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On 24 November 2012, the CPME Board adopted the "CPME Statement on the European Commission proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM/2012/369)" (CPME 2012/132 FINAL)

CPME Statement on the European Commission proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM/2012/369)

The Standing Committee of European Doctors (CPME) aims to promote the highest standards of medical training and medical practice in order to achieve the highest quality of health care for all patients in Europe. CPME is also concerned with the promotion of public health, the relationship between patients and doctors and the free movement of doctors within the European Union. CPME represents the national medical associations of 27 countries in Europe and works closely with the national medical associations of countries that have applied for EU membership as well as specialized European medical associations.

The proposal for a Regulation on clinical trials on medicinal products for human use, repealing Directive 201/20/EC, broadly revises the existing rules in order to increase the attractiveness and competitiveness of the EU for clinical research. The objective of the proposed Regulation is to simplify regulatory requirements and reduce the costs of the procedures.

Clinical research is essential for the EU citizens to access innovative treatments and medicines. Medical progress should therefore stay a constant priority of our public health policies. CPME welcomes the efforts made by the Commission to produce a sound legislative framework. Harmonization of the procedures is an important step forward towards less red tape and can be supported.

1. Ethical considerations

CPME highly regrets the complete absence of ethical considerations, which are the cornerstone of patient safety. The proposed Regulation fails to address basic and commonly accepted ethical standards. Compared to Directive 2001/20/EC, this is a clear step backwards. While understanding the sensitivity of the issue and the will of the Member States to keep their prerogatives on ethical issues, CPME believes that the common EU regulatory framework on clinical trial has to provide with basic ethical standards. [1]

Ethics committees should be involved in both Parts of the authorisation procedure for a clinical trial; when a substantial modification is applied for by the sponsor; as well as being notified of the results of the safety reporting procedure. Finally, a greater emphasis should be put on the role of Ethics committees in the clinical trials conducted in emergency situations.

Additionally, CPME believes that the time frames for the approval of a clinical trial proposed by the European Commission are too short. They should be extended.

→ CPME therefore recommends to amend Recitals 2 and 23, Articles 5; 6; 15; 32 and 40 and to add Article 4(a) (new) to the proposed Regulation.

2. Protection of the subjects

CPME strongly believes that **priority should always be given to the safety, rights and well-being of the individual. This priority should prevail over all other interests.** The World Medical Association Declaration of Helsinki on Ethical principles for medical research involving human subjects (last revision in Seoul, 2008) puts in its Article 6 the well-being of the subject on the forefront. This is however partially taken over in the proposed Regulation. CPME calls on the well-being of the patient to be included to the Regulation, as well as its prevalence over all other interests.

→ CPME therefore recommends to amend Recitals 1 and 37, as well as Articles 25.5.; 28.2. and 49 of the proposed Regulation.

[1] The proposal for a regulation of the European Commission on medical devices sets up a first step towards the recognition of the role and the involvement of ethics committees in clinical investigations. This is not the case in the proposal for clinical trials on medicinal products for human use, where ethics committees are not mentioned. However, the respective provisions foreseen in the medical devices regulation are still insufficient, CPME will issue a position paper on the medical devices regulation early 2013.

Regarding at the WMA Declaration of Helsinki, **the decision to participate in a clinical trial should be free and voluntary.** CPME advocates for this to be taken on board by the legislator. In particular the Definitions of "Subject" and "Informed consent" need to include this idea of a free and voluntary participation.

→ CPME therefore recommends to amend Articles 2(15) and 2(19), as well as Article 28.1.(c) of the proposed Regulation.

The free and voluntary decision by the subject to participate in a clinical trial needs to be taken on the grounds of thorough information given to him/her prior to the decision-taking. Indeed, CPME believes that only a well-informed patient is capable of taking an active part in his/her treatment. This definitely applies to clinical research. CPME welcomes the proposal of the Commission to make this information concise, clear, relevant and understandable to a lay person. However, CPME believes this provision should be reinforced by making it mandatory for a medical doctor to deliver the information orally to the subject and for the investigating team to deliver it in writing before the subject gives his/her informed consent.

→ CPME therefore recommends to amend Recital 24, as well as Article 29 of the proposed Regulation.

