Response of the German Medical Association

to 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)[1]

in consultation with the

Drug Commission of the German Medical Profession

and the

Standing Conference of Management Heads and Chairs of the Ethics Committees of the German State Chambers of Physicians

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PRELIMINARY REMARKS

Medical progress and the development of innovations in medical treatment must be conducted in such a way that trial subjects are protected from unreasonable risks and burdens. Standards that are now recognized worldwide were developed and established through a learning process, particularly in the middle of the 20th century. Directive 2001/20/EC enshrines in European law a set of internationally recognized ethical and scientific quality standards in the interest of the safety, reliability and ethical acceptability of clinical research involving human subjects. In a centralized manner, it builds on the set of ethical principles for research involving human subjects enshrined in the Declaration of Helsinki by the World Medical Association (WMA). The Directive also takes into account other important standards that are based on these principles, such as the Guideline for Good Clinical Practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP Guideline).

The current European Commission proposal for a regulation of the European parliament and of the Council on clinical trials on medicinal products for human use and for repealing Directive 2001/20/EC (hereinafter referred to as "the proposed Regulation") envisages a fundamental revision of existing rules. According to the stated objective, the goal is to streamline, simplify and reduce the costs of the procedures introduced in Directive 2001/20/EC in order to increase the attractiveness of the EU as a location for clinical research. These goals should be endorsed because they help provide EU citizens access to new and innovative treatments and medicines. The harmonisation of legal norms is generally welcomed because uniform standards are an essential prerequisite for uniform Member State action, but they are not a guarantee. Therefore, mechanisms that ensure agreement between Member States regarding the construction of uniform standards are still highly relevant. It is crucial that the levels of protection achieved for quality, efficacy and safety of drug testing, as well as patient safety, be maintained during the harmonisation process.

The proposed Regulation fails to live up to central ethical principles and medical convictions in practical implementation:

1) The requirement of the **acceptability** of research in humans in terms of the risks and burdens it imposes on trial subjects is one of the internationally recognized core ethical principles of medical research involving human subjects (see Declaration of Helsinki, Rev. 2008, Article 21 and, in the same sense, Article 28 (1) point (a) of the proposed Regulation.

According to recital 12 of the proposed Regulation, not only issues of an intrinsically national nature, but also ethical aspects, will not be assessed jointly by all Member States concerned during the approval process of clinical trial applications. This principle is of central importance for the development of harmonised procedures for the approval of clinical trials.

However, in the interest of creating a rapid and streamlined process, the responsibility for assessing the question of whether the conduct of a clinical trial is *acceptable* in view of the

expected benefits and burdens is assigned to the competent authority of a single Member State (Article 6 (3) in conjunction with paragraph 1). The Commission fails to recognize that this **strips the affected Member States of their decision-making authority regarding the core issue of the ethical assessment of a clinical trial** (as stipulated in Section 3.2 on p. 5 of the proposed Regulation, and in the discussion of its implementing powers, pp. 14/15)

a) The rights of the Member States concerned to participate in this assessment decision are reduced to the right to communicate any relevant "considerations" to the reporting Member State. The reporting Member State is to take those considerations "duly into account". After the reporting Member State's assessment has been made (within the shortest of deadlines), the submission of further considerations is not possible.
b) The decision of the reporting Member State as to whether the conduct of a clinical trial is acceptable is generally binding for all Member States concerned (Article 8 (2) subparagraph 1, Article 14 (4) subparagraph 1, Article 19 (2) subparagraph 1, Article 23 (2) subparagraph 1). Disagreement of the Member States concerned with the conclusion of the reporting Member State is permissible only under the very narrow provisions of Article 8 (2) subparagraph 2 and, in particular, cannot be based on grounds of their own different assessment of the question of acceptability.

2) Another internationally recognized protection standard for research in human subjects is the principle that the research protocol must be submitted for consideration, comment, guidance and approval to an independent interdisciplinary ethics committee before the study begins (Article 15 of the Declaration of Helsinki, Rev. 2008, and Section 2.6 of the ICH-GCP Guideline). In agreement with this, Directive 2001/20/EC stipulates that:

"The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion" (Article 9 (1) subparagraph 2, sentence 1, Directive 2001/20/EC).

In contrast, the proposed Regulation refrains from providing for independent review by an independent ethics committee, **thus undermining the contribution that ethics committees currently make towards the protection of study subjects, scientific quality, and public trust in clinical research.** The provisions of Article 9 of the proposed Regulation on the persons assessing the application are far from sufficient. They neither contain a basic commitment to independent review by a medical ethics committee nor provisions for an equivalent body that would meet the recognized minimum standards for ethics committees (cf. Article 6, point (k) and Article 6 of Directive 2001/20/EC and Section 1.27 and Chapter 3 of the ICH-GCP Guideline).

a) Unlike Article 9 (1) subparagraph 2 of Directive 2001/20/EC, the proposed Regulation no longer differentiates between an independent ethics committee and the competent authority of the Member State. The Commission assumes that it is sufficient to leave the determination of the responsible bodies up to the discretion of the Member States. However, effective protection of the interests of clinical trial subjects demands that the ethics committee not only be independent of the sponsor and investigator, but also independent of the state authorities, in particular, the bodies responsible for authorisation of the clinical trial or for the licencing of medicinal products. The personal independence of

ethics committee members also forbids any integration in a government agency that is bound by instructions. The proposed Regulation should uphold these principles.

b) In the opinion of the German Medical Association, an adequate assessment of the risks and burdens for study subjects and of the clinical and scientific benefits of a clinical trial can only be performed by persons who themselves have the up-to-date clinical experience and professional expertise to do so. The assessment time frames stipulated in the proposed Regulation render the involvement of such medical and ethical expertise impossible.
c) With its express provisions for the establishment and operation of ethics committees (Article 6), Directive 2001/20/EC made a significant contribution to ensuring that independent ethics committees could be established in accordance with international ethical standards to protect the rights, safety and wellbeing of clinical trial subjects, even in countries where this previously was not the case. To waive the requirement for independent ethics committees would weaken this independent protection of study subjects in third countries and in several Member States. This runs counter to the stated objective of ensuring compliance with good clinical practice within the EU as well as in third countries.
d) An ethics committee can only ensure the effective protection of study participants (a) if its opinion is considered in the assessment of the study protocol, as required by the Declaration of Helsinki and (b) if a negative decision by the Ethics Committee necessarily results in a clinical trial not being granted approval.

