should apply.*

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

**Article 23 – paragraph 2 – subparagraph 2 – point b a (new)**

*Text proposed by the Commission*

*Amendment*

***(ba) refusal of the Ethics Committee to approve the conduct of the clinical trial.***

**Amendment 45**  
**Proposal for a regulation**  
**Article 25 – paragraph 5**

*Text proposed by the Commission*

*Amendment*

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.

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

*Justification*

*The requirements for the clinical trials conducted outside the Union should be identical to those of the proposed Regulation. Equivalence to these principles would enable variations in their interpretations by third party sponsors.*

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

**Article 25 – paragraph 5 – subparagraph 1a (new)**

*Text proposed by the Commission*

*Amendment*

***Clinical data submitted as part of the Common Technical Document to apply for marketing authorisation must have been obtained from registered clinical trials that duly comply with the provisions of this Regulation.***

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

**Article 27**

*Text proposed by the Commission*

*Amendment*

The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to ***amend*** Annexes I and II with the objective to adapt them to technical progress or to take account of global regulatory developments.

The Commission shall be empowered to adopt delegated acts in accordance with Article 85 in order to ***complete*** Annexes I and II with the objective to adapt them to technical progress or to take account of global regulatory developments.

*Justification*

*For transparency reasons.*

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

**Article 28 – paragraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***2a. When the subject is required to give his/her consent for a clinical trial, the option of broad consent should be available to the subject, to be given to the treating institution, for his data to be used after the end of the clinical trial for historical, statistical or scientific research purposes, and to withdraw consent at any time.***

## *Justification*

*When a patient is enrolled in a clinical trial, he is asked to sign a form where he gives his informed consent exclusively for the duration and within the scope of the trial. After the trial is over, further follow-up data cannot be used, even for research purposes, unless the researcher acquires additional consents. Within the original consent, an option of broad consent should be made available to the patient, whereby his/her data could be allowed to be used at the behest of the treating institution for future research.*

### **Amendment 49 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 *for each trial* 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 witness *who represents the subject's interests* 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 50 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

##### *Amendment*

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 *that shall be explained*

subject about his or her right to revoke his or her informed consent.

***orally by a medical doctor to the subject.*** It shall inform the subject about his or her right to revoke his or her informed consent.

*Justification*

*According to ethical principles.*

**Amendment 51  
Proposal for a regulation**

**Article 34 – paragraph 3 – subparagraph 2 a (new)**

*Text proposed by the Commission*

*Amendment*

***In order to protect personal data and commercially confidential information and subject to the provisions of Article 78(3), the summary of the results of a clinical trial intended to obtain a marketing authorisation shall be made public 30 days after the date of the marketing authorisation or 1 year after the end of the clinical trial in case of the discontinuation of the product development.***

*Justification*

*The results of all clinical trials should be published in a timely matter. This publication should allow for information of the public, patients and researchers on the conclusions of the clinical trial, without hindering the competitiveness of European medical research. The publication period of these results is important in order to avoid any unfair competition which would undermine the competitiveness of European medical research.*

**Amendment 52  
Proposal for a regulation  
Article 37 – paragraph 2**

*Text proposed by the Commission*

*Amendment*

2. The investigator shall immediately report serious adverse events to the sponsor ***unless the protocol provides, for certain adverse events, that no reporting is required. The investigator shall record all***

2. The investigator shall immediately report serious adverse events to the sponsor, ***to the Agency and competent authorities of the concerned Member States. The investigator shall record all***

*serious adverse events*. Where necessary, the investigator shall send a follow-up report to the sponsor.

*serious* adverse events, **and the immediate report shall be followed by detailed, written reports, sent to the Agency and competent authorities of the concerned Member States and copies submitted through the EU portal**. Where necessary, the investigator shall send a follow-up report to the sponsor.

**Amendment 53**  
**Proposal for a regulation**  
**Article 55 – paragraph 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 subjects shall be archived in accordance with national legislation.