CPME welcomes the **provisions regarding vulnerable subjects** in Article 10, 30, 31 and 32. However, CPME believes that regarding incapacitated subjects and clinical trials in emergency situations some issues are unfortunately not addressed.
According to the WMA Helsinki Declaration, clinical trials should be conducted on incapacitated subjects if and only if they cannot be performed on capacitated subjects. This condition fails to be addressed in the current proposal.
Additionally, clinical trials in emergency situations should be conducted only when the direct benefit to the patient has been approved by the Ethics committee prior to the start of the study.
Finally, the definition of a "minor subject" should be clarified in order to better differentiate between minors and incapacitated subjects unable to give informed consent.

→ CPME therefore recommends to amend Recital 23, as well as Articles, 2(16), 30, 31.1.(c) and 32 of the proposed Regulation.

While understanding the need and the logic of distinguishing a clinical trial from a low-intervention clinical trial, **CPME is concerned about the exclusion from the indemnification mechanism of low-intervention clinical trials.** This is a negative signal sent to the potential subjects, and might result in their reluctancy to participate in the trials. Consequently, this would constitute a hurdle to medical research.

→ CPME therefore recommends to amend Article 72 of the proposed Regulation.

Regarding the clinical trials conducted outside the Union, CPME is concerned about the weak guarantees on patient safety. EU trials include very often countries from all over the world. More should be said on multinational trials, and more should be proposed to protect the patients, otherwise, this might be seen as encouraging a two-tier system of research ethics. CPME therefore believes that Article 25 should be more strict on the compliance with the principles laid down in the

Regulation, and that the Commission should have the possibility to conduct controls on the effective compliance of third-party sponsors with these principles.

→ CPME therefore recommends to amend Articles 25.5. and 76.1. of the proposed Regulation.

3. Medical doctors

The role of medical doctors is barely mentioned in the current legislative proposal. Qualified medical doctors have the necessary scientific skills and experience to be aware of the risks and inconveniences of a clinical trial. Thanks to their training, knowledge and experience, medical doctors have the required ethical insight for the good conduct of trials. CPME strongly advocates for the protection of patients and fears that **without a broad recognition of the role of medical doctors in the conduct of the clinical trials, patient safety would be at stake.**

The inclusion of physicians in the assessing team of the application for a clinical trial is therefore more than necessary. Physicians should also be the ones informing the subjects before they give consent of the objectives, risks and inconveniences of the trial. Finally, CPME believes that a clarification has to be made with regard to the suitability of the investigating team. The investigator should be a medical doctor and the other individuals involved in the investigating team should be healthcare professionals recognized by the Member State concerned[2].

→ CPME therefore recommends to amend Recitals 14; 24 and 31 as well as Articles 9; 28.1.(d); 31.1.(b) and 46 of the proposed Regulation.

4. Publication of results and Data sharing

CPME regrets the very weak provisions regarding the sharing and the publication of the trials results. Sharing the results and making them public, whether they are positive or negative and inconclusive, is a matter of trust in medical research. All the results should be publicly available, and this should clearly figure in the Regulation.

Additionally, EudraPharm should be the preferred platform to register the clinical trials and to publish the results obtained.

→ CPME therefore recommends to amend Articles 25.6 and 34.3. of the proposed Regulation.

5. Academic trials

It has been broadly recognised that academic trials generally suffer from a lack of funding to cover administrative aspects of the conduct of a clinical trial. The risk is therefore that public institutions, as well as public researchers might be further pushed out of these investigations.

[2] Healthcare professionals involved in the investigating team should be recognised in the Member State concerned as qualifying for being member of the investigating team because of the necessary scientific knowledge and experience in patient care.

Member States should therefore foresee mechanisms enabling academic research to be further carried, thus avoiding them to be disadvantaged in comparison with private investigations.

→ CPME therefore recommends to add Article 90(a) (new) to the proposed Regulation.

Amendment 1

Recital 1

Proposal of 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. The data generated should be reliable and robust.

Justification:

This is consistent with Article 3 of the proposed Regulation, as well as with Article 6 of the World Medical Association Declaration of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008).

Amendment 2

Recital 2

Proposal of 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***

Justification:

This is consistent with Article 15 of the World Medical Association's Declaration of Helsinki on Ethical principles for medical research involving human subjects, as well as with the ICH-GCP Guidelines (Seoul 2008).

Amendment 3

Recital 14

Proposal of the Commission	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 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.	(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, ***including a significant number of medical doctors,*** 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:

Medical doctors have the required scientific, medical and ethical qualifications and experiences to assess the application. They should therefore be part of the assessing team.