3) Medical science serves to further develop diagnostic and therapeutic possibilities, and strives for new knowledge and understanding. Nonetheless, a central medical conviction in research involving human beings is that the primary duty of care is to protect the research subjects.

“In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests” (Article 6 of the Declaration of Helsinki, Rev. 2008). The proposed Regulation itself states:

“The rights, safety and well-being of the subjects shall prevail over the interests of science and society” (Article 28 (2)).

However, on closer examination, the proposed Regulation does not do justice to this principle.

The German Medical Association shares the view hitherto prevailing and historically grounded in Germany that persons unable to give informed consent may only be involved in research within narrow limits. For the same reasons, Germany has not so far signed or ratified the Council of Europe’s Oviedo Convention for the Protection of Human Rights and the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Oviedo Convention), which has lower requirements in this respect.

Compared with the provisions of Directive 2001/20/EC and the nationally applicable provisions of the German Act on Pharmaceuticals, **the proposed Regulation reduces protection against research without direct benefit to the subject, particularly with relation to minors and in emergency situations** (Article 31, Article 32). Due to the legal form of the Regulation, it will not be possible for Member States to provide for a higher level of protection in individual cases.
The German Medical Association observes with concern that the importance of individual benefit and individual consent, particularly in vulnerable populations, is receding in the face of collective interests.

In light of this, the following sections contain the suggested amendments to the proposed Regulation considered necessary by the German Medical Association.
These include, in particular:

- Effective participation of Member States concerned in risk-benefit assessment by ensuring
  - An adequate consultation period, before the end of which the reporting Member State must not make a decision.
  - Obligation of the reporting Member State to document all comments received and, if appropriate, to justify why it deviates from the opinion to one of the Member States concerned;
  - Extension of “opt out” options for Member States concerned regarding concerns about medical acceptability.
- Explicit involvement of independent ethics committees as defined by the Declaration of Helsinki and the ICH-GCP Guideline in both Part I and Part II of the assessment;
- Assurance that a negative decision by an Ethics Committee leads to a refusal of approval;
- Escape clause for the introduction of higher standards of protection for vulnerable populations by the Member States.

Amendment 1

Recital 1

Proposal of the Commission	*Proposed amendments*
(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 ~~**and**~~**, *rights and well-being*** of subjects should be protected and the data generated should be reliable and robust.

Justification

Amended to bring the text into line with Article 6 of the WMA Declaration of Helsinki (Seoul 2008) and Article 1 (2) and Article 2 (k) of Directive 2001/20/EC

Amendment 2

Recital 2

Proposal of the Commission	*Proposed amendments*
(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 ***and to approval by an ethics committee prior to commencement***.

Justification

This addition conforms to Article 9 (1) of Directive 2001/20/EC and enshrines the principle of prior authorisation of a study protocol pursuant to Article 15 of the WMA Declaration of Helsinki (Seoul, 2008) and Section 2.6 of the ICH-GCP Guideline in the recitals of the proposed Regulation.

Amendment 3

Recital 37

Proposal of the Commission	*Proposed amendments*
(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 ~~**and**~~**,** safety ***and well-being***, the robustness and reliability of the data generated in the clinical trial, accurate reporting and interpretation, effective monitoring by the sponsor and effective inspection by Member States or the Commission.

Justification

Amended to bring the text in line with the requirements of Good Clinical Practice under Article 1 (2) and with the responsibilities of ethics committees stipulated in Article 2k of Directive 2001/20/EC.

Amendment 4

Recital 66

Proposal of the Commission	*Proposed amendments*
(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 ~~**and**~~**,** rights ***and well-being*** of subjects, cannot sufficiently be achieved by the Member States and can, by reason of the scale of the measure, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Regulation does not go beyond what is necessary in order to achieve that objective,

Justification

Amended to bring the text into line with Article 6 of the WMA Declaration of Helsinki (Seoul 2008) and with Article 1 (2) and Article 2 (k) of Directive 2001/20/EC

Amendment 5

Article 2 Definitions

Proposal of the Commission	*Proposed amendments*
(1) 'Clinical study': any investigation in relation to humans intended (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; (b) to identify any adverse reactions to one or more medicinal products; or (c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; […]	(1) 'Clinical study': any investigation in relation to humans intended (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; (b) to identify any adverse reactions to one or more medicinal products; or (c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; […]
(3) 'Low-intervention clinical trial': a clinical trial which fulfils all of the following conditions: (a) the investigational medicinal products are authorised; (b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation or their use is a standard treatment in any of the Member States concerned; (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.	(3) 'Low-intervention clinical trial': a clinical trial which fulfils all of the following conditions: (a) the investigational medicinal products are authorised; (b) according to the protocol of the clinical trial, the investigational medicinal products are used in accordance with the terms of the marketing authorisation ~~**or their use is a standard treatment in any of the Member States concerned**~~; (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned
4) 'Non-interventional study': a clinical study other than a clinical trial;. […]	4) 'Non-interventional study': a clinical study other than a clinical trial; […]
(6) 'Normal clinical practice': the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder; […]	(6) 'Normal clinical practice': the treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder; […]
(8) 'Auxiliary medicinal product': a medicinal product used in the context of a clinical trial, but not as an investigational medicinal product; […]	(8) 'Auxiliary medicinal product': ~~**a**~~ ***an authorised*** medicinal product used in the context of a clinical trial, but not as an investigational medicinal product; […]
(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	(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; […]	safety ~~**or,**~~ rights ***or well-being*** of the subjects or on the reliability and robustness of the data generated in the clinical trial; […]
(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 ~~**and management**~~***, implementation and/or financing*** of 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 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, ~~**under the age of legal competence to give informed consent**~~ ***considered a minor***.