*Amendment*

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 **20** years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national legislation.

**Amendment 54**  
**Proposal for a regulation**

**Article 68 – paragraph 2**

*Text proposed by the Commission*

Any sponsor may delegate any or all of its tasks to an individual, a company, an institution or an organisation. Such delegation shall be without prejudice to the responsibility of the sponsor.

*Amendment*

Any sponsor may delegate any or all of its **logistic** tasks to an individual, a company, an institution or an organisation. Such delegation shall be without prejudice to the **scientific and ethical** responsibility of the sponsor.

*Justification*

*For legal certainty.*

**Amendment 55**  
**Proposal for a regulation**  
**Article 75 – paragraph 5 – subparagraph 2**

*Text proposed by the Commission*

*Amendment*

***When making*** the inspection report ***available to the sponsor, the Member State referred to in the first subparagraph*** shall ***ensure that confidentiality is protected.***

***A summary of*** the inspection report shall ***be made publicly available.***

*Justification*

*Member States' inspectors are often paid by public money and both their mission and mandate are of public interest. In addition, subjects who take part to a clinical trial have the right to know whether the trial has been/is conducted in accordance with the regulation(s) in order to be able to withdraw their consent should they wish to do so.*

**Amendment 56**  
**Proposal for a regulation**  
**Article 76 – paragraph 2**

*Text proposed by the Commission*

*Amendment*

2. The Commission may conduct inspections where it considers necessary.

2. The Commission may conduct inspections where it considers necessary. ***A summary of the Commission's inspection report shall be made publicly available.***

*Justification*

*See justification for amendment to Article 75*

**Amendment 57**  
**Proposal for a regulation**  
**Article 78 – paragraph 1 – subparagraph 2**

*Text proposed by the Commission*

*Amendment*

The EU database shall contain the data and information submitted in accordance with this Regulation.

***Public access to detailed and summary raw clinical data shall be granted to safeguard public health.*** The EU database shall contain the data and information submitted in accordance with this Regulation.

**Amendment 58**  
**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 submissions of an application for authorisation of a clinical trial or a substantial modification.

*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. ***It shall also enable citizens of the Union to have access to clinical information, in easily searchable form, about medicinal products in order to enable them to make informed decisions about their health. Publicly available information contained in the database shall contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors.***

*Justification*

*Clinical trials data are scientific data and therefore belong to the public. Patients accept to participate in clinical trials because their participation will benefit the public through the advancement of science. Science is hampered when the data are never made public. Moreover, industry-funded research benefits from publicly funded research bodies - access to investigators and research teams at publicly research sites; public funding for basic research.*

**Amendment 59**  
**Proposal for a regulation**

**Article 78 – paragraph 3 – introductory part**

*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

*Amendment*

3. The EU database shall be publicly accessible ***in accordance with the provisions of Regulation (EC) 1049/2001*** unless, for parts of the data and

following grounds:

information contained therein,  
confidentiality is justified on any of the  
following grounds:

*Justification*

*It is not reasonable that all data from a clinical trial should be confidential. Also, access in line with already established rules concerning access to documents of the EU institutions.*

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

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

*Text proposed by the Commission*

– protecting commercially confidential information;

*Amendment*

– protecting commercially confidential information; ***specifically when related to clinical trials intended for the support of any marketing authorisation application for indications which have not yet been approved;***

*Justification*

*The database should not hinder the acquisition of protection linked to intellectual or industrial property, nor prevent the sponsor from benefitting from the results of its research.*

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

**Article 78 – paragraph 3 a (new)**

*Text proposed by the Commission*

*Amendment*

***3a. The definition of what is considered as commercial confidential shall be in accordance with EMA guidelines and shall not be allowed to override the interest of public health research.***