Amendment 4

Recital 23

Proposal of the Commission	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.	(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. ***An Ethics committee should positively assess the direct benefit of the clinical trial to the patient, as well as the fact that the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject;***

Justification:

The responsible Ethics committee should assess the direct benefit of the clinical trial to the patient. Emergency clinical trials should not be conducted for other means than the benefit of the concerned subject.

Amendment 5

Recital 24

Proposal of the Commission	Amendment
(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.	(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. ***The information should be given orally by a medical doctor (either the investigator or a member of the investigating team) and in writing.***

Justification:

This should appear in the recitals as it is consistent with Article 28.1.(d) and Article 29.2. of the proposed Regulation. The medical doctor should be the one to give the primary information about the clinical trial and obtain consent. Thereafter, additional information can be given by other Healthcare professionals.

Amendment 6

Recital 31

Proposal of the Commission	Amendment
(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.	(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.

Justification:

"Professionals" is more adequate.

Amendment 7

Recital 37

Proposal of the Commission	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.	(37) The information generated in the clinical trial should be recorded, handled and stored adequately for the purpose of ensuring subject rights***,*** safety ***and well-being*** and 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:

This is consistent with Article 3 of the proposed Regulation, as well as with Article 6 of the World Medical Association Declaration of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008).

Amendment 8

Recital 66

Proposal of the Commission	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 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,	(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**,** 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:

This is consistent with Article 3 of the proposed Regulation, as well as with Article 6 of the World Medical Association Declaration of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008)

Amendment 9

Article 2 - Definitions

Proposal of 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 subjects or on the reliability and robustness of the data generated in the clinical trial;	(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***,*** rights ***or well-being*** of the subjects or on the reliability and robustness of the data generated in the clinical trial;
(…)	(…)
(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;
(…)	(…)
(16) 'Minor': a subject who is, according to the laws of the Member State concerned, ~~***under the age of legal competence to give informed consent;***~~	(16) 'Minor': a subject who is, according to the laws of the Member State concerned, ***considered a minor;***
(…)	(…)
(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;

Justification:

(12) This is consistent with Article 3 of the proposed Regulation, as well as with Article 6 of the World Medical Association Declaration of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008).

(15) The World Medical Association's Declaration of Helsinki on Ethical principles for medical research involving human subjects, clearly states that the participation of a subject to a medical research, must be voluntary and free. This goes in line with Article 2.(19) of the proposed Regulation.

(16) The definition of "minor" should be left to the discretion of the Member States, as stipulated in Recital 22 of the Regulation, and must not necessarily be based on the criterion of competence to give informed consent. The proposed formulation provides for a better differentiation between minors and incapacitated persons unable to give informed consent.

(19) The definition of informed consent should include the idea of a free participation of the subject to the clinical trial.

Amendment 10

Article 4.a. (new)

Proposal of the Commission	Amendment
	Ethics Committee ***(1) The authorisation of a clinical trial shall be granted if and only if an independent Ethics committee positively assessed the clinical trial. The Ethics Committee assessment shall include, in particular, the requirements specified in Article 6.1.(a), Chapter V, Article 46 and Article 47 of the proposed Regulation.*** ***(2) The Ethics Committee shall ensure that the rights, safety and well-being of subjects are protected and prevail over all other interests.*** ***(3) The Ethics Committee must be independent of the investigator, independent of the sponsor, independent of the competent authority, and free of any other undue influence.*** ***(4) The Ethics Committee should consist of a reasonable number of members, who collectively possess the relevant qualifications and experience to be able to review and evaluate the scientific, medical and ethical aspects of the proposed trial.*** ***(5) Member States shall take the necessary measures to establish Ethics Committees and facilitate their work.***

Justification:

(1): A clinical trial should not be authorised if the ethical standards are not complied with. The role of the Ethics committee is therefore of utmost importance. A negative assessment by the Ethics committee should result in the refusal for granting the authorization of a clinical trial. The Ethics committee should be included in the risk-benefit assessment (Article 6.1.a.), as well as it should assess the requirements regarding the protection of the subject and the informed consent (Chapter V.), the suitability of the investigator and of the trial site (Articles 46 and 47).

(2) (3) (4): The protection of the subject's best interest should be the primary concern. It should be assessed on ethical grounds. For this purpose, the Ethics committee should be independent. Its

composition should enable the uptake of scientific decisions relying on strong medical and ethical grounds. This goes in line with Article 15 of the World Medical Association's Declaration of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008), as well as with the ICH-GCP guidelines.