Justification

RE: Subparagraph 1): *Amended to bring the text into line with Article 2 (a) of Directive 2001/20/EC. Phase I studies which do not investigate efficacy along with safety would otherwise be excluded from the definition of a clinical trial.*

RE: Subparagraph 2): *This definition is not acceptable as it permits the conduct of low-intervention clinical trials with investigational medicinal products in a Member State where they are not authorised if these are used as a standard treatment in any of the other Member States concerned. This would lower the safety requirements for low-intervention clinical trials. It would also make it possible to investigate off-label uses of medicinal products at the expense of statutory health insurance systems. Furthermore, standard treatments in the Member States can vary, meaning that the use of imprecise terminology could result in uncertain interpretation and a change in testing standards. Only a marketing authorisation guarantees the existence of valid data on the medicinal product, therefore the marketing authorisation of a medicinal product should be the prerequisite for its use in the scope of a low-intervention clinical trial.*

RE: Subparagraph 4): *The definition of "non-interventional study" additionally raises the status of the post-marketing surveillance study.*

RE: Subparagraph 6): *The standard of care should be based on the most up-to-date scientific knowledge, not on normal clinical practice. The definition should be defined more precisely.*

RE: Subparagraph 8): For reasons of patient safety, only authorized medicinal products should be used as auxiliary medicinal products. This is also appropriate because, under

Article 43 of the proposed Regulation, safety reporting for auxiliary medicinal products shall be made according to the rules for authorised medicinal products.

RE: Subparagraph 12): Amended to bring the text in line with Article 6 of the WMA Declaration of Helsinki (Seoul 2008) and Article 1 (2) and Article 2 (k) of Directive 2001/20/EC.

RE: Subparagraph 13): Extension of the responsibilities of the Sponsor for conduct of the study is necessary due to the newly included definition of the end of the clinical trial adopted in Annex I (13) of the proposed Regulation. If the end of the clinical trial is generally considered to be the date of the last visit of the last trial subject, then reference to the responsibility of the sponsor to perform any subsequent duties, such as the storage of documents or the responsibility to submit a summary of the results of the clinical trial in the EU database, as required under Article 34 (3) of Directive 2001/20/EC, is lacking. The added reference to the responsibility of the sponsor for financing of a clinical trial corresponds to the definition in Article 2 (e) of Directive 2001/20/EC.

The definition of “subject” is identical to the definition used in Directive 2001/20/EC and should be used as a suitable generic term for both healthy volunteers (controls) and patients who are potential participants in a clinical trial. Terminological distinction should be made as needed, for example, with regard to the therapeutic benefit of participation of a patient in a clinical trial. The proposed Regulation should be amended accordingly.

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

Amendment 6

Article 4 Prior authorisation

Proposal of the Commission	*Proposed amendments*
A clinical trial shall be subject to authorisation in accordance with this Chapter.	A clinical trial shall be subject to authorisation in accordance with this Chapter. **Article 4a (new)** ***Ethics Committee*** ***(1) Authorisation of a clinical trial must not be granted before an independent ethics committee has made a positive decision on the clinical trial. The Ethics Committee assessment shall include, in particular, the requirements specified in Chapter V, Article 46, Article 47 and Chapter XII ~~of the proposed Regulation~~.*** ***(2) The Ethics Committee shall ensure that the rights, safety and well-being of subjects are protected. It must be independent of the researcher, independent of the sponsor, and free of any other undue influence. It must act in accordance with the laws and regulations of the country or countries in which the research is to be conducted and must abide by all relevant international norms and standards. 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.*** ***(3) Member States shall take the necessary measures to establish Ethics Committees and facilitate their work.***

Justification

RE: Article 4a (new) (1) and (2):
As stipulated in Article 28 (2) of the proposed Regulation, "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. Any negative decision by the Ethics Committee must necessarily result in authorisation of the clinical trial not being granted. The Ethics Committee must operate independently of the sponsor, the investigator and the state authorities, particularly those responsible for authorising clinical trials or licencing medicinal products. The proposed Article 4a takes these objectives into account. It ensures the level of protection of study subjects provided for in Directive 2001/20/EC and is in line with internationally recognized standards of protection such as those laid down in the Declaration of Helsinki and the ICH-GCP Guideline.

RE: Article 4a, paragraph 3 (new):
With its express provisions for the establishment and operation of Ethics Committees (Article 6), Directive 2001/20/EC made a significant contribution to ensuring that independent ethics committees could be established in accordance with international ethical standards to protect the rights, safety and well-being of clinical trial subjects, even in countries where this previously was not the case. Any waiver of the requirement for independent ethics committees would weaken this independent protection of study subjects in third countries and in several Member States. This contradicts the stated objective of ensuring compliance with good clinical practice within the EU as well as in third countries. Article 6 (1) of Directive 2001/20/EC should therefore be incorporated in the proposed Regulation.

Amendment 7

Article 5 Submission of an application

Proposal of the Commission	*Proposed amendments*
1. In order to obtain an authorisation, the sponsor shall submit an application dossier to the intended Member States concerned through the portal referred to in Article 77 (hereinafter 'EU portal').	1. In order to obtain an authorisation, the sponsor shall submit an application dossier to the intended Member States concerned through the portal referred to in Article 77 (hereinafter 'EU portal').
The sponsor shall propose one of the Member States concerned as reporting Member State. Where the proposed reporting Member State does not wish to be the reporting Member State, it shall agree with another Member State concerned that the latter will be the reporting Member State. If no Member State concerned accepts to be the reporting Member State, the proposed reporting Member State shall be the reporting Member State.	~~**The sponsor shall propose one of**~~ The Member States concerned ***will determine which state shall be the*** ~~**as**~~ reporting Member State ***according to an established procedure.*** ~~**Where the proposed reporting Member State does not wish to be the reporting Member State, it shall agree with another Member State concerned that the latter will be the reporting Member State. If no Member State concerned accepts to be the reporting Member State, the proposed reporting Member State shall be the reporting Member State.**~~
2. Within six days following submission of the application dossier, the proposed reporting Member State shall notify the sponsor through the EU portal of the following:	2. Within ~~**six**~~ ***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.	(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 ~~**the time period referred to in paragraph 2**~~ ***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.	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 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.	Where the proposed reporting Member State has not notified the sponsor according to points (a) to (d) of paragraph 2 within ~~**three**~~ ***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.
5. For the purposes of this Chapter, the date on which the sponsor is notified in accordance with paragraph 2 shall be the validation date of the application. Where the sponsor is not notified, the validation date shall be the last day of the time periods referred to in paragraphs 2 and 4.	5. For the purposes of this Chapter, the date on which the sponsor is notified in accordance with paragraph 2 shall be the ~~**validation**~~ date of the application. Where the sponsor is not notified, the ~~**validation**~~ date shall be the last day of the time periods referred to in paragraphs 2 and 4.