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

**Article 78 – paragraph 5**

*Text proposed by the Commission*

*Amendment*

5. No personal data of subjects shall be publicly accessible.

5. No personal data of subjects, ***commercially confidential information or information undermining intellectual property rights*** shall be publicly accessible ***and such data shall be protected in accordance with applicable Union legislation.***

*Justification*

*It should be ensured that this Regulation preserves the added value and the expertise of European researchers as well as their legitimate interests to benefit from the results of investments used to develop a clinical trial.*

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

**Annex 1 – part 2 – point 6 – point 6 a (new)**

*Text proposed by the Commission*

*Amendment*

***whether the clinical trial significantly contributes to bringing a greater understanding of the physiology and pathology of a condition for which data is lacking, specifically for rare and ultra-rare diseases.***

*Justification*

*Many rare and ultra-rare diseases are not yet correctly identified or remain partially understood. In clinical trials associating patients affected by such conditions, the knowledge of these illnesses may be significantly improved by the resulting assessment of data. The reporting Member State must have knowledge of this added value.*

**Amendment 64**  
**Proposal for a regulation**

**Annex 3 – part 1 – point 4 a (new)**

*Text proposed by the Commission*

*Amendment*

***4a. The sponsor shall keep detailed***

*records of all adverse events reported to it by the investigator(s) and register them in the EU portal.*

## 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> Date announced in plenary	ENVI 11.9.2012
<b>Opinion by</b> Date announced in plenary	ITRE 11.9.2012
<b>Rapporteur</b> Date appointed	Amalia Sartori 26.9.2012
<b>Discussed in committee</b>	20.2.2013
<b>Date adopted</b>	19.3.2013
<b>Result of final vote</b>	+: 32 -: 23 0: 1
<b>Members present for the final vote</b>	Amelia Andersdotter, Jean-Pierre Audy, Zigmantas Balčytis, Ivo Belet, Bendt Bendtsen, Jan Březina, Reinhard Bütikofer, Maria Da Graça Carvalho, Giles Chichester, Jürgen Creutzmann, Pilar del Castillo Vera, Christian Ehler, Vicky Ford, Adam Gierek, Norbert Glante, Robert Goebbels, Fiona Hall, Jacky Hélin, Kent Johansson, Romana Jordan, Krišjānis Kariņš, Lena Kolarska-Bobińska, Bogdan Kazimierz Marcinkiewicz, Judith A. Merkies, Angelika Niebler, Jaroslav Paška, Aldo Patriciello, Vittorio Prodi, Miloslav Ransdorf, Herbert Reul, Teresa Riera Madurell, Michèle Rivasi, Salvador Sedó i Alabart, Francisco Sosa Wagner, Konrad Szymański, Britta Thomsen, Ioannis A. Tsoukalas, Claude Turmes, Marita Ulvskog, Vladimir Urutchev, Adina-Ioana Vălean, Kathleen Van Brempt, Alejo Vidal-Quadras
<b>Substitute(s) present for the final vote</b>	António Fernando Correia de Campos, Ioan Enciu, Françoise Grossetête, Jolanta Emilia Hibner, Yannick Jadot, Seán Kelly, Holger Kraemer, Bernd Lange, Werner Langen, Markus Pieper, Mario Pirillo, Vladimír Remek
<b>Substitute(s) under Rule 187(2) present for the final vote</b>	Oldřich Vlasák



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,

### **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*

(17) In practice, in order to reach

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*

(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

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*

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

*Amendment*

**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*

*Amendment*

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

(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*

*Amendment*

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

(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*

*Amendment*

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.

*(Does not affect the English version)*

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

*Text proposed by the Commission*

*Amendment*

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

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 EUdraVigilance 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*

*Amendment*

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.

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*

*Amendment*

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.

