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Committee on Industry, Research and Energy

2012/0192(COD)

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

Rapporteur: Amalia Sartori

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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	*Amendment*
(1) In a clinical trial the safety ***and rights*** of subjects should be protected and the data generated should be reliable and robust.	(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	*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.	(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	*Amendment*
(7) The procedure should be flexible and efficient, in order to avoid administrative delays for starting a clinical trial.	(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	*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.	(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	*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 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	*Amendment*
(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.	(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	*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.

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	*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 18
Proposal for a regulation

Article 2 – paragraph 2 – point 19

Text proposed by the Commission	*Amendment*
(19) 'Informed consent': a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate;	(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	A clinical trial may be conducted only if
- the rights, safety and well-being of subjects are protected; and	- 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 reliable ***and*** robust.	- 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 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	*Amendment*
– the reliability and robustness of the data generated in the clinical trial, taking account of statistical approaches, design of the trial ***and*** methodology (including sample size and randomisation, comparator and endpoints)***;***	– 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	*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.	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	*Amendment*
(a) compliance with the requirements for informed consent as set out in Chapter V;	(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	*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.	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	*Amendment*
3. In the assessment, the view of ***at least one person whose primary area of interest is non-scientific shall be taken into account. The view of at least one patient*** shall be taken into account.	3. In the assessment, the view of ***an independent Ethics Committee*** shall be taken into account.

Amendment 33
Proposal for a regulation

Article 11 – paragraph 1

Text proposed by the Commission	*Amendment*
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.	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	*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 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	*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***.	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	*Amendment*
The application may be submitted only after the notification date of the initial authorisation decision.	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	*Amendment*
(a) ***25*** days from the date of submission of the application referred to in paragraph 1 for low-intervention clinical trials;	(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	*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 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	*Amendment*
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***.	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	*Amendment*
A substantial modification may only be implemented if it has been approved in accordance with the procedure set out in this Chapter.	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	*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 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.	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	*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. It shall inform the	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	*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 ***five*** years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national legislation.	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	*Amendment*
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.	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	*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.	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	*Amendment*
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:	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 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	*Amendment*
– protecting commercially confidential information;	– 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

Title	Clinical trials on medicinal products for human use, and repeal of Directive 2001/20/EC
References	COM(2012)0369 – C7-0194/2012 – 2012/0192(COD)
Committee responsible Date announced in plenary	ENVI 11.9.2012
Opinion by Date announced in plenary	ITRE 11.9.2012
Rapporteur Date appointed	Amalia Sartori 26.9.2012
Discussed in committee	20.2.2013
Date adopted	19.3.2013
Result of final vote	+: 32 –: 23 0: 1
Members present for the final vote	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 Hénin, 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
Substitute(s) present for the final vote	António Fernando Correia de Campos, Ioan Enciu, Françoise Grossetête, Jolanta Emilia Hibner, Yannick Jadot, Seán Kelly, Holger Krahmer, Bernd Lange, Werner Langen, Markus Pieper, Mario Pirillo, Vladimír Remek
Substitute(s) under Rule 187(2) present for the final vote	Oldřich Vlasák