Justification

RE: Article 5 (1):
Giving the sponsor the right to propose the reporting Member State carries the risk that the sponsor will go "forum shopping", i.e., will select a reporting Member State from which it hopes to receive a favourable decision.
A comprehensible and transparent procedure for determining the reporting Member State should be established, for example using an organisational chart which predetermines the responsible reporting Member State, or based on the anticipated number of study subjects or study centres in the Member State. This is necessary, particularly in view of the focus on the reporting Member State associated with the proposed preparation of Part I of the

Assessment Report, and it would also be an advantage in terms of the acceptance of the proposed clinical trial in the Member State concerned.
A Member State should decline the role of reporting Member State if the number of study subjects to be included in its territory is significantly lower than that in the other Member States concerned.
Based on past experience, there can be delays in launching such portals, and operating difficulties may make it necessary to conduct training (with associated costs in some cases). Therefore, it would be advisable to provide for exceptions to the proposed submission modalities, especially in the case of investigator initiated trials (IITs) that are only to be conducted in one Member State. Contact people who speak the local language should be available.

RE: Article 5 (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 (cf. Amendments to Article 17 (2) of the proposed Regulation).

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

RE: Article 5 (5):
The term "validation" implies a validity of the application, which cannot be anticipated at that point in time.

Amendment 8

Article 6 Assessment report – Aspects covered by Part I

Proposal of the Commission	*Proposed amendments*
1. The reporting Member State shall assess the application with regard to the following aspects: (a) Compliance with Chapter V with respect to the following: (i) The anticipated therapeutic and public health benefits taking account of all of the following: – the characteristics of and knowledge about the investigational medicinal products; – the relevance of the clinical trial, taking account of the current state of scientific knowledge, and of whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products;	1. The reporting Member State shall assess the application with regard to the following aspects: (a) Compliance with Chapter V with respect to the following: (i) The anticipated therapeutic and public health benefits taking account of all of the following: – the characteristics of and knowledge about the investigational medicinal products; – the relevance of the clinical trial, taking account of the current state of scientific knowledge, and of whether the clinical trial has been recommended or imposed by regulatory authorities in charge of the assessment and authorisation of the placing on the market of medicinal products; ***– the question of whether the subjects are healthy volunteers or patients;***
– 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 and methodology (including sample size and randomisation, comparator and endpoints);
(ii) The risks and inconveniences for the subject, taking account of all of the following: – the characteristics of and knowledge about the investigational medicinal products and the auxiliary medicinal products; – the characteristics of the intervention compared to normal clinical practice; – the safety measures, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan; – the risk to subject health posed by the medical condition for which the investigational medicinal product is being investigated;	ii) The risks and inconveniences for the subject, taking account of all of the following: – the characteristics of and knowledge about the investigational medicinal products and the auxiliary medicinal products; – the characteristics of the intervention compared to normal clinical practice; – the safety measures, including provisions for risk minimisation measures, monitoring, safety reporting, and the safety plan; – the risk to subject health posed by the medical condition for which the investigational medicinal product is being investigated;
[…]	[…]
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 ~~**10**~~ ***25*** days ~~**from the validation date**~~***, but no earlier than 15 days after receipt of the successfully validated application*** for low-intervention clinical trials;
(b) within 25 days from the validation date for clinical trials other than low intervention clinical trials;	(b) within ~~**25**~~ ***35*** days ~~**from the validation date**~~***, but no earlier than 20 days after receipt of the successfully validated application*** 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 ~~**30**~~ ***40*** days ~~**from the validation date**~~***, but no earlier than 30 days after receipt of the successfully validated application*** 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.
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, it shall state the reasons for this deviation in the assessment report.***

Justification

RE: Article 6 (1):
Risk-to-benefit based assessment of the acceptability of a clinical trial in Part I of the assessment report, which is the assigned responsibility of the reporting Member State, is a core component of the ethical review of clinical trials. Other Member States concerned should be provided an effective say in the assessment of ethical aspects of clinical trials; cf. Recitals 6 and 12 of the proposed Regulation. The assessment of relevance cannot be separated from the ethical assessment.

The significance of a potential benefit in accordance with Article 6 (1)(a)(i) of the proposed Regulation for the affected study subject should be more strongly emphasized. Therapeutic benefit must be interpreted as benefit to the individual in order to achieve agreement with the provisions in Article 28 (1a) of the proposed Regulation.

RE: Article 6 (4):
Adjustment of the deadlines for the submission of Part I of the assessment report in accordance with Article 14 (3) of the proposed Regulation is necessary in order to enable an effective assessment of the application dossier and comments from the Member States concerned. In points (a) to (c), the time from the receipt of the successfully validated application should apply. 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).

RE: Article 6 (5):
As Part I of the assessment report touches on major ethical aspects that, according to Recitals 6 and 12, are to be regulated by the Member States concerned 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, it should, at least, be required to explain the reasons for this deviation. Decision-making should be made transparent in the assessment report.

Amendment 9

Article 7 Assessment report – Aspects covered by Part II

Proposal of the Commission	*Proposed amendments*
1. Each Member State concerned shall assess, for its own territory, the application with respect to the following aspects: (a) compliance with the requirements for informed consent as set out in Chapter V; (b) compliance of the arrangements for rewarding or compensating investigators and subjects with the requirements set out in Chapter VI; (c) compliance of the arrangements for recruitment of subjects with the requirements set out in Chapter V; (d) compliance with Directive 95/46/EC; (e) compliance with Article 46; (f) compliance with Article 47; (g) compliance with Article 72; (h) compliance with the applicable rules for the collection, storage and future use of biological samples of the subject.	1. Each Member State concerned shall assess, for its own territory, the application with respect to the following aspects: (a) compliance with the requirements for ***the protection of subjects and*** informed consent as set out in Chapter V; (b) compliance of the arrangements for rewarding or compensating investigators and subjects with the requirements set out in Chapter ~~**VI**~~ ***V***; (c) compliance of the arrangements for recruitment of subjects with the requirements set out in Chapter V; (d) compliance with Directive 95/46/EC; (e) compliance with Article 46***, sentence 1***; (f) compliance with Article 47; (g) compliance with Article 72; (h) compliance with ~~**the applicable rules for the collection, storage and future use of biological samples of the subject**~~ ***Directive 2004/23/EG***.
The assessment of the aspects referred to in the first subparagraph shall constitute Part II of the assessment report.	The assessment of the aspects referred to in the first subparagraph shall constitute Part II of the assessment report
2. Each Member State concerned shall complete its assessment within ten days from the validation date. It may request, with justified reasons, additional explanations from the sponsor regarding the aspects referred to in paragraph 1 only within that time period.	2. Each Member State concerned shall complete its assessment ***of the application*** within ten days from the ~~**validation**~~ ***assessment*** date ***according to Article 6 (4)***. It may request, with justified reasons, additional explanations from the sponsor regarding the aspects referred to in paragraph 1 only within that time period.