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*

*Amendment*

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

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*

*Amendment*

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

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*

*Amendment*

a description of the publication policy;

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> Date announced in plenary	ENVI 11.9.2012		
<b>Opinion by</b> Date announced in plenary	IMCO 11.9.2012		
<b>Rapporteur</b> Date appointed	Cristian Silviu Buşoi 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>	+: -: 0:	19 14 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		



9.4.2013

## **OPINION OF THE COMMITTEE ON CIVIL LIBERTIES, JUSTICE AND HOME AFFAIRS**

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: Juan Fernando López Aguilar

### **SHORT JUSTIFICATION**

The proposal aims at boosting and facilitating clinical research in the EU by simplifying the current rules for conducting clinical trials on medicinal products for human use. The proposal will replace current Directive 2001/20/EC by a Regulation which will establish a modern uniform legal framework at EU level, cutting red-tape and ending with national divergences in the implementation of Directive 2001/20/EC.

The proposal provides for the establishment of an electronic database (the EMA database), controlled by the European Medicines Agency (EMA) for the reporting of suspected unexpected serious adverse reactions. It also provides for the establishment of an EU-wide central data base (EU database) controlled by the Commission, as the single application platform for clinical trials in the EU.

Your rapporteur supports the objectives pursued by the proposal. It particularly welcomes the choice of a Regulation. It is the correct instrument to establish a uniform legal system in the Union and, hence, to create greater legal certainty and to finish with the existing regulatory and administrative burden resulting from the divergent application and implementation of Directive 2001/20/EC by the Member States.

Clinical trials have a major impact on fundamental rights of individuals, particularly the right to human dignity (Article 1), the right to life (Article 2), the right to integrity of the person (Article 3), the right for respect of private and family life (Article 7), the right to the protection of personal data (Article 8), the rights of the child (Article 24) or the right to health care (Article 35). It is essential that the future Regulation ensures the full respect of the EU Charter of Fundamental Rights. Although Recital 65 indicates that the proposal respects the fundamental rights and observes principles recognised in particular by the EU Charter of Fundamental Rights, no specific mechanism is established in order to ensure this respect.

Therefore it is necessary that a provision is made to ensure that the assessment of the respect of fundamental rights and of the measures taken to safeguard them will be part of the process of assessment regarding a clinical trial application. Articles 7(1), 31, and Annex I, Section 4, point 13 and Annex II, Section 4, should be amended accordingly.

The conducting of clinical trials implies the processing of personal data at several levels (at least sponsors, investigators, processors, EU Commission and the EMA). Personal data processed shall relate to different categories of data by which subjects are affected e.g.: subjects undergoing a clinical trial, persons giving the informed consent, sponsors, investigators, etc. Moreover different categories of personal data shall be processed, particularly "sensitive data". Your rapporteur welcomes that Recitals 52 and 59 and Article 89 (Data Protection) clearly set out that Directive 95/46/EC applies to the processing of personal data carried out pursuant to this Regulation in the Member States and Regulation (EC) No 45/2001 to the processing of personal data carried out by the Commission and the EMA in the context of this Regulation.

The Electronic database for reporting, established by the European Medicines Agency (EMA) should not contain personal data that would enable identification of patients. It should only contain pseudonymised data (key coded data) that only enable the identification of the data subject at the level of those who actually would need this information (for instance, to provide the necessary treatment), whereas this would render direct identifiability of the data subject in the EMA database impossible. Article 36 of the proposal should indicate this.

The purpose of the EU database,(Article 78), of is to streamline and facilitate the flow of information between sponsors and Member States and between the Member States. Although Recital 52 declares that no personal data of data subjects participating in a clinical trial should be recorded in the EU database, the wording of Article 78 is not clear. It provides for the "inclusion of personal data in the EU database insofar as this is necessary for the purposes for which the database is established". This does not preclude the inclusion of personal data of patients. Since the prohibition of processing of patient's personal data in the EU database is one of its essential elements, Article 78(4) should be amended to clearly establish this condition as a recital as it currently is not sufficient due to the lack of legally binding effect.

Article 78(7) refers to the rights of data subjects of information, access, rectification and deletion. It establishes a deadline of 60 days after a request is made by the data subject to have the personal data rectified or deleted. This provision should be completed in order to include the right to block personal data which is recognised by the Union's data protection law along with the subsequent rights referred to in this provision.