(5): Member States shall stay competent for the creation of the Ethics committees. This is a subsidiarity matter.

Amendment 11

Article 5 – Submission of an application

Proposal of 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: (a) whether it is the reporting Member State or which other Member State concerned 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.	2. Within ***14*** days following submission of the application dossier, the proposed reporting Member State shall notify the sponsor through the EU portal of the following: (a) whether it is the reporting Member State or which other Member State concerned 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.
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 ***14 days,*** 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.
4. 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. Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be considered as withdrawn. Where the proposed reporting Member State has not notified the sponsor according to points	4. 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. Where the sponsor has not provided comments nor completed the application within the time-period referred to in the first subparagraph, the application shall be considered as withdrawn. 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.	(a) to (d) of paragraph 2 within ***seven*** 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.

Justification:

(2) and (3): In order to determine whether a study is a "low-intervention clinical trial", it may be necessary to conduct a substantive examination, which cannot be completed in six days. According to Article 2 (3) of the proposed Regulation, for example, the terms of the marketing authorisation of investigational medicinal products and the question of their use as a standard treatment in the Member States concerned must be determined and the degree of risk and burden to the study subjects must be assessed. Such an assessment can be complex, e.g. in the case of oncological trials, and may require the assistance of an external expert. Therefore, a time period of 14 days should be provided for this notification.

(4) The time periods specified in Article 5 (4) are also very short.

Amendment 12

Article 6 – Assessment report – Aspects covered by Part I

Proposal of the Commission	Amendment
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:	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:
(a) within ~~***10***~~ days from the validation date for low-intervention clinical trials;	(a) within ***25*** days from the validation date for low-intervention clinical trials;
(b) within ~~***25***~~ days from the validation date for clinical trials other than low-intervention clinical trials;	(b) within ***35*** days from the validation date for clinical trials other than low-intervention clinical trials;
(c) within ~~***30***~~ days from the validation date for any clinical trial with an advanced therapy investigational medicinal product.	(c) within ***40*** days from the validation date for any clinical trial with an advanced therapy investigational medicinal product.
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.	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.

Justification:

Adjustment of the deadlines for the submission of Part I of the assessment report is necessary in order to enable an effective assessment of the application dossier and comments from the Member States concerned. Minimum review periods are needed to ensure that the Member States concerned have sufficient time to participate in the assessment of acceptability in accordance with Article 6 (5).

Amendment 13

Article 9 – Persons assessing the application

Proposal of the Commission	Amendment
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, ***including a significant number of medical doctors,*** who collectively have the necessary qualifications and experience.

Justification:

Medical doctors have the required scientific, medical and ethical qualifications and experiences to assess the application. They should therefore be part of the assessing team.

Amendment 14

Article 15 – General principles

Proposal of 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 an independent Ethics committee positively assessed the substantial modification prior to its approval.***

Justification:

See Article 4.a. (new) of the proposed Regulation.

Amendment 15

Article 25 – Data submitted in the application dossier

Proposal of 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. 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.	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***,*** safety ***and well-being*** and reliability and robustness of data generated in the clinical trial. 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. ***All clinical trials must be registered prior to their start in the publicly accessible EudraPharm database.***

Justification:

(5) The requirements for the clinical trials conducted outside the Union should be identical to those of the proposed Regulation. Equivalence to those principles would enable variations in their interpretation by third-party sponsors. Therefore, subjects taking part in clinical trials outside the Union might not benefit from the same safety standards.

The addition of the "well-being" of the subject is in line with Article 3 of the proposed Regulation, as well as with Article 6 of the World Medical Association Declaration of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008).

(6) For reasons of transparency, the data from all clinical trials (including phase I trials) should be documented in a public register. EudraPharm should be the preferred register as it is intended to be a source of information on clinical trials of medicinal products including products with or without a marketing authorization.

Amendment 16

Article 28 – General rules

Proposal of the Commission	Amendment
1. A clinical trial may be conducted only where all of the following conditions are met: (a) the anticipated therapeutic and public health benefits justify the foreseeable risks and inconveniences; (b) compliance with point (a) is permanently observed; (c) the subject or, where the subject is not able to give informed consent, his or her legal representative has given informed consent; (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; (e) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with Directive 95/46/EC are safeguarded. 2. The rights, safety and well-being of the subjects shall prevail over ~~***the***~~ interests ~~***of science and society.***~~	1. A clinical trial may be conducted only where all of the following conditions are met: (a) the anticipated therapeutic and public health benefits justify the foreseeable risks and inconveniences; (b) compliance with point (a) is permanently observed; (c) 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; (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 ***a medical doctor who is*** 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; (e) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him or her in accordance with Directive 95/46/EC are safeguarded. 2. The rights, safety and well-being of the subjects shall prevail over ***all other*** interests.