Justification

RE: Article 7 (1)(a):
The amendment serves to clarify that the assessment also includes procedures and provisions on aspects such as clinical trials involving minors.

RE: Article 7 (1)(b):
Amended for the correction of references, in particular, to Article 30 (1)(d) and Article 31 (1)(d) in Chapter V of the proposed Regulation.

RE: Article 7 (1)(e):
The assessment of the suitability of individuals involved in conducting the clinical trial can be limited to the investigator and his or her deputy in order to reduce the administrative burden. This does not affect later assessments of the qualifications of all study personnel in the scope of appraisals.

RE: Article 7 (1)(h):
This point should contain reference to Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

RE: Article 7 (2):
In terms of content, the assessment of aspects covered by Part II of the assessment report is inextricably linked to that of aspects covered by Part I; for example, the scope and extent of information required on study subjects and their indemnification in the event of damages is dependent, in particular, on the risk-benefit ratio. If additional requirements were attached to Part I of the assessment report and the assessment of Part II were performed first, a repeat assessment might be necessary after the completion of Part I. The proposed amendment to the time period serves to ensure that assessment of aspects covered by Part II of the assessment report will only be submitted after completion of the Part I assessment. Otherwise, the time periods provided for in Article 7 (2) would be too short for proper assessment of a clinical trial application in terms of patient safety. The proposed time period amendment increases the opportunities for Member States concerned to engage in communication and exert influence. An extension of the overall assessment period by 10 days is reasonable.

Amendment 10

Article 8 Decision on the clinical trial

Proposal of the Commission	*Proposed amendments*
2. Where the conclusion as regards Part I of the assessment report of the reporting Member State is that the conduct of the clinical trial is acceptable or acceptable subject to conditions, the conclusion of the Member State concerned shall be the same as that of the reporting Member State. Notwithstanding the first subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds: (a) significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice; (b) infringement of the national legislation referred to in Article 86. 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. […]	2. Where the conclusion as regards Part I of the assessment report of the reporting Member State is that the conduct of the clinical trial is acceptable or acceptable subject to conditions, the conclusion of the Member State concerned shall be the same as that of the reporting Member State. Notwithstanding the first subparagraph, a Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds: (a) significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice; (b) infringement of the national legislation referred to in Article 86. ***(c) if the reporting Member State has accepted a low-intervention clinical trial: non-fulfilment of the requirements of Article 2 (3) in the Member State concerned;*** ***(d) conduct of the clinical trial is medically unacceptable in consideration of the standard of care in the Member State concerned;*** ***(e) breaches of national legislation according to Article 31 (1) sentence 2 or Article 32 (1) sentence 2.*** 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. […]

Justification

Separation of the assessment report into Parts I and II limits the Member States' assessment of ethical and legal aspects.

RE: Article 8 (2)(c) (new): In its definition of "low-intervention clinical trial", Article 2 (3)(b) of the proposed Regulation refers to conditions in the Member State concerned. It is not appropriate to uniformly grant the facilitation of a low-intervention clinical trial in all Member States if the investigational product to be used is not authorised in one of the Member States concerned or if its proposed use constitutes an unauthorized use or is not a standard treatment in that Member State. In this case, the Member State concerned must have the right to prevent application of the decision of the reporting Member State in its territory.

RE: Article 8 (2)(d) (new): Article 8 (2)(a) of the proposed Regulation enables a Member State to "opt out" only if the proposed treatment in the clinical trial is inferior to that in "normal clinical practice". From a medical point of view, this is insufficient because the patient does not only have a right to normal clinical practice, but also to treatment that conforms to generally accepted professional standards of medical science. The provisions based on Principles 20 and 21 of the Declaration of Helsinki and on Section 40 (1) sentence 3, item 2 of German Act on Pharmaceuticals emphasizes the importance of the primacy of medical care of the subject.

RE: Article 8 (2e) (new): See preliminary remarks: The ethical beliefs of the Member States relating to the protection of vulnerable groups (minors and incapacitated subjects) diverge. Member States should be given the opportunity to ensure a level of protection equivalent to their other national regulations.

RE: Article 8 (2, subparagraph 3): The direct communication of a disagreement to the Commission is not justified. The time and effort required for providing such a justification is disproportionately high in view of the decision making powers of the Member States concerned. A deviation on the part of the reporting Member State from the considerations of the Member States concerned should be just as comprehensively justified as a deviation by the Member States concerned from the conclusions of the reporting Member State

Amendment 11

Article 11 Submission and assessment of applications limited to aspects covered by Part I of the assessment report

Proposal of the Commission	*Proposed amendments*
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. After the notification of the decision on the aspects covered by Part I of the assessment report, the sponsor may apply for an authorisation limited to aspects covered by Part II of the assessment report. In this case, that application shall be assessed in accordance with Article 7 and the Member State concerned shall notify its decision with regard to Part II of the assessment report in accordance with Article 8.	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. After the notification of the decision on the aspects covered by Part I of the assessment report, the sponsor may apply for an authorisation limited to aspects covered by Part II of the assessment report. In this case, that application shall be assessed in accordance with Article 7 and the Member State concerned shall notify its decision with regard to Part II of the assessment report in accordance with Article 8. ***By way of derogation from the provisions of Article 8 (1), the Member State concerned shall submit its decision within the following time periods:*** ***(a) within 25 days after the date of submission of the application for low-intervention clinical trials;*** ***(b) within 35 days after the date of submission of the application for clinical trials other than low-intervention clinical trials;*** ***(a) within 40 days after the date of submission of the application 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 the other Member States concerned.***

Justification

The focus on the reporting Member State in the proposed Regulation is further strengthened by Articles 11 and 14 because the provisions of Article 11 for other Member States concerned do not allow for comment on Part I of the assessment report on an application for

conducting a clinical trial. To enable proper assessment of the application, the time periods must be adjusted in accordance with the time periods specified in Article 14 (3) of the proposed Regulation.