The proposal does not contain a provision regarding the retention period of files and personal data processed in the EMA database and in the EU database. The establishment of a retention period is an essential data protection principle. It seems that the reason for not having fixed a retention period would be the need to keep personal data of investigators for several years after the conclusion of a clinical trial so as to detect retroactively cases of misuse. However, this does not justify an unlimited period of storage of personal data. EU data protection law provides for the possibility to set longer periods of storage of personal data in the case of scientific research subject to the establishment of appropriate safeguards. Your rapporteur

therefore considers that adequate and sufficiently long data retention periods which would enable to detect retroactively cases of misuse of clinical trials should be set.

The amendments proposed will improve the legal certainty of the proposal and will strengthen the safeguards and protections of individuals, thereby ensuring compliance with Articles 8 of the EU Charter, 16 of the Treaty on the Functioning of the European Union, Directive 95/46/EC and Regulation (EC) No 45/2001

## AMENDMENTS

The Committee on Civil Liberties, Justice and Home Affairs 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 55**

*Text proposed by the Commission*

(55) In order to carry out the activities provided for in this Regulation, Member States should be allowed to levy fees.  
***However, Member States should not require multiple payments to different bodies assessing, in a given Member State, an application for authorisation of a clinical trial.***

*Amendment*

(55) In order to carry out the activities provided for in this Regulation, Member States should be allowed to levy fees.

### **Amendment 2**

#### **Proposal for a regulation** **Article 7 – paragraph 1 – point h a (new)**

*Text proposed by the Commission*

***(ha) assessment of the respect of the rights of the subjects to human dignity, the right to physical and mental integrity, the right for respect of private and family life and the right of the child.***

*Amendment*

*Justification*

*The proposal admits that it has a major impact on fundamental rights and indicates that it respects fundamental rights. However, it does not contain a mechanism that would ensure this respect. The amendment seeks to ensure that when assessing a clinical trial application, the respect of the fundamental rights will also be assessed.*

**Amendment 3**

**Proposal for a regulation**

**Article 29 – paragraph 3 a (new)**

*Text proposed by the Commission*

*Amendment*

***3a. Consent shall not waive the rights of subjects to the respect of their rights to human dignity, the right to physical and mental integrity, the right for respect of private and family life and the right of the child.***

*Justification*

*Consent may not be a means to waive the fundamental rights to human dignity, the right to physical and mental integrity, the right for respect of private and family life and the right of the child.*

**Amendment 4**

**Proposal for a regulation**

**Article 31 – paragraph 1 – point c**

*Text proposed by the Commission*

*Amendment*

(c) the explicit wish of a minor ***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 in accordance with his or her age and maturity***;

(c) the explicit wish of a minor to refuse participation in, or to be withdrawn from, the clinical trial at any time, is ***respected, irrespective of the position of his or her legal representative, no matter what the age or maturity of the minor may be***;

## Amendment 5

### Proposal for a regulation

#### Article 31 – paragraph 1 – point h a (new)

*Text proposed by the Commission*

*Amendment*

***(ha) the interest of the patient shall always prevail over those of science and society.***

#### *Justification*

*Current Directive 2001/20/EC expressly provides, amongst the conditions to meet to conduct a clinical trial on minors that the interest of the patient shall always prevail over those of science and society. This condition should be maintained so as to make it clear that the rights of minors are protected.*

## Amendment 6

### Proposal for a regulation

#### Article 36 a (new)

*Text proposed by the Commission*

*Amendment*

#### ***Article 36a***

##### ***Personal data***

***Personal data of patients shall be processed in the database referred to in Article 36 in a manner that shall not permit the direct identification of the patient (without patients name or address) and shall be kept separately from other information processed in the database. However, persons who need to know the identity of the patient for the purposes of protecting his or her vital interest shall have the possibility to do so (via an appropriate key).***