Justification:

(c) Informed consent by the subject or his/her legal representative, should be given freely and voluntarily. This goes in line with the World Medical Association's Declaration of Helsinki on Ethical principles for medical research involving human subjects, as well as with Article 29.1. of the proposed Regulation.

(d) 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.

2. The proposed change is more broaden than the Proposal of the Commission. This comprises commercial and industrial interests rather than only restricting them to science and society. All these interests should in no way take precedence over the subject's best interest. This is consistent with Article 6 of the World Medical Association's Declaration of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008).

Amendment 17

Article 29 – Informed Consent

Proposal of 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 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 ***and after having received the corresponding information orally by the medical doctor and in writing.*** 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.
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.	2. Written information ***shall be given*** to the subject and/or the legal representative ***prior to the obtaining of his/her informed consent. It 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 ***at any time of the clinical trial.***

Justification:

The information should be given orally by a medical doctor (either the investigator or a member of the investigating team).

Written information shall also be given prior to the decision of the subject or his/her legal representative to give informed consent.

The right of withdrawal of the informed consent should be possible at any time, as laid down in Article 28.3.

Amendment 18

Article 30 – Clinical trials on incapacitated subjects

Proposal of the Commission	Amendment
1. In the case of incapacitated subjects who have not given, or have not refused to give, informed consent before the onset of their incapacity, a clinical trial may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:	1. In the case of incapacitated subjects who have not given, or have not refused to give, informed consent before the onset of their incapacity, a clinical trial may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:
	(a)(new). The clinical trial cannot instead be performed on a capacitated subject;
(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, whereby consent shall represent the subject's presumed will;
(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;	(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;
(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;	(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;
(d) no incentives or financial inducements are given except compensation for participation in the clinical trial;	(d) no incentives or financial inducements are given except compensation for participation in the clinical trial;
(e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;	(e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;
(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 life-threatening or debilitating medical condition from which the subject suffers;
(g) 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;	(g) 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;
(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 no risk at all.

Justification:

Clinical trials should be performed on incapacitated subjects if and only if they cannot be performed on capacitated subjects. This goes in line with Article 27 of the World Medical Association's Declaration of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008).

Amendment 19

Article 31 – Clinical trials on minors

Proposal of the Commission	Amendment
1. A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:	1. A clinical trial on minors may be conducted only where, in addition to the conditions set out in Article 28, all of the following conditions are met:
(a) the informed consent of the legal representative has been obtained, whereby consent shall represent the minor's presumed will;	(a) the informed consent of the legal representative has been obtained, whereby consent shall represent the minor's presumed will;
(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;	(b) the minor has received all relevant information in a way adapted to his or her age and maturity, ***from a medical doctor (either the investigator or the member of the investigating team)*** trained or experienced in working with children, regarding the trial, the risks and the benefits;
(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 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;***~~
(d) no incentives or financial inducements are given except compensation for participation in the clinical trial;	(d) no incentives or financial inducements are given except compensation for participation in the clinical trial;
(e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;	(e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;
(f) such research either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;	(f) such research either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;
(g) 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;	(g) 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;
(h) some direct benefit for the group of patients is obtained from the clinical trial.	(h) some direct benefit for the group of patients is obtained from the clinical trial.

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 20

Article 32 – Clinical trials in emergency situations

Proposal of the Commission	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) 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 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.	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 impossibility to obtain prior informed consent and to supply prior information; (e) ***the Ethics committee positively assesses the direct benefit of the clinical trial to the patient, as well as the fact that*** the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject;

Justification:

The responsible Ethics committee should assess the direct benefit of the clinical trial to the patient. Emergency clinical trials should not be conducted for other means than the benefit of the concerned subject.

Amendment 21

Article 34 – End of the clinical trial, early termination of the clinical trial

Proposal of the Commission	Amendment
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.	3. Within one year from the end of a clinical trial, the sponsor shall submit to the EU database ***and to the public EudraPharm database*** a summary of the results of the clinical trial, ***whether the results are positive or negative and inconclusive.*** 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.