Amendment 12

Article 14 Subsequent addition of a Member State concerned

Proposal of the Commission	*Proposed amendments*
4. Where the conclusion as regards Part I of the assessment report of the reporting Member State is that the conduct of the clinical trial is acceptable or acceptable subject to conditions, the conclusion of the additional Member State concerned shall be the same as that of the reporting Member State referred to in Article 6(3).	4. Where the conclusion as regards Part I of the assessment report of the reporting Member State is that the conduct of the clinical trial is acceptable or acceptable subject to conditions, the conclusion of the additional Member State concerned shall be the same as that of the reporting Member State referred to in Article 6(3).
Notwithstanding the first subparagraph, an additional Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds:	~~**Notwithstanding the first subparagraph, an additional Member State concerned may disagree with the conclusion of the reporting Member State only on the following grounds:**~~
(a) significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice; (b) infringement of the national legislation referred to in Article 86.	~~**(a) significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice;**~~ ~~**(b) infringement of the national legislation referred to in Article 86.**~~
Where the additional 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 additional 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.**~~ ***Article 8 (2) subparagraph 2 applies accordingly.***

Justification

See Article 8

Amendment 13

Article 15 General principles

Proposal of the Commission	*Proposed amendments*
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 been approved by an independent ethics committee before its implementation***.

Justification

See Article 4a new of the proposed Regulation.

Amendment 14

Article 17 Validation of an application for authorisation of a substantial modification of an aspect covered by Part I of the assessment report

Proposal of the Commission	*Proposed amendments*
2. Within four days following submission of the application dossier, the reporting Member State shall notify the sponsor through the EU portal of the following: (a) whether the substantial modification concerns an aspect covered by Part I of the assessment report; (b) whether the application is complete in accordance with Annex II; (c) where the clinical trial is a low-intervention clinical trial, whether it will remain a low-intervention clinical trial after its substantial modification	2. Within ~~four~~ ***ten*** days following submission of the application dossier, the reporting Member State shall notify the sponsor through the EU portal of the following: (a) whether the substantial modification concerns an aspect covered by Part I of the assessment report; (b) whether the application is complete in accordance with Annex II; (c) where the clinical trial is a low-intervention clinical trial, whether it will remain a low-intervention clinical trial after its substantial modification

Justification

As the aspects specified in points (a) and (c) require substantive examination, four days are insufficient. See also the justification to Article 5 (2) of the proposed Regulation.

Amendment 15

Article 19 Decision on the substantial modification of an aspect covered by Part I of the assessment report

Proposal of the Commission	*Proposed amendments*
2. Where the conclusion of he reporting Member State is that the substantial modification is acceptable or acceptable subject to conditions, the conclusion of the Member State concerned shall be the same as that of the reporting Member State.	2. Where the conclusion of he reporting Member State is that the substantial modification is acceptable or acceptable subject to conditions, the conclusion of the Member State concerned shall be the same as that of the reporting Member State.
Notwithstanding the first subparagraph, a Member State concerned may disagree with that conclusion of the reporting Member State only on the following grounds:	~~**Notwithstanding the first subparagraph, a Member State concerned may disagree with that conclusion of the reporting Member State only on the following grounds:**~~
(a) significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice; (b) infringement of the national legislation referred to in Article 86.	~~**(a) significant differences in normal clinical practice between the Member State concerned and the reporting Member State which would lead to a subject receiving an inferior treatment than in normal clinical practice;**~~ ~~**(b) infringement of the national legislation referred to in Article 86.**~~
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.**~~ ***Article 8 (2) subparagraph 2 applies accordingly.***

Justification

See Article 8.

Amendment 16

Article 20 Validation, assessment and decision regarding a substantial modification of an aspect covered by Part II of the assessment report

Proposal of the Commission	*Proposed amendments*
5. The Member State concerned shall assess the application and shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused. Notification shall be done by way of one single decision within ten days from the validation date.	5. The Member State concerned shall assess the application and shall notify the sponsor through the EU portal as to whether the substantial modification is authorised, whether it is authorised subject to conditions, or whether authorisation is refused. Notification shall be done by way of one single decision within ten days from the ~~**validation**~~ ***assessment*** date ***according to Article 6 (4)***.

Justification

In terms of content, the assessment of aspects covered by Part II of the assessment report is inextricably linked to that of aspects covered by Part I; for example, the required scope and extent of information provided to study subjects and their indemnification in the event of damages is dependent, in particular, on the risk-benefit ratio. If additional requirements were attached to Part I of the assessment report and the assessment of Part II were performed first, a repeat assessment might be necessary after the completion of Part I. The proposed amendment to the time period serves to ensure that assessment of aspects covered by Part II of the assessment report will only be submitted after completion of the Part I assessment (cf. justification of proposed amendment to Article 7 (2)).

Amendment 17

Article 22 Assessment of a substantial modification of aspects covered by Parts I and II of the assessment report – Assessment of the aspects covered by Part II of the assessment report

Proposal of the Commission	*Proposed amendments*
1. Each Member State concerned shall assess, for its territory, the aspects of the substantial modification which are covered by Part II of the assessment report within ten days from the validation date.	1. Each Member State concerned shall assess, for its territory, the aspects of the substantial modification which are covered by Part II of the assessment report within ten days from the ~~**validation**~~ ***assessment*** date ***according to Article 6 (4)***. .

Justification

See Article 20 (5)

Amendment 18

Article 25 Data submitted in the application dossier

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

It is assumed that the data from all clinical trials (including phase I trials) will be documented in a public register. In addition, time limits should be defined for the registration of clinical trials and for the publication of clinical trial data. In the USA, for example, a clinical trial must be registered within 21 days of the recruitment of the first patient, and the results must generally be published no later than one year after completion of the trial.