#### *Justification*

*The purpose of the ESMA database is such that it does not need to enable the direct identification of patients. Therefore the ESMA database should only contain pseudonymised data that only enable the identification of the data subject at the level of those who actually need this identification to provide the necessary care on patients if needed.*

## Amendment 7

### Proposal for a regulation

#### Article 39 – paragraph 1 a (new)

*Text proposed by the Commission*

*Amendment*

***1a. The annual report referred to in paragraph 1 shall only contain aggregate and anonymous data.***

#### *Justification*

*An annual report must only contain aggregate information and does not need to contain personal details of patients. This amendment takes into consideration the opinion of the European Data Protection Supervisor (EDPS).*

## Amendment 8 Proposal for a regulation

#### Article 41 a (new)

*Text proposed by the Commission*

*Amendment*

#### ***Article 41 a***

##### ***Storage of personal data***

***Personal data processed in the electronic database set up by the Agency shall be stored for a maximum period of 5 years after the conclusion of a clinical trial. Upon expiry of this period, the personal data processed shall be stored separately for an additional period of 20 years in a pseudonymised manner (key coded) and with access restricted during this period for the purpose of detecting cases of misuse. Once this period has elapsed, personal data shall be deleted.***

#### *Justification*

*Data conservation is an essential principle of Union's data protection law. The proposal does not provide for a retention period in the EMA database and in the EU data base. An unlimited retention period does not respect data protection law. The amendment fixes retention periods sufficiently long to enable to detect retroactively cases of misuse of clinical trials. This amendment takes into consideration the opinion of the European Data Protection Supervisor (EDPS).*

## Amendment 9

### 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 subjects shall be archived in accordance with national legislation.

*Amendment*

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 **a maximum period of** five years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national legislation.

*Justification*

*Data conservation is an essential principle of Union' data protection law. The proposal should set a maximum retention period and not a minimal one. A minimum retention period does not contribute to ensure legal certainty. This amendment takes into consideration the opinion of the European Data Protection Supervisor (EDPS).*

## Amendment 10 Proposal for a regulation

### Article 76 – paragraph 2 a (new)

*Text proposed by the Commission*

*Amendment*

**2a. The Commission shall report to the European Parliament annually on the controls and inspections conducted pursuant to this Article.**

## Amendment 11

### Proposal for a regulation Article 78 – paragraph 4

*Text proposed by the Commission*

*Amendment*

4. The EU database shall contain personal data only insofar as this is necessary for the

4. The EU database shall contain personal data only insofar as this is necessary for the

purposes of paragraph 2.

purposes of paragraph 2. ***In no case personal data of patients participating in a clinical trial shall be processed in the EU database.***

#### *Justification*

*Recital 52 declares that no personal data of data subjects participating in a clinical trial should be recorded in the EU database. The wording of Article 78 is not clear and does not preclude the inclusion of personal data of patients. Since the prohibition of processing of patient's personal data in the EU database is one of its essential elements, it must be clearly in the legal provision establishing it and not only in a recital. It also takes account of the opinion of the (EDPS).*

### **Amendment 12**

#### **Proposal for a regulation Article 78 – paragraph 7**

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

7. The Commission and Member States shall ensure that the data subject may effectively exercise his or her rights to information, to access, to rectify and to object in accordance with Regulation (EC) No 45/2001 and national data protection laws implementing Directive 95/46/EC respectively. They shall ensure that the data subject may effectively exercise the right of access to data relating to him or her, and the right to have inaccurate or incomplete data corrected and erased. Within their respective responsibilities, the Commission and Member States shall ensure that inaccurate and unlawfully processed data is deleted, in accordance with the applicable legislation. Corrections and deletions shall be carried out as soon as possible, but no later than within 60 days after a request being made by a data subject.