Justification:

For reasons of transparency, the data from all clinical trials (including phase I trials) should be documented in a public register. EudraPharm should be the preferred register as it is intended to be a source of information on clinical trials of medicinal products including products with or without a marketing authorization.

The results, whether positive or negative and inconclusive, should be made public. This is a matter of patient trust. This goes in line with Article 30 of the World Medical Association's Declaration of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008).

Amendment 22

Article 40 – Assessment by Member States

Proposal of the Commission	Amendment
1. The Agency shall, by electronic means, forward to the relevant Member States the information reported in accordance with Article 38 and 39 2. Member States shall cooperate in assessing the information reported in accordance with Articles 38 and 39.	1. The Agency shall, by electronic means, forward to the relevant Member States the information reported in accordance with Article 38 and 39 2. Member States shall cooperate in assessing the information reported in accordance with Articles 38 and 39. ***3. The responsible Ethics Committee shall be duly notified of the results of this information***

Justification:

For reasons of patient safety, this amendment is necessary to ensure the involvement of the Ethics Committee in the flow of information on adverse events and serious adverse events, in line with Articles 16 and 17 of Directive 2001/20/EC.

Amendment 23

Article 46 – Suitability of individuals involved in conducting the clinical trial

Proposal of the Commission	Amendment
The investigator shall be a medical doctor as defined in national law, ***or a person following a profession which is recognised in the Member State concerned as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care.*** Other individuals involved in conducting a clinical trial shall be ***suitably qualified by education, training and experience to perform their tasks.***	The investigator shall be a medical doctor as defined in national law, ~~***or a person following a profession which is recognised in the Member State concerned as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care.***~~ Other individuals involved in conducting a clinical trial shall be ***professionals recognised in the Member State concerned as qualifying for being member of the investigating team because of the necessary scientific knowledge and experience in patient care.***

Justification:

The investigator should be a qualified medical doctor as he has the necessary scientific knowledge and experience to conduct the trial and is aware of the risks and inconveniences for the subjects.

Clinical trials should only be conducted by professionals recognized in their Member States. It is of utmost importance that patients while undergoing a clinical trial are handled by healthcare professionals, as they are qualified and experienced in patient care.

Amendment 24

Article 49 – Reporting of serious breaches

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

Justification:

The addition of "well-being" goes in line with Article 3 of the proposed Regulation, as well as with Article 6 of the World Medical Association Declaration of Helsinki on Ethical principles for medical research involving human subjects (Seoul 2008).

Amendment 25

Article 72 – Damage compensation

Proposal of the Commission	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 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 ***and*** low-intervention clinical trials ***as defined in Articles 2.(2) and 2.(3)***, 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.

Justification:

Excluding low clinical trials from the indemnification mechanism will result in a two-speed protection framework. Patient safety is here unequal. It might even create reluctancy of the patients to participate in low-intervention clinical trials. This would be counterproductive for medical research.

Amendment 26

Article 76 – Union controls and Union inspections

Proposal of the Commission	Amendment
1. The Commission may conduct controls in order to verify (a) whether Member States correctly supervise compliance with this Regulation; (b) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that point 8 of Annex I to Directive 2001/83/EC is complied with; (c) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that Article 25(3) of this Regulation is complied with.	1. The Commission may conduct controls in order to verify (a) whether Member States correctly supervise compliance with this Regulation; (b) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that point 8 of Annex I to Directive 2001/83/EC is complied with; (c) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that Article 25(3) of this Regulation is complied with; ***(c)(new) whether the regulatory system applicable to clinical trials conducted outside the Union ensures that Article 25(5) of this Regulation is complied with.***

Justification:

Compliance with Article 25(5) of the proposed Regulation should be guaranteed. The compliance with the principles defined in Article 3 of the proposed Regulation when a clinical trial is conducted outside the Union, should be controlled by the Commission.

Amendment 27

Article 90.a. (new) – Academic trials

Proposal of the Commission	Amendment
	Academic trials ***According to their applicable national laws, Member States may financially and/or logistically support the conduct of academic trials.***

Justification:

It has been broadly recognized that academic trials generally suffer from a lack of funding to cover administrative aspects of the conduct of a clinical trial. The risk is therefore that public institutions, as well as public researchers might be further pushed out of these investigations. Member States should therefore foresee mechanisms enabling academic research to be further carried, thus avoiding them to be disadvantaged in comparison with private investigations.