Amendment 19

Article 28 General rules

Proposal of the Commission	*Proposed amendments*
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;	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 in writing, his or her legal representative has given informed consent; (d) the subject or, where the subject is not able to give informed consent (usually in written form), 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;

Justification

RE: Point (a)
Uniform standards for the assessment of benefits and clinical relevance should be defined in order to standardize their application.

RE: Point (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.

Amendment 20

Article 29 Informed consent

Proposal of the Commission	*Proposed amendments*
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**~~ ***comprehensively and comprehensibly*** informed of the nature, significance, implications and risks of the clinical trial ***and after having received the corresponding information 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.

Justification

A (further unspecified) restriction of informed consent is otherwise permissible; the provision of written information corresponding to informed consent documents serves to inform the subject and is consistent with the provisions of Article 2 (j) of Directive 2001/20/EC.

Amendment 21

Article 31 Clinical trials on minors

Proposal of the Commission	*Proposed amendments*
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; (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; (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; (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; (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.	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; (b) the minor has received all relevant information in a way adapted to his or her age and maturity, from ~~**professionals**~~ ***a medical doctor (either the investigator or member of the trial team)*** trained or experienced in working with children, regarding the trial, the risks and the benefits; (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; (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; (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. ***Member States may impose additional requirements for the protection of subjects.***

Justification

RE: Point (b):
See Article 28 (1) point (b)

RE: Point (c):
The proposed amendment serves to ensure that refusal by a minor is duly taken into consideration by the investigator. Otherwise, there would be a breach of the fundamental rights of the minor under Article 3 in conjunction with Article 8 of the European Convention on Human Rights and Article 1 in conjunction with Article 3 (1) of the Charter of Fundamental Rights of the European Union, each in conjunction with Article 6 (1) or (3) of the EU Treaty .

RE: Sentence 2:
An escape clause is necessary in order to align the provisions for protection of vulnerable populations with applicable standards in the Member States.

Amendment 22

Article 32 Clinical trials in emergency situations

Proposal of the Commission	*Proposed amendments*
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) ***and (h)*** 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. ***Member States may impose additional requirements for the protection of subjects.***

Justification

Adults able to give informed consent could be included in the clinical trial, according to Article 32 of the proposed Regulation, without prior information and, according to Article 28 (1) of the proposed Regulation, without potential personal or group benefit. An obligation to comply with a potential refusal does not exist. The exploitation of patients associated with this provision is incompatible with the fundamental rights under the European Convention on Human Rights and the Charter of Fundamental Rights of the EU. Therefore, Article 32 of the proposed Regulation should be supplemented in accordance with the provisions of Article 5 (i) of 2001/20/EC regarding a potential direct benefit to the patient outweighing the risks of the clinical trial.

It should be ensured that temporarily incapacitated subjects are included as persons unable to give informed consent according to the laws of the Member State concerned, as stipulated in Article 2 (17) of the proposed Regulation. Otherwise, temporarily incapacitated subjects

would only be given protection under Article 28 of the proposed Regulation, making it possible to subject them to research purely for third-party benefit in emergency situations, even without the consent of their legal representative.

An escape clause is necessary in order to align the provisions for protection of vulnerable populations with applicable standards in the Member States.

Amendment 23

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

Proposal of the Commission	*Proposed amendments*
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. 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, an obligation to publish the results of clinical trials in the EudraPharm database should be introduced and implemented.

Amendment 24

Article 39 Annual reporting by the sponsor to the Agency

Proposal of the Commission	*Proposed amendments*
1. Regarding non-authorised investigational medicinal products other than placebo, and authorised investigational medicinal products which, according to the protocol, are not used in accordance with the terms of the marketing authorisation, the sponsor shall submit annually by electronic means to the Agency a report on the safety of each investigational medicinal product used in a clinical trial for which it is the sponsor.	1. Regarding non-authorised investigational medicinal products other than placebo, and authorised investigational medicinal products which, according to the protocol, are not used in accordance with the terms of the marketing authorisation, the sponsor shall submit ~~**annually**~~ ***every six months*** by electronic means to the Agency a report on the safety of each investigational medicinal product used in a clinical trial for which it is the sponsor.

Justification

For reasons of patient safety, a six-month period should apply.

Amendment 25

Article 40 Assessment by Member States

Proposal of the Commission	*Proposed amendments*
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 involved in the assessment 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 26

Article 49 Reporting of serious breaches

Proposal of the Commission	*Proposed amendments*
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,~~ rights ***and well-being*** of the subjects or the reliability and robustness of the data generated in the clinical trial.

Justification

Amended to bring the text in line with Article 6 of the WMA Declaration of Helsinki (Seoul 2008) and with Article 1 (2) and Article 2 (k) of Directive 2001/20/EC

Amendment 27

Article 73 National indemnification mechanism

Proposal of the Commission	*Proposed amendments*
1. Member States shall provide for a national indemnification mechanism for compensating damage as referred to in Article 72.	~~**1. Member States shall provide for a national indemnification mechanism for compensating damage as referred to in Article 72.**~~
2. The sponsor shall be deemed to comply with Article 72 where it makes use of the national indemnification mechanism in the Member State concerned.	~~**2. The sponsor shall be deemed to comply with Article 72 where it makes use of the national indemnification mechanism in the Member State concerned.**~~
3. The use of the national indemnification mechanism shall be free of charge where, for objective reasons, the clinical trial was not intended, at the time of submission of the application for authorisation of that clinical trial, to be used for obtaining a marketing authorisation for a medicinal product.	~~**3. The use of the national indemnification mechanism shall be free of charge where, for objective reasons, the clinical trial was not intended, at the time of submission of the application for authorisation of that clinical trial, to be used for obtaining a marketing authorisation for a medicinal product.**~~
For all other clinical trials, the use of the national indemnification mechanism may be subject to a fee. Member States shall establish that fee on a not-for-profit basis, taking into account the risk of the clinical trial, the potential damage, and the likelihood of the damage.	~~**For all other clinical trials, the use of the national indemnification mechanism may be subject to a fee. Member States shall establish that fee on a not-for-profit basis, taking into account the risk of the clinical trial, the potential damage, and the likelihood of the damage.**~~

Justification

In the proposed Regulation, it is unclear through which agencies the indemnification mechanism should operate. Moreover, the justification for the establishment of such a mechanism on p. 10 of the Regulation is inconclusive. At the present time, it is not possible to predict which effects this might have on the liability systems of the Member States.