##### *Amendment*

7. The Commission and Member States shall ensure that the data subject may effectively exercise his or her rights to information, to access, to rectify, ***to block*** and to object in accordance with Regulation (EC) No 45/2001 and national data protection laws implementing Directive 95/46/EC respectively. They shall ensure that the data subject may effectively exercise the right of access to data relating to him or her, and the right to have inaccurate or incomplete data corrected, ***blocked*** and erased. Within their respective responsibilities, the Commission and Member States shall ensure that inaccurate and unlawfully processed data is deleted, in accordance with the applicable legislation. Corrections, ***blocking*** and deletions shall be carried out as soon as possible, but no later than within 60 days after a request being made by a data subject.

#### *Justification*

*The right to block personal data, which is also recognised by EU data protection law along*

*with the rights referred to in this Article needs to be included in the proposal. This amendment takes account of the EDPS opinion.*

### **Amendment 13**

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

#### **Article 78 – paragraph 7 a (new)**

*Text proposed by the Commission*

*Amendment*

***7a. Personal data processed in the electronic database set up by the Agency shall be stored for a maximum period of 5 years after the conclusion of a clinical trial. Upon expiry of this period, the personal data processed shall be stored separately for an additional period of 20 years in a pseudonymised manner (key coded) and with access restricted during this period for the purpose of detecting cases of misuse. Once this period has elapsed, personal data shall be deleted.***

#### *Justification*

*The proposal does not provide for a retention period in the EU data base. EU data protection law provides for the possibility to set longer periods of storage of personal data in the case of scientific research subject to the establishment of appropriate safeguards. The amendment fixes retention periods sufficiently long to enable to detect retroactively cases of misuse of clinical trials. It takes account of the opinion of the EDPS.*

### **Amendment 14**

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

#### **Annex I – part 4 – point 13 – indent 16 a (new)**

*Text proposed by the Commission*

*Amendment*

***– a description of the assessment of the impact on the rights of the subjects to human dignity, the right to physical and mental integrity, the right for respect of private and family life and the right of the child and measures taken to safeguard them.***

## *Justification*

*In order to assess that the clinical trial respects fundamental rights the Application dossier for initial application should include the description of the assessment conducted on the impact of fundamental rights and measures taken to safeguard them. This amendment is consistent with Amendment 1.*

### **Amendment 15 Proposal for a regulation**

#### **Annex 1 – part 12 – point 54 – indent 1**

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

– in trials with **minors or** incapacitated subjects, the procedures to obtain informed consent from the parent(s) or legal representative, and the involvement of the **minor or** incapacitated subject shall be described;

##### *Amendment*

– in trials with incapacitated subjects, the procedures to obtain informed consent from the parent(s) or legal representative, and the involvement of the incapacitated subject shall be described;

### **Amendment 16 Proposal for a regulation**

#### **Annex 1 – part 12 – point 54 – indent 1 a (new)**

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

##### *Amendment*

***– in trials with minors, the procedures to obtain informed consent from the minor and the parents or legal representative, and the involvement of the minor, shall be described;***

### **Amendment 17**

#### **Proposal for a regulation Annex II – part 4 – point 4 – indent 2 a (new)**

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

##### *Amendment*

***– a description of the assessment of the impact on the rights of the subjects to human dignity, the right to physical and mental integrity, the right for respect of***

*private and family life and the right of the child and measures taken to safeguard them.*

*Justification*

*In order to assess whether the clinical trial respects fundamental rights the Application dossier for initial application should include the description of the assessment conducted on the impact of fundamental rights and measures taken to safeguard them. This amendment is consistent with Amendment 1.*