Amendment 28

Article 83 One fee per activity per Member State

Proposal of the Commission	*Proposed amendments*
A Member State shall not require, for an assessment as referred to in Chapters II and III, multiple payments to different bodies involved in this assessment.	~~**A Member State shall not require, for an assessment as referred to in Chapters II and III, multiple payments to different bodies involved in this assessment.**~~

Justification

It should be left to the Member States to determine issues concerning the collection of fees.

Amendment 29

Article 91 Repeal

Proposal of the Commission	*Proposed amendments*
2. By way of derogation from the paragraph 1, where the request for authorisation of a clinical trial has been submitted before the date provided for in Article 92(2) [application date] pursuant to Directive 2001/20/EC, that clinical trial shall continue to be governed by that Directive until [please set a specific date – five years after publication of this Regulation].	2. By way of derogation from the paragraph 1, where the request for authorisation of a clinical trial has been submitted before the date provided for in Article 92(2) [application date] pursuant to Directive 2001/20/EC, that clinical trial shall continue to be governed by that Directive ~~**until [please set a specific date – five years after publication of this Regulation]**~~.

Justification

Directive 2001/20/EC should remain valid for all ongoing clinical trials until their completion.

Amendment 30

Article 92 Transitional provision

Proposal of the Commission	*Proposed amendments*
By way of derogation from Article 91(1), where the request for authorisation of a clinical trial is submitted between [please set a specific date - two years from the publication of this Regulation] and [please set a specific date - three years after publication] that clinical trial may be started in accordance with Articles 6, 7 and 9 of Directive 2001/20/EC. That clinical trial shall continue to be governed by that Directive until [please set a specific date – five years after publication of this Regulation].	*By way of derogation from Article 91(1), where the request for authorisation of a clinical trial is submitted between [please set a specific date - two years from the publication of this Regulation] and [please set a specific date - three years after publication] that clinical trial may be started in accordance with Articles 6, 7 and 9 of Directive 2001/20/EC. That clinical trial shall continue to be governed by that Directive* ~~**until [please set a specific date – five years after publication of this Regulation]**~~.

Justification

See Article 91

Amendment 31

Annex I Application dossier for initial application

Proposal of the Commission	*Proposed amendments*
[…]	[…]
4. Without prejudice to Article 26, the application dossier for an application referred to in Article 14 shall be limited to sections 11 to 17 of this Annex.	4. Without prejudice to Article 26, the application dossier for an application referred to in Article 14 shall be limited to ~~**sections 11 to 17 of this**~~ ***the documents specified in*** Annex ***I***.
[…]	[…]
17. The protocol shall be accompanied by a synopsis of the protocol.	17. The protocol shall be accompanied by a synopsis of the protocol ***in the national language(s) of each Member State concerned***.
[…]	[…]
57. Description of the qualification of the principal investigators in a current curriculum vitae and other relevant documents shall be submitted. Any previous training in the principles of GCP or experience obtained from work with clinical trials and patient care shall be described.	57. Description of the qualification of the principal investigators ***and their deputies*** in a current curriculum vitae and other relevant documents shall be submitted. Any previous training in the principles of GCP or experience obtained from work with clinical trials and patient care shall be described.
58. Any conditions, such as economic interests, that might be suspected to influence the impartiality of the principal investigators shall be presented.	58. Any conditions, such as economic interests, that might be suspected to influence the impartiality of the principal investigators ***and their deputies*** shall be presented.
[…]	[…]
59. A written statement on the suitability of the trial sites by the head of the clinic/institution at the trial site or by some other responsible person, according to the system in the Member State shall be submitted.	59. A written statement on the suitability of the trial sites by the head of the clinic/institution at the trial site or by some other responsible person, according to the system in the Member State shall be submitted. ***This shall contain the particulars of the human, material and spatial resources of the clinical trial site, as well as information on ongoing and planned clinical trials in the same therapeutic area at the clinical trial site.***
[…]	[…]
60. Information on financial transactions and compensation paid to subjects and	60. Information on financial transactions and compensation paid to subjects and

investigator/site for participating in the clinical trial shall be submitted. 61. Description of any agreement between the sponsor and the site shall be submitted	investigator/site for participating in the clinical trial shall be submitted. 61. Description of any agreement between the sponsor and the site shall be submitted. ***62. Information on the financing of the clinical trial shall be submitted.***

Justification

RE: Section 1 (4):
Assessment by another Member State concerned encompasses the aspects covered by Part II of the assessment report and corresponds in this respect to assessment by the Member State concerned in accordance with Article 7 of the proposed Regulation. Furthermore, it is not possible to assess certain aspects, such as conformity with Articles 46, 47 und 72, without certain information, such as the trial protocol. Therefore, other Member States concerned should receive a complete set of the documents listed in Annex I.

RE: Section 4 (17):
To enable proper assessment of an application for authorisation of a clinical trial, it is of central importance to have a synopsis of the protocol in the respective national language(s).

RE: Section 13 (56):
It is necessary to name a deputy principal investigator because, in the absence of the principal investigator, the deputy bears in full the same responsibility as the principal investigator. Therefore, for reasons of patient safety, it is necessary that assessment of the suitability of the investigator pursuant to Article 7 (1) point (e) of the proposed Regulation also include assessment of the suitability of his or her deputy.

RE: Section 14 (59):
A written statement on the suitability of a trial site for the conduct of a clinical trial by the head of the clinic/institution *alone is insufficient for an assessment of the suitability of trial sites by the Member State concerned in accordance with Article 7 (1) point (f) of the proposed Regulation. The proposed amendments are based on the requirements in Section 4.2 of the ICH-GCP Guideline.*

RE: Section 16 (62) (new):
Adequate funding is essential for the proper conduct of a clinical trial. The amendment serves to ensure that the text is in line with Section 6.14 of the ICH-GCP Guideline, which stipulates that the protocol must contain information on financing of the clinical trial.