## 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> Date announced in plenary	ENVI 11.9.2012
<b>Opinion by</b> Date announced in plenary	LIBE 11.3.2013
<b>Rapporteur</b> Date appointed	Juan Fernando López Aguilar 21.2.2013
<b>Discussed in committee</b>	21.2.2013                      8.4.2013
<b>Date adopted</b>	8.4.2013
<b>Result of final vote</b>	+:                      40 -:                      2 0:                      1
<b>Members present for the final vote</b>	Jan Philipp Albrecht, Edit Bauer, Emine Bozkurt, Arkadiusz Tomasz Bratkowski, Philip Claeys, Carlos Coelho, Agustín Díaz de Mera García Consuegra, Ioan Enciu, Frank Engel, Cornelia Ernst, Héléne Flautre, Kinga Gál, Kinga Göncz, Ágnes Hankiss, Anna Hedh, Salvatore Iacolino, Sophia in 't Veld, Livia Járóka, Teresa Jiménez-Becerril Barrio, Timothy Kirkhope, Monica Luisa Macovei, Véronique Mathieu Houillon, Anthea McIntyre, Nuno Melo, Claude Moraes, Georgios Papanikolaou, Jacek Protasiewicz, Carmen Romero López, Birgit Sippel, Rui Tavares, Nils Torvalds, Wim van de Camp, Josef Weidenholzer, Tatjana Ždanoka, Auke Zijlstra
<b>Substitute(s) present for the final vote</b>	Jan Mulder, Salvador Sedó i Alabart, Marie-Christine Vergiat
<b>Substitute(s) under Rule 187(2) present for the final vote</b>	Preslav Borissov, Verónica Lope Fontagné, Gabriel Mato Adrover, Vittorio Prodi, José Ignacio Salafranca Sánchez-Neyra





## 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>Date submitted to Parliament</b>	17.7.2012		
<b>Committee responsible</b> Date announced in plenary	ENVI 11.9.2012		
<b>Committee(s) asked for opinion(s)</b> Date announced in plenary	ITRE 11.9.2012	IMCO 11.9.2012	LIBE 11.3.2013
<b>Rapporteur(s)</b> Date appointed	Glenis Willmott 12.10.2012		
<b>Discussed in committee</b>	19.2.2013	20.3.2013	
<b>Date adopted</b>	29.5.2013		
<b>Result of final vote</b>	+: -: 0:	64 0 0	
<b>Members present for the final vote</b>	Martina Anderson, Elena Oana Antonescu, Sophie Auconie, Paolo Bartolozzi, Sergio Berlato, Lajos Bokros, Milan Cabrnoch, Martin Callanan, Yves Cochet, Tadeusz Cymański, Chris Davies, Anne Delvaux, Bas Eickhout, Edite Estrela, Jill Evans, Elisabetta Gardini, Gerben-Jan Gerbrandy, Matthias Groote, Françoise Grossetête, Satu Hassi, Jolanta Emilia Hibner, Karin Kadenbach, Christa Kläß, Eija-Riitta Korhola, Jo Leinen, Corinne Lepage, Peter Liese, Zofija Mazej Kukovič, Linda McAvan, Radvilė Morkūnaitė-Mikulėnienė, Miroslav Ouzký, Vladko Todorov Panayotov, Gilles Pargneaux, Antonia Parvanova, Andrés Perelló Rodríguez, Mario Pirillo, Pavel Poc, Frédérique Ries, Anna Rosbach, Oreste Rossi, Dagmar Roth-Behrendt, Daciana Octavia Sârbu, Horst Schnellhardt, Richard Seeber, Theodoros Skylakakis, Bogusław Sonik, Claudiu Ciprian Tănăsescu, Salvatore Tatarella, Glenis Willmott, Sabine Wils		
<b>Substitute(s) present for the final vote</b>	Margrete Auken, Christofer Fjellner, Romana Jordan, Philippe Juvin, Toine Manders, Judith A. Merkies, Michèle Rivasi, Christel Schaldemose, Renate Sommer, Alda Sousa, Marita Ulvskog, Vladimir Urutchev, Kathleen Van Brempt, Anna Záborská		
<b>Substitute(s) under Rule 187(2) present for the final vote</b>	Kārlis Šadurskis		
<b>Date tabled</b>	10.6.2013		